Investments in Pharmaceuticals Before and After TRIPS

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ABSTRACT

The TRIPS Agreement, which specifies minimum levels of intellectual property protection for countries in the World Trade Organization, has increased levels of patent protection around the world. Using variation across countries in the timing of patent laws and the severity of disease, we test the hypothesis that increased patent protection results in greater drug development effort. We find that patent protection in wealthy countries is associated with increases in research and development (R&D) effort. However, the introduction of patents in developing countries has not been followed by greater R&D investment in the diseases that are most prevalent there.

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I. Introduction

Over the last twenty years, most countries have adopted intellectual property (IP) rights. The establishment of the World Trade Organization (WTO) in 1994 was an important driver of this expansion: minimum levels of copyright, trademark and patent protection are a requirement for a country's membership in the WTO as specified by the Agreement on Trade-Related Aspects of Intellectual Property Rights, known as the TRIPS Agreement. IP protection involves a trade-off between dynamic efficiency (associated with incentives for innovation) and static efficiency (tied to access to innovation), and the TRIPS Agreement has long been the subject of debate about the appropriate balance. The extension of patents on pharmaceuticals has been especially controversial for developing and least-developed countries, where access to treatments is limited. Advocates for drug access argue that IP should be minimal, while advocates of drug innovation argue that IP creates incentives for R&D.

Developing and least-developed countries have resisted patents on pharmaceuticals due to concerns about short run costs: because patents eliminate generic competition for treatments during their terms, patents potentially lead to higher prices and thus reduced patient access. However, if patents create incentives to develop drugs for conditions that are prevalent in poorer countries, then patents may be tolerable in developing countries despite the static inefficiency. While diseases of all kinds may afflict the population of a low-income country, a group of so-called "neglected" diseases is of particular interest. Neglected diseases are those conditions for which most deaths occur in developing and least-developed countries, and include HIV, tuberculosis, malaria, river blindness and leprosy. The term "neglected" refers to the relative lack of treatments available to address them, despite their prevalence.[1]

In this article, we seek to inform the debate on the benefits and costs of the TRIPS Agreement by examining the effect of increased global IP rights on the development of

pharmaceutical treatments. Specifically, we test for the dynamic benefits of IP protection by examining research and development (R&D) efforts in the form of clinical trials on specific diseases over time. If patent protection is effective in inducing innovation, then we should observe more R&D on diseases relevant to local populations as patent protection was extended to developing and least-developed countries. Instead, if patents are ineffective at inducing R&D on so-called "neglected" diseases, then no response in R&D effort would occur with the extension of patents to poor countries.

Our analysis relies on the fact that disease prevalence varies across countries, and countries complied with TRIPS at different times. We exploit cross-sectional variation over time in both the adoption of TRIPS and the potential market size of diseases to estimate the relationship between R&D effort and patent protection. We also examine whether this relationship differs across diseases and countries.

The results indicate that, in general, R&D effort is positively associated with the sizes of markets in which patent protection applies. However, the relationship between patent protection and R&D effort varies by country income level. There is a strong association between pharmaceutical patents and R&D effort for diseases that are prevalent in high-income countries, but not for neglected diseases. The establishment of patent protection in poorer countries is not linked to greater R&D effort for diseases that have no market in developed countries. In other words, the introduction of patent protection has not been followed by an increase in R&D on diseases that primarily affect the world's poor. Lanjouw & Cockburn (2001) concluded "[i]t is too early to tell…" the effect of TRIPS on "new pills for poor people" (p. 287) in 2001. This study finds that TRIPS had yet to yield those pills as of 2006. The results suggest that the trade-off between incentives for innovation (i.e., dynamic efficiency) and access to treatments (i.e., static efficiency) is quite different for rich countries than for the developing world.

It is important to note that this paper examines only some potential *gains* from TRIPS for developing and least-developed countries rather than attempting a comprehensive assessment of all benefits and costs of the policies. In particular, we do not assess the costs of new R&D projects, and so we cannot conclude that dynamic efficiency arose from the extension of patent protection among wealthier countries. We find few gains for poorer countries, however, which leads us to the conclusion that the extension of IP protection under TRIPS could not have led to dynamic efficiencies arising from new research on neglected diseases. While quite important in developed countries, patents do not appear to increase innovation incentives elsewhere. This finding is consistent with the notion that the research required for significant advances on neglected diseases is too costly for profit-seeking pharmaceutical firms to justify given the expected returns, or put another way, that profits from such treatments in developing countries – even with patent protection – do not allow firms to recoup their development costs.

In the next section, we discuss the TRIPS Agreement and its requirements in more detail. Section III outlines the theoretical underpinnings to our empirical approach, which we describe in Section IV. We explain our data sources and measures in Section V and present results in Section VI. Section VII concludes.

II. The TRIPS Agreement

The WTO, including the TRIPS Agreement, was established in 1994 during the Uruguay Round of the General Agreement on Tariffs and Trade. Membership in the WTO provides participating countries with trade privileges arising from extensively streamlined administrative procedures. Countries cannot join the WTO without adopting TRIPS, which established minimum levels of copyright, trademark, industrial design, trade secret, and patent protection, and thus affects firms in a range of industries. The rationale is that all WTO members should offer similar

intellectual-property protection to facilitate trade. In theory, member countries will cultivate and promote commerce by adopting and enforcing laws that protect intellectual property.

Since discussions over TRIPS began, the Agreement has been controversial. According to the WTO, TRIPS "attempts to strike a balance between the long term social objective of providing incentives for future inventions and creation, and the short term objective of allowing people to use existing inventions and creations….Intellectual property protection encourages inventors and creators because they can expect to earn some future benefits from their creativity. This encourages new inventions, such as new drugs, whose development costs can sometimes be extremely high, so private rights also bring social benefits" (WTO Fact Sheet 2006). The minimum term of patent protection is now 20 years, and member states must grant patents for both products and processes in most areas of technology, including pharmaceuticals. TRIPS specifies dispute resolution procedures when a member state is accused of failing to comply with the agreement., and states that penalties for infringement must be sufficient to deter violations.

The major controversy is over whether the right balance was struck, particularly in the case of patent protection for pharmaceuticals. Arguments in favor of TRIPS emphasize that intellectual property rights should integrate developing and least-developed countries into the global economy by reducing risks and enhancing incentives to established multinational corporations that operate in these markets. Proponents also noted that the prospect of higher profitability resulting from IP protection would induce additional research on neglected diseases, or those that primarily affect poorer countries.

Concerns arose because patents could allow firms to increase prices and reduce access to treatments. Critics of TRIPS pointed in particular to the case of HIV treatments (Westerhaus and Castro 2006, Cohen 2006, Outterson 2009).[2] The adoption of patent protection in developing countries raised the possibility of very expensive treatments for the growing epidemic. To address

these issues, the original TRIPS Agreement included a number of exceptions for poorer countries. Subsequently, TRIPS was revised several times in response to concerns about the effects of patents in developing and least-developed countries. In addition to formal revisions, the interpretation of TRIPS, compliance and enforcement have changed over time and affected how TRIPS is implemented in practice (Correa 2001).[3]

Because TRIPS constituted a major change in many countries, the TRIPS Agreement itself provided specific deadlines for compliance that vary according to the development status of member states. According to the WTO:

> "When the WTO agreements took effect on 1 January 1995, developed countries were given one year to ensure that their laws and practices conform with the TRIPS agreement. Developing countries and (under certain conditions) transition economies were given five years, until 2000. Least-developed countries have 11 years, until 2006 — now extended to 2016 for pharmaceutical patents.
>
> "If a developing country did not provide product patent protection in a particular area of technology when the TRIPS Agreement came into force (1 January 1995), it had up to 10 years to introduce the protection. But for pharmaceutical and agricultural chemical products, the country had to accept the filing of patent applications from the beginning of the transitional period, though the patent did not need to be granted until the end of this period. If the government allowed the relevant pharmaceutical or agricultural chemical to be marketed during the transition period, it had to — subject to certain conditions — provide an exclusive marketing right for the product for five years, or until a product patent was granted, whichever was shorter."

(http://www.wto.org/english/theWTO_e/whatis_e/tif_e/agrm7_e.htm)

The WTO uses the United Nations' definition of least-developed countries for the purpose of establishing compliance deadlines. All other WTO members identify themselves as either developing or developed upon applying for WTO membership. New members joining after 1995 were generally required to implement TRIPS immediately as part of their ascension agreements with the WTO, and could not use a transition period. Appendix B provides a list of WTO members and their compliance dates. Figure 1 shows how TRIPS compliance changed over time across countries with different 1995 income levels (as defined by the World Bank).

In addition to different deadlines for countries of lower income levels, TRIPS included other exemptions that had the effect of weakening patent protection for pharmaceutical products in some situations. The "Bolar provision" allows a patented invention to be used in the process of conducting research on new drugs as well as in obtaining marketing approval for generic drugs prior to patent expiration. This provision has been invoked in the United States, Canada, Europe, India and China, among others.

Another exemption, granted under the Doha Declaration in 2002, allows countries that meet certain criteria to issue a compulsory license on a patented drug as long as the licensed products are manufactured for domestic use only (i.e., not for export), and with "reasonable" compensation to the patent holder.[4] Implementing the Doha policy has proven challenging, however, because TRIPS and subsequent revisions specify neither what constitutes a national health emergency nor how a reasonable payment should be calculated. Compulsory licenses have so far been rare and mainly issued on drugs for treating HIV (for example, in Thailand, Brazil, Malaysia, Indonesia, South Africa, Zambia and Mozambique) despite the health costs associated with the HIV epidemic in other countries of sub-Saharan Africa. Nonetheless, the threat of compulsory licenses may be an

important influence on pharmaceutical distribution in these countries. Where compulsory licenses have been issued, they too have been controversial, particularly in the case of Brazil and Thailand. In response to Thailand's decision to issue a compulsory license on a hypertension drug as well as an HIV treatment, Abbott Laboratories (whose patent on the HIV treatment Kaletra was at issue) announced that it would no longer supply Thailand with any products. The US Trade Representative put Thailand on its Priority Watch List and the WHO cautioned Thailand to improve its relationship with pharmaceutical firms.

The discussion over compulsory licenses highlighted that such orders may have little effect on national health when complementary institutions such as clinics and pharmacies for administering pharmaceuticals are absent. Furthermore, the compulsion to issue a license is meaningless in the absence of local manufacturers to which the license could be assigned (Westerhaus and Castro 2006). This last concern was addressed in 2003, when the WTO agreed on exceptions to rules that restricted trade in compulsory licensed products. After 2003, member states that declared a national health emergency and ordered a compulsory license could import those products from generic manufacturers located elsewhere if they lacked domestic manufacturing capacity. These changes and exceptions make the precise date of compliance by country difficult to estimate, as we explain below.

III. Theoretical development

We assume that pharmaceutical firms seek to maximize profits when they make R&D investments by forming expectations about the profit that may be eventually obtained if the R&D leads to a successfully commercialized product. We focus on three factors that influence expected profits in a potential market: intellectual property protection, potential volume and ability to pay or

income level. IP protection and income are related to the price a firm expects to charge, and potential market size is related to the quantity a firm expects to sell.

The role of patent protection

The development of new pharmaceuticals is an expensive and lengthy process. DiMasi et al. (2004) estimated that developing a new drug during the 1990s cost about $400-500 million on average, and the time required from project inception to the commercial introduction of a new drug averaged 4-10 years. Though there is debate over the proper way to account for the required investment (DiMasi et al. 2005), there is no dispute that the fixed costs of drug development are very large relative to the marginal costs of production, and that there is a high failure rate of development projects. In contrast, the cost of imitating a pharmaceutical innovation tends to be relatively small (Grabowski 2002). IP protection, particularly in the form of patents, provides a means for innovators to earn a return on their investments in R&D by granting a legal monopoly that normally allows firms to charge higher prices than possible when facing competition. While not the only mechanism for inducing innovation, patents are considered of particular importance in the pharmaceutical sector relative to other industries because of the high fixed cost of drug development (Cohen et al 2000).[5]

As pharmaceutical executives and investors allocate resources between research projects, they consider tradeoffs associated with potential return in the global market. The effect of a single country's change in patent protection on R&D investments is difficult to assess for a number of reasons. Most individual countries represent a small share of the total pharmaceutical market, and even a dramatic change in one country may not result in a large shift in expected profits and subsequent R&D investment. In addition, changes the interpretation of patent law, and the economic development occurring concurrently with the implementation of patent systems and changes in other countries may be difficult to control for. Another concern is that patenting activity

may have changed due to shifts in the management of research or innovative capacity (Kortum and Lerner (1998)). As a result, direct tests of the link between patent protection and R&D investment in pharmaceuticals are rare. Sakakibara and Branstetter (2001) found little change in R&D attributable to a change in Japanese patent law in 1988. Qian (2007) studied pharmaceutical patent changes in a cross-section of countries between 1978 and 2002 and concluded that domestic R&D did not increase due to a strengthening of patent protection alone. Rather, the effect of patent protection was moderated by a country's level of economic development. However, Lichtenberg and Waldfogel (2003) found that the 1983 Orphan Drug Act in the United States, which increased the period of patent protection for drugs to treat rare conditions, stimulated the development of drugs for such diseases. We complement these studies by offering additional evidence on the response in global pharmaceutical R&D to the extension of patent protection.

The role of market size

Economic theory predicts that profit-maximizing firms seek to amortize fixed costs over the sale of many units. Given the high fixed R&D costs of developing a new drug, larger potential markets tend to be more attractive. There is ample empirical evidence of the relationship between market size and investments in drug development. Ward and Dranove (1995) associated a 10 percent increase in demand in a therapeutic area with a 5-8 percent increase in R&D spending. Lichtenberg and Waldfogel (2003) linked market size to R&D investment; indeed, this relationship – and the consequential absence of investment in treatments for rare conditions – was the basis for the Orphan Drug Act in the US. Finkelstein (2004) examined the response of pharmaceutical firms to the implementation of US federal policies that required childhood vaccination against six diseases. This paper found that research firms responded to the dramatic increase in expected demand by doubling the number of drugs in clinical trials. Acemoglu and Linn (2004) studied the relationship between market size and drug launches in the US. The results associate an increase of 1% in market

size with a 4% increase in the number of new drugs introduced. Thus, the projected size of the market is an important factor in decisions to invest in pharmaceutical R&D.

The role of income

Typically, the greater the percentage of income required to purchase a good, the more elastic the demand. Consumers of pharmaceuticals in poorer countries are likely to have higher demand elasticity than those in developed countries in part because of their lower incomes and in part because patients in poorer countries may pay for treatments out-of-pocket instead of through insurance. Economic theory associates more elastic demand with lower profit-maximizing markups (Lerner index) for a price-discriminating monopolist. Given that the marginal costs of drug production may not vary extensively by country, the difference in elasticity implies that, all else equal, pharmaceutical firms distributing patent-protected therapies tend to charge lower prices per patient in developing countries than in developed countries. As a result, the share of a pharmaceutical firm's profits from developed countries may be much higher than from developing countries, even before accounting for differences in the number of patients eligible for treatment. This possibility is consistent with the fact that members of the trade association PhRMA derive more than 80% of their revenues from sales in the US, Canada, Europe and Japan.

For diseases that affect patients in countries of all income levels, the higher mark-ups that are optimal in developed countries may enable firms to recoup R&D investments, and allowing firms to sell in the rest of the world as long as developing-country markets support prices that are high enough to cover the marginal costs of production.[6] Absent patent protection, competition from imitators (generics) tends to drive price down to marginal cost and reduce the innovator's share of sales. The extension of patent protection under TRIPS should thus increase expected profits. The higher the income level of the country adopting IP protection, the greater the increase in expected profit and thus the greater the incentive to invest in R&D.[7]

In the case of treatments for diseases that afflict relatively few patients in developed countries, namely the "neglected" diseases (in Section V, we describe precisely how we define these diseases), a firm can justify research only if it expects to recoup its R&D investment through sales in developing countries. The challenges of achieving sufficient expected profits to cover the investment may be exacerbated by the comparatively low level of recent scientific discovery in relevant areas, thus making the required R&D investment relatively large. In many of these countries, the market may not viably support a price sufficient to cover marginal production costs even for a firm with patent protection and monopoly pricing power. As noted in other work (e.g., Kremer 2002, Danzon and Towse 2003), patent protection may therefore not be sufficient to induce R&D investment on neglected diseases. For this reason, Kremer has proposed the use of alternative incentive mechanisms such as advance market commitments (AMCs) to motivate investment.

To summarize, we expect R&D investments in pharmaceuticals to depend on the strength of patent protection, the expected size of the total potential market for a treatment, and the income level in the countries for which the drug is intended. TRIPS had the effect of changing the strength of patent protection in countries with different disease patterns and with different income levels. R&D investment should increase with the degree of patent protection for diseases whose market is global, and more so for relatively wealthy countries. However, patent protection may not affect incentives for R&D investment in diseases with markets in only poor countries where patients cannot afford to pay a significant markup over marginal cost. In the following section, we specify an empirical test for these hypotheses.

An important facet of our analysis is that we do not assess differences in the costs of the R&D required to generate drugs that are effective for addressing diseases that primarily affect the poor versus those that do not. Our approach should be interpreted in light of the possibility that the costs of R&D on neglected diseases may be significantly greater either because the science on these

diseases is not as well developed as for global diseases or even because of prospecting by innovating firms to open up fruitful new areas for development (Kitch 1977, Burk and Lemley 2009). Similarly, we cannot account for different expectations about post-patenting imitation that might arise for neglected vs. non-neglected diseases and or account for differences in research productivity. Firms may choose to patent or not to patent strategically – so as to enhance or avoid coordinating in science and further augment their control over particular therapies (Burk and Lemley 2009), and this consideration is beyond the scope of this paper.

IV. Empirical methods

Our empirical strategy is to examine R&D efforts at the disease level, exploiting changes in both patent protection and disease patterns that varied over time and across countries. We are particularly interested in the effect of patent protection on R&D efforts for neglected diseases and its interaction with the income level of countries that strengthen their patent laws. We start with a basic model relating R&D effort and market size, and subsequently add interactions with disease type, patent protection and income levels. Descriptions of our measures of each are in the next section.

The unit of analysis throughout is a disease-year. We begin by estimating the relationship between yearly R&D investment in a disease area and the total potential market size of the disease. That is,

$$Y_{dt} = \alpha_0 + \alpha_1 M_{dt} + AX_{dt} + \varepsilon_{dt} \qquad (1)$$

where Y_{dt} is a measure of R&D effort in disease *d* in year *t*, M_{dt} is a measure of potential market size disease *d* in year *t*, and X is a vector of controls comprised of the availability of substitute products and year fixed effects. Substitute products are represented by the number of available treatments for the disease in 1990, several years prior to TRIPS. We include this control because R&D investments made subsequent to the adoption of TRIPS would be moderated by the opportunities left open by

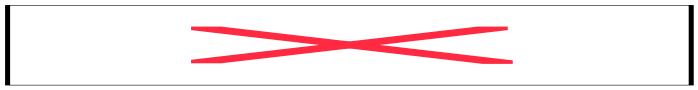
established treatments. Year fixed effects are included to reflect changes over time arising from macroeconomic factors, changes in global trade conditions, and other influences that affected all firms. We expect a positive coefficient on M_{dt}, i.e. that $\alpha_1 > 0$.

Next, we decompose potential market size by disease type to explore whether R&D effort responded differently to global diseases than to neglected diseases, which we define precisely below. We estimate the following equation:

$$Y_{dt} = \beta_0 + \beta_1 M_{dt} * \text{Global} + \beta_2 M_{dt} * \text{Neglected} + BX_{dt} + \varepsilon_{dt} \qquad (2)$$

where Global = 1 if disease *d* is a global disease, Neglected = 1 if disease *d* is a neglected disease and other variables are defined as above. While global diseases clearly have a higher level of R&D effort, β_1 and β_2 reflect the change in R&D associated with a change in potential market size. Subsequent specifications investigate the source of the difference between β_1 and β_2, if any.

One such source may be that neglected diseases primarily affect countries that historically lacked patent protection. If this is the main driver of the difference in R&D effort, then increasing patent protection in countries with high prevalence of neglected diseases should lead to a greater level of R&D effort relative to countries without high prevalence of neglected diseases. The TRIPS policy "experiment" allows us to examine this by estimating:



(3)

M_{dt}*Global*IP_t is the total potential market size of disease d in year t across all countries with IP, where disease d is a global disease; M_{dt}*Global*$NoIP_t$ is the total potential market size of a global disease *d* in year *t* across all countries without IP; and so on. The difference between γ_3 and γ_4 reflects how effective TRIPS has been at inducing R&D for neglected diseases.

Patent protection may not induce R&D on either global or neglected diseases in less wealthy countries if the ability of patients to pay is extremely low. Our final specification evaluates the

impact of patent protection across both disease types and the level of income of countries affected by a particular disease:

$$
\begin{aligned}
Y_{dt} = {} & \eta_0 + \eta_1 M_{dt} * Global * IP_t * High + \eta_2 M_{dt} * Global * NoIP_t * High \\
& + \eta_3 M_{dt} * Global * IP_t * UpperMiddle + \eta_4 M_{dt} * Global * NoIP_t * UpperMiddle \\
& + \eta_5 M_{dt} * Global * IP_t * LowerMiddle + \eta_6 M_{dt} * Global * NoIP_t * LowerMiddle \\
& + \eta_7 M_{dt} * Global * IP_t * Low + \eta_8 M_{dt} * Global * NoIP_t * Low \\
& + \eta_9 M_{dt} * Neglected * IP_t * High + \eta_{10} M_{dt} * Neglected * NoIP_t * High \\
& + \eta_{11} M_{dt} * Neglected * IP_t * UpperMiddle + \eta_{12} M_{dt} * Neglected * NoIP_t * UpperMiddle \\
& + \eta_{13} M_{dt} * Neglected * IP_t * LowerMiddle + \eta_{14} M_{dt} * Neglected * NoIP_t * LowerMiddle \\
& + \eta_{15} M_{dt} * Neglected * IP_t * Low + \eta_{16} M_{dt} * Neglected * NoIP_t * Low \\
& + \mathbf{N} X_{dt} + \varepsilon_{dt}
\end{aligned}
\tag{4}
$$

M_{dt}*Global*IP_t*High is the total potential market size of global disease *d* in year *t* across high-income countries with IP. M_{dt}*Global*$NoIP_t$*High is the total potential market size of global disease *d* in year *t* across high-income countries without IP. Similarly, M_{dt}*Neglected*IP_t*UpperMiddle is the total potential market size of neglected disease *d* in year *t* across upper middle-income countries with IP, etc. We expect that patent protection has a smaller effect on profits in poorer countries than in rich countries and therefore a smaller effect on R&D incentives, so that $\eta_1 > \eta_3 > \eta_5 > \eta_7$ and $\eta_9 > \eta_{11} > \eta_{13} > \eta_{15}$. A market for a global disease may exist in relatively rich countries, and thus there may be a positive effect of patent protection in poorer countries on profits and R&D effort on global diseases, implying that $\eta_5 > \eta_6$ and $\eta_7 > \eta_9$. For neglected diseases, however, we expect $\eta_{13} = \eta_{14} = 0$ and $\eta_{15} = \eta_{16} = 0$: patent protection in countries where patients have very low ability to pay does not induce R&D effort because expected revenues do not cover the fixed costs of development.

A concern is that patent protection is an endogenous policy choice. Historically, countries have adopted IP protection in response to demands from domestic innovators, or after achieving a rather high level of development (Qian 2007). We argue that in the case of TRIPS, developing and least-developed countries were clearly resistant to adopting or strengthening IP protection and did

so only because they expected large benefits of membership in the WTO. Another recent paper examining the TRIPS agreement concluded "the Agreement's implementation is an external factor, not entirely influenced by the country's level of economic development…[Changes in IP due to TRIPS] can be used as a natural experiment to understand how IPR influences economic activities and behaviors" (Hamdan-Livramento 2009). However, if resistant countries also adopted policies aimed at undermining patent protection or pricing power (such as widespread use of compulsory licensing or stringent price controls) or failed to enforce patent laws, our results may understate the effect of IP protection on R&D efforts. We interpret our results in light of this possibility.

V. Data and measures

The analysis depends on information about R&D efforts over time and by disease, measures of potential market size (assessed as disease prevalence) over time and across countries, and country-level factors such as IP law and income level. Sources and the construction of variables are described below. Table 1 provides summary statistics. Our final dataset spans 17 years (1990-2006).

R&D effort

Our measure of R&D effort is the number of new clinical trials initiated by the industry in a year for a specific disease. These trials reflect the majority of R&D expenditures in the industry. Ideally, our measure of R&D effort would be research expenditures by disease and by year. Unfortunately, publicly traded firms generally do not report R&D spending by disease and, furthermore, many pharmaceutical firms are not publicly traded and do not disclose any financial information about their spending on R&D. Despite the limitations, we believe that the information we employ about the number of clinical trials is among the most comprehensive available on early-stage R&D projects by disease and by year. Our source is the R&D Focus database produced by IMS Health. Typically used by pharmaceutical firms to monitor the research activities of

competitors, R&D Focus provides a history of all projects known to be in development from the mid-1980s through the present. This includes projects that failed in clinical trials, those that were successfully launched, and those that continue in development. Each record is a pharmaceutical project and may be associated with multiple indications and multiple firms. The history of the project's progression through each stage of development is compiled by IMS from patent and regulatory filings, presentations at medical conferences, press releases, and information disclosed to financial analysts.

To capture early R&D efforts, we focus on the first stage of human clinical testing, i.e. Phase I trials.[8] Because our dependent variable Y_{dt} is a count of new Phase I trials in disease *d* in year *t*, we estimate regressions as negative binomials. We trim the dependent variable to 75 (less than 1% of our observations have a value above this). The information in the IMS database also allows us to construct a count of existing treatments for each disease in 1990, which we use as a control for competition.

Disease prevalence and type

We proxy for "potential market size," or disease-level demand, by a measure of disease burden by country and year. The WHO publishes the number of deaths attributed to a disease as recorded by national civil registration systems on an annual basis. A better measure would account for how a disease affects quality of life. One such measure is the disability-adjusted life year (DALY), which has been controversial because it incorporates subjective judgments about disease severity. In addition, estimates of DALYs by the WHO are limited to only a single cross-section, and thus reliance on the available estimates would ignore changes over time in disease prevalence or severity. We therefore do not use DALYs.[9] In our regressions, we define potential market size as the log of the sum of all deaths from disease *d* across all countries (or subset of countries, depending on the specification) in year *t*.

We faced two main challenges in using the WHO Mortality Data. First, the coverage of the dataset is not comprehensive. For example, all data is missing for particular countries in some years; coverage of China is not complete; and there is very little information on some least-developed countries such as Afghanistan, Malawi and Madagascar. Given the limitations on data collection efforts, we are likely to underestimate deaths in the poorest countries. We used multiple imputation techniques to deal with the missing values and correct standard errors. Rather than estimating a missing value through simulation (i.e. single imputation), multiple imputation involves substituting a set of values that reflect the uncertainty about the predictions of the missing values. The datasets with the imputed values are analyzed and their results are combined to adjust estimates of variance accordingly. An important assumption, which cannot be verified, is that the data is missing at random. We create five imputed datasets using the EM algorithm with the MI procedure in SAS.[10] Summary statistics for pre- and post-imputation deaths are included in Table 1. Our results are not sensitive to the number of imputations or to the algorithm used.

Another challenge involved matching disease definitions from the WHO with those in the R&D Focus database. The WHO uses the International Classification of Diseases (ICD) codes, while R&D Focus provides indications and therapeutic classifications for each drug development project. For each indication in the R&D Focus database, we identified a likely ICD code using medical dictionaries. The most detailed ICD codes in the WHO Mortality Data were not available for a sufficient number of countries or years and were often too specific to match to R&D Focus indications. We use instead a condensed list of 84 categories of diseases or conditions that covers everything in the WHO mortality data except "external causes" that are not typically addressed with pharmaceutical therapies, such as car accidents, falls, and intentional self-harm. These diseases are listed in Appendix A.[11]

Although there is no official definition, there is widespread agreement about the set of neglected diseases in the health policy and development literatures. We categorized a disease as "neglected" using Table 1 of Moran et al. (2009). Moran et al. (2009) used a three-step filter to identify neglected diseases: first, the disease must disproportionately affect developing countries; second, new treatments are needed; and finally, no commercial market is thought to exist. The list of neglected diseases generated by this categorization includes all the neglected tropical diseases identified by the WHO as well as those considered by Lanjouw and Cockburn (2001). It also includes all the diseases that qualify for a "Priority Review Voucher" in the US.[12] More than 90% of deaths from these diseases occur in countries that are developing and least developed. We define all non-neglected diseases as "global." Global diseases affect countries of all income levels, and include cardiovascular conditions, neurological disorders, and cancer.

Questions arise about whether HIV is a global or neglected disease. Moran et al. (2009) and the WHO consider HIV a neglected disease, although HIV affects large numbers of people in developed countries as well. While many treatments for HIV now exist, not all are well-suited for use in developing countries or, in particular, for children (who constitute a much larger fraction of HIV patients outside developed countries than in developed countries). HIV qualifies as a "neglected" disease if there are insufficient incentives to develop appropriate treatments for developing countries, which now report a greater need for 3rd and 4th line therapies. In our main analysis, we consider HIV as a neglected disease, but in robustness checks, we run analyses that first classify HIV as a global disease and then drop HIV from the data. Overall, our results are robust to these changes.

IP measures and other country information

The WTO established a timetable for compliance with TRIPS. We use these rules, described in Section II, to estimate the dates of compliance for every country. Original WTO members that

self-identified as "developed" are considered compliant in 1995. For developed countries that joined the WTO after 1995, we code compliance as of the membership date. WTO member countries identified as "least-developed" were required to comply by January 1, 2005, with the deadline extended until January 1, 2006 and even further during the Doha round to 2016. Thus, for least-developed countries, we assume that compliance will occur only in 2016. For self-identified developing countries that were WTO members at the time of TRIPS adoption in 1995, we code the year of compliance as 2000. For countries that joined after 1995 (except for those that were least developed), we code compliance as the date of membership unless we found different information about the compliance date on the WTO website.[13]

Measuring TRIPS compliance using the WTO rules has several drawbacks. First among them is that, while a country may claim to comply with TRIPS, its enforcement of patent and other IP protections may be in doubt. We check for robustness using two alternative measures of patent protection and enforcement. Walter Park kindly shared his updated index of IP protection and enforcement compliance, which he has used in a number of published analyses (see, e.g., Ginarte and Park 1997). This measure is more nuanced than our TRIPS dummy variable, but it is not available for 40 countries in our dataset and is available only at five-year intervals. The Ginarte-Park index has separate elements for chemical patents and for enforcement; we use both the existence of chemical patents and strong enforcement to create a dummy variable indicating whether a country has chemical/pharmaceutical patent protection and enforces patent laws.[14] For developed countries that joined the WTO in 1995 and for which the Ginarte-Park index indicated the presence and enforcement of pharmaceutical patents in 1990, we adjusted our TRIPS dummy variable to indicate compliance as of 1990. This avoids characterizing the membership of the United States in the WTO as requiring a major shift in IP law. Recent work by Hamdan-Livramento (2009) investigates in much greater detail the state of patent law and enforcement in 53 developing countries, and the

author generously shared his index of TRIPS compliance with us. This analysis was especially relevant because the investigated developing countries encompassed the majority for which IP laws changed after TRIPS. We use the components of the index related to pharmaceutical patents and enforcement, where available. For countries not covered by the Hamdan-Livramento index, we use our initial measure of TRIPS compliance.

There are a number of differences across these three measures of IP laws and enforcement. Appendix B contains the list of countries used in our analysis, the year of compliance required by the WTO, the first year of both pharmaceutical patents and enforcement according to the Ginarte-Park index and the first year of both pharmaceutical patents and enforcement according to the Hamdan-Livramento index.[15] A limitation on all the measures of IP compliance is that they do not capture expectations that firms may have about the state of future patent protection in a country. Since drug development is a lengthy process, firms may make investment decisions based on whether they believe a country will afford intellectual property protection some years in the future, providing a measure of time for the R&D to yield a commercialized product. In other words, an influential factor in decisions about R&D may be a country's intention to adopt patent protection as a condition of WTO membership rather than the precise timing of compliance. Even in these situations, the compliance date is likely to be critical both because of the resolution of uncertainty about intentions to implement IP mechanisms and because, after the date of compliance, firms have remedy for IP violations via the WTO dispute resolution process. We report results using the compliance dates under each method of estimation and note the differences in our results that are obtained under each approach.

Another important factor influencing R&D decisions for which we cannot account relates to the forecasted possibility of compulsory licensing. Firms may be reluctant to invest in R&D for diseases that are likely to be the subject of compulsory licensing. While few such licenses were issued

during our sample period (which ends in 2006), our failure to account for these expectations would lead us to underestimate the impact of "true" patent protection. However, even if these expectations had shaped R&D decisions, our models would accurately reflect the overall effect of TRIPS given its various exemptions.

We use the World Bank's World Development Indicators dataset for information on country income levels. The World Bank categorizes countries as high income, upper middle income, lower middle income and low income. We report the 1995 income level for each country listed in Appendix B. Because the unit of analysis is the disease-year rather than the country, we are limited in our ability to control for many additional geographic factors that might influence pricing and volumes. Among the omitted variables that concern us are the urban or rural location of potential patients within each country and the presence or absence of complementary institutions such as hospitals, clinics and pharmacies. Unfortunately, this information is incomplete for large numbers of countries, and especially for developing and least-developed countries. Because we are interested in these countries, we use a very parsimonious set of controls for which we have reasonably complete data. Note that not all low-income countries are least-developed countries as defined by the United Nations, and therefore some introduced patent protection during our sample period (see Appendix B).

VI. Results

Our baseline results from estimating equations 1-4 are presented in Table 2, with robustness checks in Tables 3-5 and a summary of the robustness checks in Table 6. The dependent variable in all specifications is the number of drug development projects for disease *d* entering Phase I clinical trials in year *t*. The regressions are estimated as negative binomials (Poisson models were rejected due to overdispersion). All specifications include year fixed effects and a control for the number of

treatments available for disease *d* in 1990. Standard errors, which are in parentheses below the coefficients, are clustered by disease and corrected to reflect the use of multiple imputation to deal with missing values for disease data.

For our baseline specifications, we define IP_t using WTO rules for TRIPS compliance and categorize HIV as a neglected disease. Column 1 corresponds to equation 1, column 2 to equation 2, and so on. Since the market size measures are in logs, their coefficients may be interpreted as elasticities. The final column of Table 2 provides the marginal effect evaluated at the sample means. As expected, R&D effort is positively associated with overall potential market size ($\alpha_1 = 0.035$ with a standard error of 0.003). If we separate diseases into global and neglected, the coefficients on both measures of potential market size are also positive and statistically significant (0.034 and 0.029, respectively). R&D effort in the aggregate and for both global and neglected diseases is positively related to increases in the number of potential patients. However, the coefficients on global and neglected disease market sizes are statistically different from each other.

Our main focus is the source of the difference between the R&D response to global and neglected diseases. One possibility, which we cannot test directly, is that drug development is more expensive for neglected diseases than for global diseases, which might mean that the potential market size for a neglected disease would have to be greater than for a global disease to induce an equivalent amount of R&D effort. This effect could be compounded if early scientific efforts on a disease open up the prospect of a stream of patentable innovations over time after the first drugs are commercialized (Kitch 1977). Another possible explanation is that neglected diseases primarily affect countries that have had weak patent systems historically, which may lead investing organizations to hesitate in committing R&D out of concern than patents will not be enforced. Firms also may anticipate that drugs introduced into developing countries may be quickly imitated or licensed, thereby blunting their abilities to obtain profit from them. We address these possibilities in the

specification presented in column 3, which decomposes market size not only by disease type but also by prevalence in countries with or without TRIPS-compliant patent systems. The difference between γ_1 and γ_2 reflects the relationship between the adoption of IP and R&D efforts for global diseases, and the difference between γ_3 and γ_4 does likewise for neglected diseases. For both types of diseases, there is a strong positive association between TRIPS compliance and R&D effort, with R&D more responsive to IP-protected market size for global diseases than for neglected diseases. Thus, we find that IP protection is associated with increased R&D effort for both types of diseases, but there remains a statistically significant difference between the response to IP-protected market size for global diseases and IP-protected neglected diseases.

In Section III, we noted that patent protection might not lead to greater expected profits in countries where most patients are unable to pay even the marginal cost of producing a treatment. Our final specification, which estimates equation 4, separates potential market size by disease type, existence of patent protection and the income level of those afflicted. By separating countries by income level, the analysis allows for differences in the relationships between TRIPS compliance and R&D effort based on projections of ability to pay. As expected, we find the greatest increment to R&D effort associated with increases in potential market size in high-income countries with patent protection. This relationship holds for both global and neglected diseases: the coefficients η_1 and η_9 are 0.353 and 0.342, respectively. Both are statistically significant different from zero, but not from each other, which suggests that R&D costs for the two types of diseases are roughly the same.[16] In high income countries – where ability to pay is less likely to be blunted by poverty and the absence of complementary services such as clinics, personnel, etc., – the adoption of patent protection seems to induce research on diseases that are prevalent in the population. The relationship does *not* hold for less wealthy countries, regardless of patent protection. In other words, R&D effort is not associated with the implementation of TRIPS in lower-income countries. None of the coefficients

on potential market size outside of the high-income category are positive or significantly greater than zero. These results suggest that while patent protection is effective at inducing R&D for diseases prevalent in high income countries, it is not sufficient for diseases that have no market outside the developing world. The difference between R&D effort directed at global diseases and neglected diseases is driven mainly by the difference in income of those affected, rather than a difference in patent protection.

We re-ran our analysis to check the robustness of our results across different definitions and measures. A summary of the tests of coefficients in equation 4 across these many specifications is presented in Table 6. Tables 3, 4, and 5 report the details of the regressions. In Table 3, we report on regressions that allow for a lag in the response of R&D to the extension of patent protection. We conduct this test because our baseline model assumes that firms can respond immediately to the introduction of patent protection by initiating Phase I trials. If preclinical research is required, the Phase I response may be delayed by several years. Table 3 contains the results of specifications identical to those in Table 2, except that market size is lagged by three years to allow for preclinical testing.[17] The results are similar to those in the main model. Although we observe a statistically significant coefficient on IP-protected market size for global diseases in middle-income countries, the coefficients for neglected disease market size remain insignificant.

Table 4 estimates equation 4 using alternative definitions of IP. Column 1 is our baseline specification, using WTO rules for TRIPS compliance. Column 2 uses the Ginarte-Park definition, and Column 3 uses the Hamdan-Livramento definition. While some of the parameter estimates differ across specifications (which is expected, since we noted variation across these measures in Section V), the overall pattern remains. No coefficient on market size is significantly greater than zero outside of the high-income category, though the difference between IP and no IP is positive for the lower middle-income group.

We examine the sensitivity of results to the classification of HIV in Table 5. The first column again contains our baseline results in which HIV is classified as a neglected disease. Column 2 classifies HIV as global, and Column 3 excludes HIV from the analysis. Once again, we find the same pattern of coefficients across income types with one important difference. While the coefficients η_1 and η_2 (market size for the high income category for global and neglected diseases) are quite similar when HIV is defined as neglected, there is a wide gap between them in columns 2 and 3. This result arises from the fact that HIV is the most prevalent "neglected disease" in rich countries, which means that and significant R&D, both public and private, has been invested to address it. Unfortunately, available measures of R&D effort are not sufficiently nuanced to capture differences across projects in dosage formulations or combinations best suited to developing or least-developed countries (such as pediatric and heat-stable presentations), and thus we cannot test formally for differences in R&D investments for HIV targeted at higher and lower income countries.

To put our results into some perspective, we note that Acemoglu and Linn (2004) estimated that a 1% increase in potential market size in the US led to a 4% increase in the number of new drugs introduced. They remark in their paper that this estimate is quite large. However, our estimates are in line with more recent work by Dubois et al. (2011), although we are looking at new clinical trials (or drug candidates) rather than drug approvals, and our sample includes a much larger set of countries. Unlike these previous papers, we explicitly compare the elasticity of market size across countries and the presence of patent protection. Our findings indicate that for a neglected disease and with patent protection, R&D is roughly four times as responsive to an increase in log market size in a high-income country than to an upper middle-income country. The summary of tests of coefficient differences in Table 6 suggests that while there are statistically significant differences between IP and no-IP coefficients in high-income countries, this pattern does not appear for other

income levels. In addition, the difference between global and neglected diseases is not generally statistically significant. Indeed, for lower income levels without IP, R&D is sometimes estimated to be more responsive to neglected disease needs than to global, which could reflect the efforts of non-governmental organizations (NGOs) and others that are not profit-driven.

Although we have reported many robustness checks in this paper, it is important to qualify our findings in several ways. One concern is the potential endogeneity of IP protection and enforcement. It may be that countries only adopt and enforce patent laws when they have achieved a minimum level of income and development. Economic development may occur simultaneously with the implementation of patent protections (as was an objective of the WTO). In practice, developing and least-developed countries have often attempted to delay and weaken the requirements of TRIPS, and ultimately implemented the policy to achieve other benefits from WTO membership. We find only weak evidence that IP rights have an impact in developing and least-developed countries, but this may reflect an unwillingness to enforce these rights and understate the real effect of strong, enforceable patents.

More generally, expectations about future policies related to profitability and IP rights, which are not observed, are important to incentives. Price controls are an example of a policy (widespread in developed countries) that could dampen profits even in the presence of patents. The use of compulsory licensing is another, and this is not restricted to developing and least-developed countries. For example, the Canadian government once extensively issued compulsory licenses (although prior to TRIPS). Even in the US, in 2001 the government considered compulsory licenses for Cipro, a treatment for anthrax, and in 2005 on Tamiflu, a treatment for avian influenza.[18] If governments are expected to issue compulsory licenses for some drugs, R&D investment choices may reflect these expectations. As noted previously, few compulsory licenses were issued during our sample period. However, the option of compulsory licenses is an important aspect of how TRIPS

compliance affects R&D incentives, and the use of price regulation is not addressed by TRIPS at all. Thus, while we may underestimate the impact of "true" patent protection, our results should still accurately reflect the impact of TRIPS in particular.

Another concern is that our data source may not reflect all research activities. For example, IMS may focus on the activities of firms more intensively than on the activities of universities, foundations, and NGOs in assembling its R&D Focus data. If this bias in coverage exists, we would underestimate the number of projects underway. If universities and other nonprofits are more likely to focus on neglected diseases and are sensitive to the IP environment, then we might be biased towards finding less effort on such diseases. However, this is unlikely to be a major problem for several reasons. First, we compared the IMS R&D Focus coverage to two competing databases from PJB Publications and Thomson Scientific. The coverage of IMS included firms located in a larger set of countries than the other two. Second, about 17% of the organizations covered by IMS R&D Focus are universities, foundations, or other non-profit organizations. Third, the controversy over TRIPS and increased attention to the burden of disease in the developing world – through the Gates Foundation or the Clinton Health Initiative, for example – may have made all types of organizations more likely to "advertise" and disclose their R&D activities directed at neglected diseases, which may cause an upward bias in our estimate of the impact of patent protection. It should be noted that increased funding from these NGOs and others may also have stimulated additional R&D for neglected diseases, but this should be unrelated to the presence of patent protection (many NGOs oppose patent protection, in fact).

The WHO Mortality Data is a compilation of information provided by each member country, which may vary in quality. In particular, the prevalence of HIV appears to be understated in many developing and least-developed countries.[19] Omitting HIV from our sample does not change the qualitative results, however. In addition, an earlier version of this paper yielded similar findings

based on the WHO's Global Burden of Disease dataset. Ultimately, we used the WHO Mortality Data because it includes time-series variation as well as more specific disease categories.

VII. Conclusion

This paper examines how R&D investment in pharmaceuticals has changed with the adoption of the TRIPS Agreement. Particularly in the case of patents for pharmaceutical treatments, TRIPS involves a trade-off between dynamic efficiency, i.e. incentives for R&D investment, and static inefficiency, i.e. access to drugs. An important issue for developing and least-developed countries is whether the introduction of patent protection for drugs has led to dynamic benefits in the form of an increase in R&D effort to treat diseases that are especially prevalent there.

We conclude that patent protection in developing and least-developed countries does not appear to have induced investment in new treatments for diseases that primarily affect poorer countries. R&D on neglected diseases is not associated with increases in the potential market size in low-income countries, whether or not those markets provided patent protection. This is not to claim that patents are irrelevant: patent protection is associated with greater R&D investment in diseases that affect high income countries, and the treatments developed as a result may benefit people in poorer countries too. The existence of a market in rich countries allows firms to recover their R&D investments. Consequently, global diseases – those present in countries of all income levels – attract research effort. However, patent protection is not sufficient to induce R&D for diseases that have no significant potential market in high-income countries. If those affected, or their governments, lack the ability to pay prices much higher than the marginal cost of producing treatments, firms are unable to recoup the fixed costs of R&D regardless of the level of patent protection. This effect may arise both because revenues are projected to be low and because the costs of innovation are high, and our findings suggest the former is more likely.

Our study focuses on only one possible effect of the introduction of IP rights. Importantly, we do not tackle the issue of whether access to treatments in developing countries decreased, or how investments in health-delivery systems in developing countries may have changed in response to TRIPS implementation. Other possible effects include an increase in technology transfer to developing countries and greater incentives for domestic R&D activity. WTO membership, possible only with the adoption of TRIPS, may have provided other benefits to developing countries that we do not consider here.

The results of this research suggest that alternative mechanisms for inducing R&D effort on neglected diseases may be more effective than the extension of patent protection alone. Recently, such mechanisms have received increased attention from policy makers and other organizations. For example, the first advance market commitment for a pneumococcal vaccine was established in 2007 by GAVI. The US introduced a system of priority review vouchers targeted at neglected diseases in 2007. In 2008, UNITAID proposed the use of a patent pool for pediatric HIV treatments. We hope that such efforts will soon yield new treatments for diseases that principally affect patients in less wealthy countries.

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Table 1: Summary statistics

Number of countries	192				
Number of diseases	84				
Number of years	17				
	N	**Mean**	**Std Dev**	**Min**	**Max**
Phase I starts (all)	1428	8.086	17.704	0	229
Phase I starts (trimmed)	1428	7.386	12.479	0	75
Total deaths in disease/country/year (before imputation)	106952	2277.120	14036.820	0	824861
Total deaths in disease/country/year (after imputation)	648261	2352.310	16832.280	0	940496
Treatments in 1990	1428	9.89	16.99	0	83
Ln(Total Deaths)	1428	10.296	2.486	3.022	14.910
Ln(Deaths)*global disease	1428	9.141	3.810	2.079	14.910
Ln(Deaths)*neglected disease	1428	3.224	2.821	2.079	13.162
Ln(Deaths)*IP*global disease	1428	8.539	4.043	1.386	14.910
Ln(Deaths)*IP*neglected disease	1428	2.444	2.746	1.386	13.030
Ln(Deaths)*no IP*global disease	1428	6.389	3.941	1.386	14.358
Ln(Deaths)*no IP*neglected disease	1428	2.246	2.430	1.386	12.647
Ln(Deaths)*high income*IP*global	1428	7.716	4.464	0.000	13.980
Ln(Deaths)*high income*IP*neglected	1428	1.072	2.835	0.000	12.354
Ln(Deaths)*high income*no IP*global	1428	3.135	3.759	0.000	11.297
Ln(Deaths)*high income*no IP*neglected	1428	0.427	1.606	0.000	9.741

Ln(Deaths)*upper middle income*IP*global	1428	5.417	4.021	0.000	12.476
Ln(Deaths)*upper middle income*IP*neglected	1428	0.735	2.207	0.000	11.242
Ln(Deaths)*upper middle income*no IP*global	1428	4.074	4.485	0.000	12.284
Ln(Deaths)*upper middle income*no IP*neglected	1428	0.701	2.338	0.000	11.241
Ln(Deaths)*lower middle income*IP*global	1428	5.190	4.781	0.000	14.183
Ln(Deaths)*lower middle income*IP*neglected	1428	0.808	2.535	0.000	12.029
Ln(Deaths)*lower middle income*no IP*global	1428	5.061	4.396	0.000	14.055
Ln(Deaths)*lower middle income*no IP*neglected	1428	0.850	2.542	0.000	12.039
Ln(Deaths)*low income*IP*global	1428	3.669	3.754	0.000	12.523
Ln(Deaths)*low income*IP*neglected	1428	0.580	1.941	0.000	10.418
Ln(Deaths)*low income*no IP*global	1428	4.652	3.561	0.000	12.473
Ln(Deaths)*low income*no IP*neglected	1428	0.767	2.240	0.000	10.886

The unit of observation is a disease-year for all variables except total deaths in disease/country/year. Summary statistics are calculated for HIV defined as a neglected disease and IP protection as TRIPS compliant. Multiple imputation methods were used to complete missing observations on deaths, as described in the text.

Table 2: Negative binomial regressions of Y = number of new Phase I trials in disease-year

Variable	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Marginal Effect
Ln(Total Deaths)	0.035**				0.1330
	(0.003)				
Ln(Deaths)*global disease		0.034**			0.1296
		(0.003)			
Ln(Deaths)*neglected disease		0.029**			0.1094
		(0.004)			
Ln(Deaths)*IP*global disease			0.068**		0.2517
			(0.006)		
Ln(Deaths)*IP*neglected disease			0.057**		0.2124
			(0.008)		
Ln(Deaths)*no IP*global disease			-0.007		-0.0278
			(0.007)		
Ln(Deaths)*no IP*neglected disease			-0.005		-0.0198
			(0.009)		
Ln(Deaths)*high income*IP*global				0.357**	1.0791
				(0.030)	
Ln(Deaths)*high income*IP*neglected				0.294**	0.8902
				(0.049)	
Ln(Deaths)*high income*no IP*global				0.086*	0.2623
				(0.048)	

Ln(Deaths)*high income*no	-0.168**	-0.5073
IP*neglected	(0.076)	
Ln(Deaths)*upper middle	-0.050**	-0.1535
income*IP*global	(0.020)	
Ln(Deaths)*upper middle	0.074	0.2240
income*IP*neglected	(0.171)	
Ln(Deaths)*upper middle income*no	-0.111**	-0.3376
IP*global	(0.049)	
Ln(Deaths)*upper middle income*no	0.007	0.0229
IP*neglected	(0.089)	
Ln(Deaths)*lower middle	0.026	0.0802
income*IP*global	(0.045)	
Ln(Deaths)*lower middle	-0.000	-0.0004
income*IP*neglected	(0.218)	
Ln(Deaths)*lower middle income*no	-0.046	-0.1404
IP*global	(0.043)	
Ln(Deaths)*lower middle income*no	0.190*	0.5753
IP*neglected	(0.101)	
Ln(Deaths)*low income*IP*global	-0.048	-0.1462
	(0.034)	
Ln(Deaths)*low income*IP*neglected	-0.083	-0.2522
	(0.129)	
Ln(Deaths)*low income*no IP*global	-0.031	-0.0955
	(0.025)	

Ln(Deaths)*low income*no IP*neglected				-0.230**	-0.6952
				(0.056)	
Treatments in 1990	0.056**	0.056**	0.058**	0.051**	
	(0.002)	(0.002)	(0.002)	(0.002)	
Intercept			-		
	-1.57**	-1.50**	0.601**	-2.20**	
	(0.217)	(0.220)	(0.259)	(0.316)	
Number of Observations Used	1428	1428	1428	1428	
Log likelihood	19218.1	19220.1	19241.5	19387.4	

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 3: Robustness to lagged measures of market size

Variable	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Marginal Effect
Ln(Total Deaths)	0.057**				0.1321
	(0.002)				
Ln(Deaths)*global disease		0.034**			0.1284
		(0.002)			
Ln(Deaths)*neglected disease		0.028**			0.1069
		(0.004)			
Ln(Deaths)*IP*global disease			0.065**		0.2421
			(0.006)		
Ln(Deaths)*IP*neglected disease			0.055**		0.2055
			(0.009)		
Ln(Deaths)*no IP*global disease			0.003		0.0143
			(0.006)		
Ln(Deaths)*no IP*neglected disease			0.002		0.0109
			(0.009)		
Ln(Deaths)*high income*IP*global				0.353**	1.0422
				(0.033)	
Ln(Deaths)*high income*IP*neglected				0.342**	1.0098
				(0.060)	
Ln(Deaths)*high income*no IP*global				0.145**	0.4289
				(0.043)	

Ln(Deaths)*high income*no	-0.142*	-.4208
IP*neglected	(0.073)	
Ln(Deaths)*upper middle	-0.019	-.0578
income*IP*global	(0.016)	
Ln(Deaths)*upper middle	-0.042	-.1254
income*IP*neglected	(0.176)	
Ln(Deaths)*upper middle income*no	-0.162**	-.4797
IP*global	(0.045)	
Ln(Deaths)*upper middle income*no	-0.207**	-.6117
IP*neglected	(0.087)	
Ln(Deaths)*lower middle	0.024	0.0706
income*IP*global	(0.045)	
Ln(Deaths)*lower middle	0.088	0.2619
income*IP*neglected	(0.206)	
Ln(Deaths)*lower middle income*no	-0.078	-.2313
IP*global	(0.047)	
Ln(Deaths)*lower middle income*no	0.411**	1.2126
IP*neglected	(0.105)	
Ln(Deaths)*low income*IP*global	-0.037	-.1097
	(0.042)	
Ln(Deaths)*low income*IP*neglected	-0.113	-.3342
	(0.119)	
Ln(Deaths)*low income*no IP*global	-0.028	-.0845
	(0.023)	

Ln(Deaths)*low income*no IP*neglected				-0.349**	-1.030
				(0.058)	
Treatments in 1990	0.035**	0.057**	0.059**	0.049**	
	(0.002)	(0.002)	(0.002)	(0.002)	
Intercept	-1.58**	-1.52**	-0.936**	-2.01**	
	(0.213)	(0.216)	(0.246)	(0.291)	
Number of Observations Used	1428	1428	1428	1428	
Log likelihood	19222.9	19225.3	19237.8	19400.6	

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 4: Robustness to IP definition

Variable	TRIPS	Hamdan	Ginarte-Park
Ln(Deaths)*high income*IP*global	0.357**	0.481**	0.418**
	(0.030)	(0.051)	(0.033)
Ln(Deaths)*high income*IP*neglected	0.294**	0.224	0.223**
	(0.049)	(0.183)	(0.051)
Ln(Deaths)*high income*no IP*global	0.086*	0.145**	0.027
	(0.048)	(0.061)	(0.031)
Ln(Deaths)*high income*no IP*neglected	-0.168**	-0.101	-0.047
	(0.076)	(0.185)	(0.060)
Ln(Deaths)*upper middle income*IP*global	-0.050**	-0.051**	-0.058**
	(0.020)	(0.019)	(0.021)
Ln(Deaths)*upper middle income*IP*neglected	0.074	-0.016	0.049
	(0.171)	(0.084)	(0.139)
Ln(Deaths)*upper middle income*no IP*global	-0.111**	0.039	-0.038
	(0.049)	(0.052)	(0.040)
Ln(Deaths)*upper middle income*no	0.007	-0.086	-0.023
IP*neglected	(0.089)	(0.088)	(0.055)
Ln(Deaths)*lower middle income*IP*global	0.026	-0.009	0.015
	(0.045)	(0.033)	(0.058)
Ln(Deaths)*lower middle income*IP*neglected	-0.000	0.009	0.103
	(0.218)	(0.089)	(0.175)

Ln(Deaths)*lower middle income*no IP*global	-0.046	-0.468**	-0.140**
	(0.043)	(0.056)	(0.039)
Ln(Deaths)*lower middle income*no	0.190*	0.291*	0.160*
IP*neglected	(0.101)	(0.143)	(0.079)
Ln(Deaths)*low income*IP*global	-0.048	0.009	0.002
	(0.034)	(0.022)	(0.036)
Ln(Deaths)*low income*IP*neglected	-0.083	-0.063	-0.215**
	(0.129)	(0.051)	(0.075)
Ln(Deaths)*low income*no IP*global	-0.031	0.026	-0.029
	(0.025)	(0.028)	(0.024)
Ln(Deaths)*low income*no IP*neglected	-0.230**	-0.270**	-0.165*
	(0.056)	(0.072)	(0.077)
Treatments in 1990	0.051**	0.050**	0.052**
	(0.002)	(0.002)	(0.002)
Intercept	-2.20**	-1.62**	-2.11**
	(0.316)	(0.291)	(0.302)
Number of Observations Used	1428	1428	1428
Log likelihood	19387.4	19430.1	19394.9

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 5: Robustness to HIV classification

Variable	Neglected	Global	Omitted
Ln(Deaths)*high income*IP*global	0.357**	0.397**	0.380**
	(0.030)	(0.030)	(0.030)
Ln(Deaths)*high income*IP*neglected	0.294**	0.215**	0.218**
	(0.049)	(0.072)	(0.071)
Ln(Deaths)*high income*no IP*global	0.086*	0.035	0.069
	(0.048)	(0.043)	(0.048)
Ln(Deaths)*high income*no IP*neglected	-0.168**	-0.272**	-0.267**
	(0.076)	(0.095)	(0.095)
Ln(Deaths)*upper middle income*IP*global	-0.050**	-0.056**	-0.052**
	(0.020)	(0.020)	(0.020)
Ln(Deaths)*upper middle income*IP*neglected	0.074	0.087	0.086
	(0.171)	(0.178)	(0.176)
Ln(Deaths)*upper middle income*no IP*global	-0.111**	-0.051	-0.103**
	(0.049)	(0.045)	(0.050)
Ln(Deaths)*upper middle income*no	0.007	0.035	0.028
IP*neglected	(0.089)	(0.091)	(0.091)
Ln(Deaths)*lower middle income*IP*global	0.026	0.012	0.012
	(0.045)	(0.044)	(0.045)
Ln(Deaths)*lower middle income*IP*neglected	-0.000	0.090	0.090
	(0.218)	(0.260)	(0.257)
	-0.046	-0.048	-0.042

Ln(Deaths)*lower middle income*no IP*global	-0.046	-0.048	-0.042
	(0.043)	(0.042)	(0.043)
Ln(Deaths)*lower middle income*no	0.190*	0.145	0.135
IP*neglected	(0.101)	(0.115)	(0.116)
Ln(Deaths)*low income*IP*global	-0.048	-0.057*	-0.050
	(0.034)	(0.031)	(0.034)
Ln(Deaths)*low income*IP*neglected	-0.083	-0.209	-0.211
	(0.129)	(0.204)	(0.203)
Ln(Deaths)*low income*no IP*global	-0.031	-0.050**	-0.027
	(0.025)	(0.023)	(0.025)
Ln(Deaths)*low income*no IP*neglected	-0.230**	-0.022	-0.020
	(0.056)	(0.089)	(0.089)
Treatments in 1990	0.051**	0.051**	0.051**
	(0.002)	(0.002)	(0.002)
Intercept	-2.20**	-2.55**	-2.44**
	(0.316)	(0.323)	(0.330)
Number of Observations Used	1428	1428	1411
Log likelihood	19387.4	19392.0	18970.2

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 6: Summary of tests of coefficients

	Baseline	Lagged market size	Ginarte-Park	Hamden	HIV as global	Excluding HIV
IP vs no IP, high income, neglected	0.47**	0.52**	0.21	0.33**	0.43**	0.43**
IP vs. no IP, high income, global	0.26**	0.21**	0.30**	0.42**	0.32**	0.29**
Global vs. neglected, high income, IP	0.04	-0.00	0.28*	0.18**	0.19**	0.18**
Global vs. neglected, high income, no IP	0.25**	0.30**	0.20	0.09	0.30**	0.31**
IP vs no IP, upper middle income, neglected	0.05	0.13	0.02	0.05	0.06	0.07
IP vs. no IP, upper middle income, global	0.09	0.16**	-0.11*	-0.05	0.04	0.07
Global vs. neglected, upper middle income, IP	-0.11	0.03	-0.01	-0.09	-0.13	-0.12
Global vs.	-0.14	0.00	0.12	0.01	-0.11	-0.13

neglected, upper middle income, no IP						
IP vs no IP, lower middle income, neglected	-0.16	-0.25	-0.16	-0.07	-0.05	-0.04
IP vs. no IP, lower middle income, global	0.06	0.13**	0.55**	0.19**	0.04	0.04
Global vs. neglected, lower middle income, IP	0.08	-0.00	-0.01	-0.01	0.01	0.01
Global vs. neglected, lower middle income, no IP	-0.14	-0.39**	-0.73**	-0.29**	-0.09	-0.08
IP vs. no IP, low income, neglected	0.15	0.24	0.23**	-0.00	-0.16	-0.17
IP vs. no IP, low income, global	0.01	0.01	0.00	0.04	0.02	0.00
Global vs. neglected, low income, IP	-0.03	-0.00	0.00	0.11	0.04	0.04

Global vs. neglected, low income, no IP	0.10	0.22**	0.24**	0.06	-0.14	-0.13

* = significant at 5%, ** = significant at 1%. Wald tests of coefficients corresponding to Equation 4 for various specifications.

Appendix A: Disease list; * indicates a neglected disease category

Cause of death		ICD10 codes
Certain infectious and parasitic diseases	Cholera*	A00
	Diarrhoea and gastroenteritis of presumed infectious origin	A09
	Other intestinal infectious diseases (includes typhoid)*	A01-A08
	Respiratory tuberculosis*	A15-A16
	Other tuberculosis*	A17-A19
	Plague	A20
	Tetanus	A33-A35
	Diphtheria	A36
	Whooping cough	A37
	Meningococcal infection	A39
	Septicaemia	A40-A41
	Infections with a predominantly sexual mode of transmission	A50-A64
	Acute poliomyelitis	A80
	Rabies	A82
	Yellow fever	A95
	Other arthropod-borne viral fevers and viral haemorrhagic fevers*	A90-A94, A96-A99

	Measles	B05
	Viral hepatitis	B15-B19
	Human immunodeficiency virus [HIV] disease*	B20-B24
	Malaria*	B50-B54
	Leishmaniasis*	B55
	Trypanosomiasis*	B56-B57
	Schistosomiasis	B65
	Remainder of certain infectious and parasitic diseases (includes leprosy, trachoma and Buruli ulcer)*	A21-A32, A38, A42-A49, A65-A79, A81, A83-A89, B00-B04, B06-B09, B25-B49, B58-B64, B66-B94, B99
Neoplasms	Malignant neoplasm of lip, oral cavity and pharynx	C00-C14
	Malignant neoplasm of oesophagus	C15
	Malignant neoplasm of stomach	C16
	Malignant neoplasm of colon, rectum and anus	C18-C21
	Malignant neoplasm of liver and intrahepatic bile ducts	C22
	Malignant neoplasm of pancreas	C25
	Malignant neoplasm of larynx	C32

Malignant neoplasm of trachea, bronchus and lung	C33-C34
Malignant melanoma of skin	C43
Malignant neoplasm of breast	C50
Malignant neoplasm of cervix uteri	C53
Malignant neoplasm of other and unspecified parts of uterus	C54-C55
Malignant neoplasm of ovary	C56
Malignant neoplasm of prostate	C61
Malignant neoplasm of bladder	C67
Malignant neoplasm of meninges, brain and other parts of central nervous system	C70-C72
Non-Hodgkin's lymphoma	C82-C85
Multiple myeloma and malignant plasma cell neoplasms	C90
Leukaemia	C91-C95
Remainder of malignant neoplasms	C17, C23-C24, C26-C31, C37-C41, C44-C49, C51-C52, C57-C60, C62-C66,C68-C69,C73-C81,C88,C96-C97
Remainder of neoplasms	D00-D48

Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Anaemias	D50-D64
	Remainder of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D65-D89
Endocrine, nutritional and metabolic diseases	Diabetes mellitus	E10-E14
	Malnutrition	E40-E46
	Remainder of endocrine, nutritional and metabolic diseases	E00-E07, E15-E34, E50-E88
	Mental and behavioural disorders	F01-F99
	Mental and behavioural disorders due to psychoactive substance use	F10-F19
	Remainder of mental and behavioural disorders	F20-F99
Diseases of the nervous system	Meningitis*	G00, G03
	Alzheimer's disease	G30
	Remainder of diseases of the nervous system	G04-G25, G31-G98
	Diseases of the eye and adnexa	H00-H57
	Diseases of the ear and mastoid process	H60-H93
Diseases of the		

circulatory system	Acute rheumatic fever and chronic rheumatic heart diseases*	I00-I09
	Hypertensive diseases	I10-I13
	Ischaemic heart diseases	I20-I25
	Other heart diseases	I26-I51
	Cerebrovascular diseases	I60-I69
	Atherosclerosis	I70
	Remainder of diseases of the circulatory system	I71-I99
Diseases of the respiratory system	Influenza	J10-J11
	Pneumonia*	J12-J18
	Other acute lower respiratory infections	J20-J22
	Chronic lower respiratory diseases	J40-J47
	Remainder of diseases of the respiratory system	J00-J06, J30-J39, J60-J98
Diseases of the digestive system	Gastric and duodenal ulcer	K25-K27
	Diseases of the liver	K70-K76
	Remainder of diseases of the digestive system	K00-K22, K28-K66, K80-K92
	Diseases of the skin and subcutaneous tissue	L00-L98
	Diseases of the musculoskeletal system and connective tissue	M00-M99

Diseases of the genitourinary system	Glomerular and renal tubulo-interstitial diseases	N00-N15
	Remainder of diseases of the genitourinary system	N17-N98
Pregnancy, childbirth and the puerperium	Pregnancy with abortive outcome	O00-O07
	Other direct obstetric deaths	O10-O92
	Indirect obstetric deaths	O98-O99
	Remainder of pregnancy, childbirth and the puerperium	O95-O97
	Certain conditions originating in the perinatal period	P00-P96
	Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99

Investments in Pharmaceuticals Before and After TRIPS

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ABSTRACT

The TRIPS Agreement, which specifies minimum levels of intellectual property protection for countries in the World Trade Organization, has increased levels of patent protection around the world. Using variation across countries in the timing of patent laws and the severity of disease, we test the hypothesis that increased patent protection results in greater drug development effort. We find that patent protection in wealthy countries is associated with increases in research and development (R&D) effort. However, the introduction of patents in developing countries has not been followed by greater R&D investment in the diseases that are most prevalent there.

JEL codes: O34, O32, F13, I18, L65

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I. Introduction

Over the last twenty years, most countries have adopted intellectual property (IP) rights. The establishment of the World Trade Organization (WTO) in 1994 was an important driver of this expansion: minimum levels of copyright, trademark and patent protection are a requirement for a country's membership in the WTO as specified by the Agreement on Trade-Related Aspects of Intellectual Property Rights, known as the TRIPS Agreement. IP protection involves a trade-off between dynamic efficiency (associated with incentives for innovation) and static efficiency (tied to access to innovation), and the TRIPS Agreement has long been the subject of debate about the appropriate balance. The extension of patents on pharmaceuticals has been especially controversial for developing and least-developed countries, where access to treatments is limited. Advocates for drug access argue that IP should be minimal, while advocates of drug innovation argue that IP creates incentives for R&D.

Developing and least-developed countries have resisted patents on pharmaceuticals due to concerns about short run costs: because patents eliminate generic competition for treatments during their terms, patents potentially lead to higher prices and thus reduced patient access. However, if patents create incentives to develop drugs for conditions that are prevalent in poorer countries, then patents may be tolerable in developing countries despite the static inefficiency. While diseases of all kinds may afflict the population of a low-income country, a group of so-called "neglected" diseases is of particular interest. Neglected diseases are those conditions for which most deaths occur in developing and least-developed countries, and include HIV, tuberculosis, malaria, river blindness and leprosy. The term "neglected" refers to the relative lack of treatments available to address them, despite their prevalence.[1]

In this article, we seek to inform the debate on the benefits and costs of the TRIPS Agreement by examining the effect of increased global IP rights on the development of

pharmaceutical treatments. Specifically, we test for the dynamic benefits of IP protection by examining research and development (R&D) efforts in the form of clinical trials on specific diseases over time. If patent protection is effective in inducing innovation, then we should observe more R&D on diseases relevant to local populations as patent protection was extended to developing and least-developed countries. Instead, if patents are ineffective at inducing R&D on so-called "neglected" diseases, then no response in R&D effort would occur with the extension of patents to poor countries.

Our analysis relies on the fact that disease prevalence varies across countries, and countries complied with TRIPS at different times. We exploit cross-sectional variation over time in both the adoption of TRIPS and the potential market size of diseases to estimate the relationship between R&D effort and patent protection. We also examine whether this relationship differs across diseases and countries.

The results indicate that, in general, R&D effort is positively associated with the sizes of markets in which patent protection applies. However, the relationship between patent protection and R&D effort varies by country income level. There is a strong association between pharmaceutical patents and R&D effort for diseases that are prevalent in high-income countries, but not for neglected diseases. The establishment of patent protection in poorer countries is not linked to greater R&D effort for diseases that have no market in developed countries. In other words, the introduction of patent protection has not been followed by an increase in R&D on diseases that primarily affect the world's poor. Lanjouw & Cockburn (2001) concluded "[i]t is too early to tell…" the effect of TRIPS on "new pills for poor people" (p. 287) in 2001. This study finds that TRIPS had yet to yield those pills as of 2006. The results suggest that the trade-off between incentives for innovation (i.e., dynamic efficiency) and access to treatments (i.e., static efficiency) is quite different for rich countries than for the developing world.

It is important to note that this paper examines only some potential *gains* from TRIPS for developing and least-developed countries rather than attempting a comprehensive assessment of all benefits and costs of the policies. In particular, we do not assess the costs of new R&D projects, and so we cannot conclude that dynamic efficiency arose from the extension of patent protection among wealthier countries. We find few gains for poorer countries, however, which leads us to the conclusion that the extension of IP protection under TRIPS could not have led to dynamic efficiencies arising from new research on neglected diseases. While quite important in developed countries, patents do not appear to increase innovation incentives elsewhere. This finding is consistent with the notion that the research required for significant advances on neglected diseases is too costly for profit-seeking pharmaceutical firms to justify given the expected returns, or put another way, that profits from such treatments in developing countries – even with patent protection – do not allow firms to recoup their development costs.

In the next section, we discuss the TRIPS Agreement and its requirements in more detail. Section III outlines the theoretical underpinnings to our empirical approach, which we describe in Section IV. We explain our data sources and measures in Section V and present results in Section VI. Section VII concludes.

II. The TRIPS Agreement

The WTO, including the TRIPS Agreement, was established in 1994 during the Uruguay Round of the General Agreement on Tariffs and Trade. Membership in the WTO provides participating countries with trade privileges arising from extensively streamlined administrative procedures. Countries cannot join the WTO without adopting TRIPS, which established minimum levels of copyright, trademark, industrial design, trade secret, and patent protection, and thus affects firms in a range of industries. The rationale is that all WTO members should offer similar

intellectual-property protection to facilitate trade. In theory, member countries will cultivate and promote commerce by adopting and enforcing laws that protect intellectual property.

Since discussions over TRIPS began, the Agreement has been controversial. According to the WTO, TRIPS "attempts to strike a balance between the long term social objective of providing incentives for future inventions and creation, and the short term objective of allowing people to use existing inventions and creations….Intellectual property protection encourages inventors and creators because they can expect to earn some future benefits from their creativity. This encourages new inventions, such as new drugs, whose development costs can sometimes be extremely high, so private rights also bring social benefits" (WTO Fact Sheet 2006). The minimum term of patent protection is now 20 years, and member states must grant patents for both products and processes in most areas of technology, including pharmaceuticals. TRIPS specifies dispute resolution procedures when a member state is accused of failing to comply with the agreement., and states that penalties for infringement must be sufficient to deter violations.

The major controversy is over whether the right balance was struck, particularly in the case of patent protection for pharmaceuticals. Arguments in favor of TRIPS emphasize that intellectual property rights should integrate developing and least-developed countries into the global economy by reducing risks and enhancing incentives to established multinational corporations that operate in these markets. Proponents also noted that the prospect of higher profitability resulting from IP protection would induce additional research on neglected diseases, or those that primarily affect poorer countries.

Concerns arose because patents could allow firms to increase prices and reduce access to treatments. Critics of TRIPS pointed in particular to the case of HIV treatments (Westerhaus and Castro 2006, Cohen 2006, Outterson 2009).[2] The adoption of patent protection in developing countries raised the possibility of very expensive treatments for the growing epidemic. To address

these issues, the original TRIPS Agreement included a number of exceptions for poorer countries. Subsequently, TRIPS was revised several times in response to concerns about the effects of patents in developing and least-developed countries. In addition to formal revisions, the interpretation of TRIPS, compliance and enforcement have changed over time and affected how TRIPS is implemented in practice (Correa 2001).[3]

Because TRIPS constituted a major change in many countries, the TRIPS Agreement itself provided specific deadlines for compliance that vary according to the development status of member states. According to the WTO:

> "When the WTO agreements took effect on 1 January 1995, developed countries were given one year to ensure that their laws and practices conform with the TRIPS agreement. Developing countries and (under certain conditions) transition economies were given five years, until 2000. Least-developed countries have 11 years, until 2006 — now extended to 2016 for pharmaceutical patents.
>
> "If a developing country did not provide product patent protection in a particular area of technology when the TRIPS Agreement came into force (1 January 1995), it had up to 10 years to introduce the protection. But for pharmaceutical and agricultural chemical products, the country had to accept the filing of patent applications from the beginning of the transitional period, though the patent did not need to be granted until the end of this period. If the government allowed the relevant pharmaceutical or agricultural chemical to be marketed during the transition period, it had to — subject to certain conditions — provide an exclusive marketing right for the product for five years, or until a product patent was granted, whichever was shorter."

(http://www.wto.org/english/theWTO_e/whatis_e/tif_e/agrm7_e.htm)

The WTO uses the United Nations' definition of least-developed countries for the purpose of establishing compliance deadlines. All other WTO members identify themselves as either developing or developed upon applying for WTO membership. New members joining after 1995 were generally required to implement TRIPS immediately as part of their ascension agreements with the WTO, and could not use a transition period. Appendix B provides a list of WTO members and their compliance dates. Figure 1 shows how TRIPS compliance changed over time across countries with different 1995 income levels (as defined by the World Bank).

In addition to different deadlines for countries of lower income levels, TRIPS included other exemptions that had the effect of weakening patent protection for pharmaceutical products in some situations. The "Bolar provision" allows a patented invention to be used in the process of conducting research on new drugs as well as in obtaining marketing approval for generic drugs prior to patent expiration. This provision has been invoked in the United States, Canada, Europe, India and China, among others.

Another exemption, granted under the Doha Declaration in 2002, allows countries that meet certain criteria to issue a compulsory license on a patented drug as long as the licensed products are manufactured for domestic use only (i.e., not for export), and with "reasonable" compensation to the patent holder.[4] Implementing the Doha policy has proven challenging, however, because TRIPS and subsequent revisions specify neither what constitutes a national health emergency nor how a reasonable payment should be calculated. Compulsory licenses have so far been rare and mainly issued on drugs for treating HIV (for example, in Thailand, Brazil, Malaysia, Indonesia, South Africa, Zambia and Mozambique) despite the health costs associated with the HIV epidemic in other countries of sub-Saharan Africa. Nonetheless, the threat of compulsory licenses may be an

important influence on pharmaceutical distribution in these countries. Where compulsory licenses have been issued, they too have been controversial, particularly in the case of Brazil and Thailand. In response to Thailand's decision to issue a compulsory license on a hypertension drug as well as an HIV treatment, Abbott Laboratories (whose patent on the HIV treatment Kaletra was at issue) announced that it would no longer supply Thailand with any products. The US Trade Representative put Thailand on its Priority Watch List and the WHO cautioned Thailand to improve its relationship with pharmaceutical firms.

The discussion over compulsory licenses highlighted that such orders may have little effect on national health when complementary institutions such as clinics and pharmacies for administering pharmaceuticals are absent. Furthermore, the compulsion to issue a license is meaningless in the absence of local manufacturers to which the license could be assigned (Westerhaus and Castro 2006). This last concern was addressed in 2003, when the WTO agreed on exceptions to rules that restricted trade in compulsory licensed products. After 2003, member states that declared a national health emergency and ordered a compulsory license could import those products from generic manufacturers located elsewhere if they lacked domestic manufacturing capacity. These changes and exceptions make the precise date of compliance by country difficult to estimate, as we explain below.

III. Theoretical development

We assume that pharmaceutical firms seek to maximize profits when they make R&D investments by forming expectations about the profit that may be eventually obtained if the R&D leads to a successfully commercialized product. We focus on three factors that influence expected profits in a potential market: intellectual property protection, potential volume and ability to pay or

income level. IP protection and income are related to the price a firm expects to charge, and potential market size is related to the quantity a firm expects to sell.

The role of patent protection

The development of new pharmaceuticals is an expensive and lengthy process. DiMasi et al. (2004) estimated that developing a new drug during the 1990s cost about $400-500 million on average, and the time required from project inception to the commercial introduction of a new drug averaged 4-10 years. Though there is debate over the proper way to account for the required investment (DiMasi et al. 2005), there is no dispute that the fixed costs of drug development are very large relative to the marginal costs of production, and that there is a high failure rate of development projects. In contrast, the cost of imitating a pharmaceutical innovation tends to be relatively small (Grabowski 2002). IP protection, particularly in the form of patents, provides a means for innovators to earn a return on their investments in R&D by granting a legal monopoly that normally allows firms to charge higher prices than possible when facing competition. While not the only mechanism for inducing innovation, patents are considered of particular importance in the pharmaceutical sector relative to other industries because of the high fixed cost of drug development (Cohen et al 2000).[5]

As pharmaceutical executives and investors allocate resources between research projects, they consider tradeoffs associated with potential return in the global market. The effect of a single country's change in patent protection on R&D investments is difficult to assess for a number of reasons. Most individual countries represent a small share of the total pharmaceutical market, and even a dramatic change in one country may not result in a large shift in expected profits and subsequent R&D investment. In addition, changes the interpretation of patent law, and the economic development occurring concurrently with the implementation of patent systems and changes in other countries may be difficult to control for. Another concern is that patenting activity

may have changed due to shifts in the management of research or innovative capacity (Kortum and Lerner (1998)). As a result, direct tests of the link between patent protection and R&D investment in pharmaceuticals are rare. Sakakibara and Branstetter (2001) found little change in R&D attributable to a change in Japanese patent law in 1988. Qian (2007) studied pharmaceutical patent changes in a cross-section of countries between 1978 and 2002 and concluded that domestic R&D did not increase due to a strengthening of patent protection alone. Rather, the effect of patent protection was moderated by a country's level of economic development. However, Lichtenberg and Waldfogel (2003) found that the 1983 Orphan Drug Act in the United States, which increased the period of patent protection for drugs to treat rare conditions, stimulated the development of drugs for such diseases. We complement these studies by offering additional evidence on the response in global pharmaceutical R&D to the extension of patent protection.

The role of market size

Economic theory predicts that profit-maximizing firms seek to amortize fixed costs over the sale of many units. Given the high fixed R&D costs of developing a new drug, larger potential markets tend to be more attractive. There is ample empirical evidence of the relationship between market size and investments in drug development. Ward and Dranove (1995) associated a 10 percent increase in demand in a therapeutic area with a 5-8 percent increase in R&D spending. Lichtenberg and Waldfogel (2003) linked market size to R&D investment; indeed, this relationship – and the consequential absence of investment in treatments for rare conditions – was the basis for the Orphan Drug Act in the US. Finkelstein (2004) examined the response of pharmaceutical firms to the implementation of US federal policies that required childhood vaccination against six diseases. This paper found that research firms responded to the dramatic increase in expected demand by doubling the number of drugs in clinical trials. Acemoglu and Linn (2004) studied the relationship between market size and drug launches in the US. The results associate an increase of 1% in market

size with a 4% increase in the number of new drugs introduced. Thus, the projected size of the market is an important factor in decisions to invest in pharmaceutical R&D.

The role of income

Typically, the greater the percentage of income required to purchase a good, the more elastic the demand. Consumers of pharmaceuticals in poorer countries are likely to have higher demand elasticity than those in developed countries in part because of their lower incomes and in part because patients in poorer countries may pay for treatments out-of-pocket instead of through insurance. Economic theory associates more elastic demand with lower profit-maximizing markups (Lerner index) for a price-discriminating monopolist. Given that the marginal costs of drug production may not vary extensively by country, the difference in elasticity implies that, all else equal, pharmaceutical firms distributing patent-protected therapies tend to charge lower prices per patient in developing countries than in developed countries. As a result, the share of a pharmaceutical firm's profits from developed countries may be much higher than from developing countries, even before accounting for differences in the number of patients eligible for treatment. This possibility is consistent with the fact that members of the trade association PhRMA derive more than 80% of their revenues from sales in the US, Canada, Europe and Japan.

For diseases that affect patients in countries of all income levels, the higher mark-ups that are optimal in developed countries may enable firms to recoup R&D investments, and allowing firms to sell in the rest of the world as long as developing-country markets support prices that are high enough to cover the marginal costs of production.[6] Absent patent protection, competition from imitators (generics) tends to drive price down to marginal cost and reduce the innovator's share of sales. The extension of patent protection under TRIPS should thus increase expected profits. The higher the income level of the country adopting IP protection, the greater the increase in expected profit and thus the greater the incentive to invest in R&D.[7]

In the case of treatments for diseases that afflict relatively few patients in developed countries, namely the "neglected" diseases (in Section V, we describe precisely how we define these diseases), a firm can justify research only if it expects to recoup its R&D investment through sales in developing countries. The challenges of achieving sufficient expected profits to cover the investment may be exacerbated by the comparatively low level of recent scientific discovery in relevant areas, thus making the required R&D investment relatively large. In many of these countries, the market may not viably support a price sufficient to cover marginal production costs even for a firm with patent protection and monopoly pricing power. As noted in other work (e.g., Kremer 2002, Danzon and Towse 2003), patent protection may therefore not be sufficient to induce R&D investment on neglected diseases. For this reason, Kremer has proposed the use of alternative incentive mechanisms such as advance market commitments (AMCs) to motivate investment.

To summarize, we expect R&D investments in pharmaceuticals to depend on the strength of patent protection, the expected size of the total potential market for a treatment, and the income level in the countries for which the drug is intended. TRIPS had the effect of changing the strength of patent protection in countries with different disease patterns and with different income levels. R&D investment should increase with the degree of patent protection for diseases whose market is global, and more so for relatively wealthy countries. However, patent protection may not affect incentives for R&D investment in diseases with markets in only poor countries where patients cannot afford to pay a significant markup over marginal cost. In the following section, we specify an empirical test for these hypotheses.

An important facet of our analysis is that we do not assess differences in the costs of the R&D required to generate drugs that are effective for addressing diseases that primarily affect the poor versus those that do not. Our approach should be interpreted in light of the possibility that the costs of R&D on neglected diseases may be significantly greater either because the science on these

diseases is not as well developed as for global diseases or even because of prospecting by innovating firms to open up fruitful new areas for development (Kitch 1977, Burk and Lemley 2009). Similarly, we cannot account for different expectations about post-patenting imitation that might arise for neglected vs. non-neglected diseases and or account for differences in research productivity. Firms may choose to patent or not to patent strategically – so as to enhance or avoid coordinating in science and further augment their control over particular therapies (Burk and Lemley 2009), and this consideration is beyond the scope of this paper.

IV. Empirical methods

Our empirical strategy is to examine R&D efforts at the disease level, exploiting changes in both patent protection and disease patterns that varied over time and across countries. We are particularly interested in the effect of patent protection on R&D efforts for neglected diseases and its interaction with the income level of countries that strengthen their patent laws. We start with a basic model relating R&D effort and market size, and subsequently add interactions with disease type, patent protection and income levels. Descriptions of our measures of each are in the next section.

The unit of analysis throughout is a disease-year. We begin by estimating the relationship between yearly R&D investment in a disease area and the total potential market size of the disease. That is,

$$Y_{dt} = \alpha_0 + \alpha_1 M_{dt} + AX_{dt} + \varepsilon_{dt} \qquad (1)$$

where Y_{dt} is a measure of R&D effort in disease *d* in year *t*, M_{dt} is a measure of potential market size disease *d* in year *t*, and X is a vector of controls comprised of the availability of substitute products and year fixed effects. Substitute products are represented by the number of available treatments for the disease in 1990, several years prior to TRIPS. We include this control because R&D investments made subsequent to the adoption of TRIPS would be moderated by the opportunities left open by

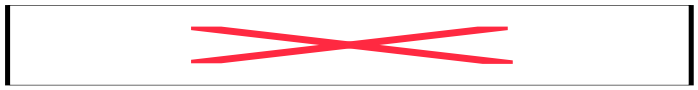
established treatments. Year fixed effects are included to reflect changes over time arising from macroeconomic factors, changes in global trade conditions, and other influences that affected all firms. We expect a positive coefficient on M_{dt}, i.e. that $\alpha_1 > 0$.

Next, we decompose potential market size by disease type to explore whether R&D effort responded differently to global diseases than to neglected diseases, which we define precisely below. We estimate the following equation:

$$Y_{dt} = \beta_0 + \beta_1 M_{dt} * \text{Global} + \beta_2 M_{dt} * \text{Neglected} + BX_{dt} + \varepsilon_{dt} \qquad (2)$$

where Global = 1 if disease *d* is a global disease, Neglected = 1 if disease *d* is a neglected disease and other variables are defined as above. While global diseases clearly have a higher level of R&D effort, β_1 and β_2 reflect the change in R&D associated with a change in potential market size. Subsequent specifications investigate the source of the difference between β_1 and β_2, if any.

One such source may be that neglected diseases primarily affect countries that historically lacked patent protection. If this is the main driver of the difference in R&D effort, then increasing patent protection in countries with high prevalence of neglected diseases should lead to a greater level of R&D effort relative to countries without high prevalence of neglected diseases. The TRIPS policy "experiment" allows us to examine this by estimating:



(3)

M_{dt}*Global*IP_t is the total potential market size of disease d in year t across all countries with IP, where disease d is a global disease; M_{dt}*Global*$NoIP_t$ is the total potential market size of a global disease *d* in year *t* across all countries without IP; and so on. The difference between γ_3 and γ_4 reflects how effective TRIPS has been at inducing R&D for neglected diseases.

Patent protection may not induce R&D on either global or neglected diseases in less wealthy countries if the ability of patients to pay is extremely low. Our final specification evaluates the

impact of patent protection across both disease types and the level of income of countries affected by a particular disease:

$$
\begin{aligned}
Y_{dt} = {} & \eta_0 + \eta_1 M_{dt} * Global * IP_t * High + \eta_2 M_{dt} * Global * NoIP_t * High \\
& + \eta_3 M_{dt} * Global * IP_t * UpperMiddle + \eta_4 M_{dt} * Global * NoIP_t * UpperMiddle \\
& + \eta_5 M_{dt} * Global * IP_t * LowerMiddle + \eta_6 M_{dt} * Global * NoIP_t * LowerMiddle \\
& + \eta_7 M_{dt} * Global * IP_t * Low + \eta_8 M_{dt} * Global * NoIP_t * Low \\
& + \eta_9 M_{dt} * Neglected * IP_t * High + \eta_{10} M_{dt} * Neglected * NoIP_t * High \\
& + \eta_{11} M_{dt} * Neglected * IP_t * UpperMiddle + \eta_{12} M_{dt} * Neglected * NoIP_t * UpperMiddle \\
& + \eta_{13} M_{dt} * Neglected * IP_t * LowerMiddle + \eta_{14} M_{dt} * Neglected * NoIP_t * LowerMiddle \\
& + \eta_{15} M_{dt} * Neglected * IP_t * Low + \eta_{16} M_{dt} * Neglected * NoIP_t * Low \\
& + \mathbf{N} X_{dt} + \varepsilon_{dt}
\end{aligned}
\tag{4}
$$

M_{dt}*Global*IP_t*High is the total potential market size of global disease *d* in year *t* across high-income countries with IP. M_{dt}*Global*$NoIP_t$*High is the total potential market size of global disease *d* in year *t* across high-income countries without IP. Similarly, M_{dt}*Neglected*IP_t*UpperMiddle is the total potential market size of neglected disease *d* in year *t* across upper middle-income countries with IP, etc. We expect that patent protection has a smaller effect on profits in poorer countries than in rich countries and therefore a smaller effect on R&D incentives, so that $\eta_1 > \eta_3 > \eta_5 > \eta_7$ and $\eta_9 > \eta_{11} > \eta_{13} > \eta_{15}$. A market for a global disease may exist in relatively rich countries, and thus there may be a positive effect of patent protection in poorer countries on profits and R&D effort on global diseases, implying that $\eta_5 > \eta_6$ and $\eta_7 > \eta_9$. For neglected diseases, however, we expect $\eta_{13} = \eta_{14} = 0$ and $\eta_{15} = \eta_{16} = 0$: patent protection in countries where patients have very low ability to pay does not induce R&D effort because expected revenues do not cover the fixed costs of development.

A concern is that patent protection is an endogenous policy choice. Historically, countries have adopted IP protection in response to demands from domestic innovators, or after achieving a rather high level of development (Qian 2007). We argue that in the case of TRIPS, developing and least-developed countries were clearly resistant to adopting or strengthening IP protection and did

so only because they expected large benefits of membership in the WTO. Another recent paper examining the TRIPS agreement concluded "the Agreement's implementation is an external factor, not entirely influenced by the country's level of economic development…[Changes in IP due to TRIPS] can be used as a natural experiment to understand how IPR influences economic activities and behaviors" (Hamdan-Livramento 2009). However, if resistant countries also adopted policies aimed at undermining patent protection or pricing power (such as widespread use of compulsory licensing or stringent price controls) or failed to enforce patent laws, our results may understate the effect of IP protection on R&D efforts. We interpret our results in light of this possibility.

V. Data and measures

The analysis depends on information about R&D efforts over time and by disease, measures of potential market size (assessed as disease prevalence) over time and across countries, and country-level factors such as IP law and income level. Sources and the construction of variables are described below. Table 1 provides summary statistics. Our final dataset spans 17 years (1990-2006).

R&D effort

Our measure of R&D effort is the number of new clinical trials initiated by the industry in a year for a specific disease. These trials reflect the majority of R&D expenditures in the industry. Ideally, our measure of R&D effort would be research expenditures by disease and by year. Unfortunately, publicly traded firms generally do not report R&D spending by disease and, furthermore, many pharmaceutical firms are not publicly traded and do not disclose any financial information about their spending on R&D. Despite the limitations, we believe that the information we employ about the number of clinical trials is among the most comprehensive available on early-stage R&D projects by disease and by year. Our source is the R&D Focus database produced by IMS Health. Typically used by pharmaceutical firms to monitor the research activities of

competitors, R&D Focus provides a history of all projects known to be in development from the mid-1980s through the present. This includes projects that failed in clinical trials, those that were successfully launched, and those that continue in development. Each record is a pharmaceutical project and may be associated with multiple indications and multiple firms. The history of the project's progression through each stage of development is compiled by IMS from patent and regulatory filings, presentations at medical conferences, press releases, and information disclosed to financial analysts.

To capture early R&D efforts, we focus on the first stage of human clinical testing, i.e. Phase I trials.[8] Because our dependent variable Y_{dt} is a count of new Phase I trials in disease *d* in year *t*, we estimate regressions as negative binomials. We trim the dependent variable to 75 (less than 1% of our observations have a value above this). The information in the IMS database also allows us to construct a count of existing treatments for each disease in 1990, which we use as a control for competition.

Disease prevalence and type

We proxy for "potential market size," or disease-level demand, by a measure of disease burden by country and year. The WHO publishes the number of deaths attributed to a disease as recorded by national civil registration systems on an annual basis. A better measure would account for how a disease affects quality of life. One such measure is the disability-adjusted life year (DALY), which has been controversial because it incorporates subjective judgments about disease severity. In addition, estimates of DALYs by the WHO are limited to only a single cross-section, and thus reliance on the available estimates would ignore changes over time in disease prevalence or severity. We therefore do not use DALYs.[9] In our regressions, we define potential market size as the log of the sum of all deaths from disease *d* across all countries (or subset of countries, depending on the specification) in year *t*.

We faced two main challenges in using the WHO Mortality Data. First, the coverage of the dataset is not comprehensive. For example, all data is missing for particular countries in some years; coverage of China is not complete; and there is very little information on some least-developed countries such as Afghanistan, Malawi and Madagascar. Given the limitations on data collection efforts, we are likely to underestimate deaths in the poorest countries. We used multiple imputation techniques to deal with the missing values and correct standard errors. Rather than estimating a missing value through simulation (i.e. single imputation), multiple imputation involves substituting a set of values that reflect the uncertainty about the predictions of the missing values. The datasets with the imputed values are analyzed and their results are combined to adjust estimates of variance accordingly. An important assumption, which cannot be verified, is that the data is missing at random. We create five imputed datasets using the EM algorithm with the MI procedure in SAS.[10] Summary statistics for pre- and post-imputation deaths are included in Table 1. Our results are not sensitive to the number of imputations or to the algorithm used.

Another challenge involved matching disease definitions from the WHO with those in the R&D Focus database. The WHO uses the International Classification of Diseases (ICD) codes, while R&D Focus provides indications and therapeutic classifications for each drug development project. For each indication in the R&D Focus database, we identified a likely ICD code using medical dictionaries. The most detailed ICD codes in the WHO Mortality Data were not available for a sufficient number of countries or years and were often too specific to match to R&D Focus indications. We use instead a condensed list of 84 categories of diseases or conditions that covers everything in the WHO mortality data except "external causes" that are not typically addressed with pharmaceutical therapies, such as car accidents, falls, and intentional self-harm. These diseases are listed in Appendix A.[11]

Although there is no official definition, there is widespread agreement about the set of neglected diseases in the health policy and development literatures. We categorized a disease as "neglected" using Table 1 of Moran et al. (2009). Moran et al. (2009) used a three-step filter to identify neglected diseases: first, the disease must disproportionately affect developing countries; second, new treatments are needed; and finally, no commercial market is thought to exist. The list of neglected diseases generated by this categorization includes all the neglected tropical diseases identified by the WHO as well as those considered by Lanjouw and Cockburn (2001). It also includes all the diseases that qualify for a "Priority Review Voucher" in the US.[12] More than 90% of deaths from these diseases occur in countries that are developing and least developed. We define all non-neglected diseases as "global." Global diseases affect countries of all income levels, and include cardiovascular conditions, neurological disorders, and cancer.

Questions arise about whether HIV is a global or neglected disease. Moran et al. (2009) and the WHO consider HIV a neglected disease, although HIV affects large numbers of people in developed countries as well. While many treatments for HIV now exist, not all are well-suited for use in developing countries or, in particular, for children (who constitute a much larger fraction of HIV patients outside developed countries than in developed countries). HIV qualifies as a "neglected" disease if there are insufficient incentives to develop appropriate treatments for developing countries, which now report a greater need for 3rd and 4th line therapies. In our main analysis, we consider HIV as a neglected disease, but in robustness checks, we run analyses that first classify HIV as a global disease and then drop HIV from the data. Overall, our results are robust to these changes.

IP measures and other country information

The WTO established a timetable for compliance with TRIPS. We use these rules, described in Section II, to estimate the dates of compliance for every country. Original WTO members that

self-identified as "developed" are considered compliant in 1995. For developed countries that joined the WTO after 1995, we code compliance as of the membership date. WTO member countries identified as "least-developed" were required to comply by January 1, 2005, with the deadline extended until January 1, 2006 and even further during the Doha round to 2016. Thus, for least-developed countries, we assume that compliance will occur only in 2016. For self-identified developing countries that were WTO members at the time of TRIPS adoption in 1995, we code the year of compliance as 2000. For countries that joined after 1995 (except for those that were least developed), we code compliance as the date of membership unless we found different information about the compliance date on the WTO website.[13]

Measuring TRIPS compliance using the WTO rules has several drawbacks. First among them is that, while a country may claim to comply with TRIPS, its enforcement of patent and other IP protections may be in doubt. We check for robustness using two alternative measures of patent protection and enforcement. Walter Park kindly shared his updated index of IP protection and enforcement compliance, which he has used in a number of published analyses (see, e.g., Ginarte and Park 1997). This measure is more nuanced than our TRIPS dummy variable, but it is not available for 40 countries in our dataset and is available only at five-year intervals. The Ginarte-Park index has separate elements for chemical patents and for enforcement; we use both the existence of chemical patents and strong enforcement to create a dummy variable indicating whether a country has chemical/pharmaceutical patent protection and enforces patent laws.[14] For developed countries that joined the WTO in 1995 and for which the Ginarte-Park index indicated the presence and enforcement of pharmaceutical patents in 1990, we adjusted our TRIPS dummy variable to indicate compliance as of 1990. This avoids characterizing the membership of the United States in the WTO as requiring a major shift in IP law. Recent work by Hamdan-Livramento (2009) investigates in much greater detail the state of patent law and enforcement in 53 developing countries, and the

author generously shared his index of TRIPS compliance with us. This analysis was especially relevant because the investigated developing countries encompassed the majority for which IP laws changed after TRIPS. We use the components of the index related to pharmaceutical patents and enforcement, where available. For countries not covered by the Hamdan-Livramento index, we use our initial measure of TRIPS compliance.

There are a number of differences across these three measures of IP laws and enforcement. Appendix B contains the list of countries used in our analysis, the year of compliance required by the WTO, the first year of both pharmaceutical patents and enforcement according to the Ginarte-Park index and the first year of both pharmaceutical patents and enforcement according to the Hamdan-Livramento index.[15] A limitation on all the measures of IP compliance is that they do not capture expectations that firms may have about the state of future patent protection in a country. Since drug development is a lengthy process, firms may make investment decisions based on whether they believe a country will afford intellectual property protection some years in the future, providing a measure of time for the R&D to yield a commercialized product. In other words, an influential factor in decisions about R&D may be a country's intention to adopt patent protection as a condition of WTO membership rather than the precise timing of compliance. Even in these situations, the compliance date is likely to be critical both because of the resolution of uncertainty about intentions to implement IP mechanisms and because, after the date of compliance, firms have remedy for IP violations via the WTO dispute resolution process. We report results using the compliance dates under each method of estimation and note the differences in our results that are obtained under each approach.

Another important factor influencing R&D decisions for which we cannot account relates to the forecasted possibility of compulsory licensing. Firms may be reluctant to invest in R&D for diseases that are likely to be the subject of compulsory licensing. While few such licenses were issued

during our sample period (which ends in 2006), our failure to account for these expectations would lead us to underestimate the impact of "true" patent protection. However, even if these expectations had shaped R&D decisions, our models would accurately reflect the overall effect of TRIPS given its various exemptions.

We use the World Bank's World Development Indicators dataset for information on country income levels. The World Bank categorizes countries as high income, upper middle income, lower middle income and low income. We report the 1995 income level for each country listed in Appendix B. Because the unit of analysis is the disease-year rather than the country, we are limited in our ability to control for many additional geographic factors that might influence pricing and volumes. Among the omitted variables that concern us are the urban or rural location of potential patients within each country and the presence or absence of complementary institutions such as hospitals, clinics and pharmacies. Unfortunately, this information is incomplete for large numbers of countries, and especially for developing and least-developed countries. Because we are interested in these countries, we use a very parsimonious set of controls for which we have reasonably complete data. Note that not all low-income countries are least-developed countries as defined by the United Nations, and therefore some introduced patent protection during our sample period (see Appendix B).

VI. Results

Our baseline results from estimating equations 1-4 are presented in Table 2, with robustness checks in Tables 3-5 and a summary of the robustness checks in Table 6. The dependent variable in all specifications is the number of drug development projects for disease *d* entering Phase I clinical trials in year *t*. The regressions are estimated as negative binomials (Poisson models were rejected due to overdispersion). All specifications include year fixed effects and a control for the number of

treatments available for disease *d* in 1990. Standard errors, which are in parentheses below the coefficients, are clustered by disease and corrected to reflect the use of multiple imputation to deal with missing values for disease data.

For our baseline specifications, we define IP_t using WTO rules for TRIPS compliance and categorize HIV as a neglected disease. Column 1 corresponds to equation 1, column 2 to equation 2, and so on. Since the market size measures are in logs, their coefficients may be interpreted as elasticities. The final column of Table 2 provides the marginal effect evaluated at the sample means. As expected, R&D effort is positively associated with overall potential market size ($\alpha_1 = 0.035$ with a standard error of 0.003). If we separate diseases into global and neglected, the coefficients on both measures of potential market size are also positive and statistically significant (0.034 and 0.029, respectively). R&D effort in the aggregate and for both global and neglected diseases is positively related to increases in the number of potential patients. However, the coefficients on global and neglected disease market sizes are statistically different from each other.

Our main focus is the source of the difference between the R&D response to global and neglected diseases. One possibility, which we cannot test directly, is that drug development is more expensive for neglected diseases than for global diseases, which might mean that the potential market size for a neglected disease would have to be greater than for a global disease to induce an equivalent amount of R&D effort. This effect could be compounded if early scientific efforts on a disease open up the prospect of a stream of patentable innovations over time after the first drugs are commercialized (Kitch 1977). Another possible explanation is that neglected diseases primarily affect countries that have had weak patent systems historically, which may lead investing organizations to hesitate in committing R&D out of concern than patents will not be enforced. Firms also may anticipate that drugs introduced into developing countries may be quickly imitated or licensed, thereby blunting their abilities to obtain profit from them. We address these possibilities in the

specification presented in column 3, which decomposes market size not only by disease type but also by prevalence in countries with or without TRIPS-compliant patent systems. The difference between γ_1 and γ_2 reflects the relationship between the adoption of IP and R&D efforts for global diseases, and the difference between γ_3 and γ_4 does likewise for neglected diseases. For both types of diseases, there is a strong positive association between TRIPS compliance and R&D effort, with R&D more responsive to IP-protected market size for global diseases than for neglected diseases. Thus, we find that IP protection is associated with increased R&D effort for both types of diseases, but there remains a statistically significant difference between the response to IP-protected market size for global diseases and IP-protected neglected diseases.

In Section III, we noted that patent protection might not lead to greater expected profits in countries where most patients are unable to pay even the marginal cost of producing a treatment. Our final specification, which estimates equation 4, separates potential market size by disease type, existence of patent protection and the income level of those afflicted. By separating countries by income level, the analysis allows for differences in the relationships between TRIPS compliance and R&D effort based on projections of ability to pay. As expected, we find the greatest increment to R&D effort associated with increases in potential market size in high-income countries with patent protection. This relationship holds for both global and neglected diseases: the coefficients η_1 and η_9 are 0.353 and 0.342, respectively. Both are statistically significant different from zero, but not from each other, which suggests that R&D costs for the two types of diseases are roughly the same.[16] In high income countries – where ability to pay is less likely to be blunted by poverty and the absence of complementary services such as clinics, personnel, etc., – the adoption of patent protection seems to induce research on diseases that are prevalent in the population. The relationship does *not* hold for less wealthy countries, regardless of patent protection. In other words, R&D effort is not associated with the implementation of TRIPS in lower-income countries. None of the coefficients

on potential market size outside of the high-income category are positive or significantly greater than zero. These results suggest that while patent protection is effective at inducing R&D for diseases prevalent in high income countries, it is not sufficient for diseases that have no market outside the developing world. The difference between R&D effort directed at global diseases and neglected diseases is driven mainly by the difference in income of those affected, rather than a difference in patent protection.

We re-ran our analysis to check the robustness of our results across different definitions and measures. A summary of the tests of coefficients in equation 4 across these many specifications is presented in Table 6. Tables 3, 4, and 5 report the details of the regressions. In Table 3, we report on regressions that allow for a lag in the response of R&D to the extension of patent protection. We conduct this test because our baseline model assumes that firms can respond immediately to the introduction of patent protection by initiating Phase I trials. If preclinical research is required, the Phase I response may be delayed by several years. Table 3 contains the results of specifications identical to those in Table 2, except that market size is lagged by three years to allow for preclinical testing.[17] The results are similar to those in the main model. Although we observe a statistically significant coefficient on IP-protected market size for global diseases in middle-income countries, the coefficients for neglected disease market size remain insignificant.

Table 4 estimates equation 4 using alternative definitions of IP. Column 1 is our baseline specification, using WTO rules for TRIPS compliance. Column 2 uses the Ginarte-Park definition, and Column 3 uses the Hamdan-Livramento definition. While some of the parameter estimates differ across specifications (which is expected, since we noted variation across these measures in Section V), the overall pattern remains. No coefficient on market size is significantly greater than zero outside of the high-income category, though the difference between IP and no IP is positive for the lower middle-income group.

We examine the sensitivity of results to the classification of HIV in Table 5. The first column again contains our baseline results in which HIV is classified as a neglected disease. Column 2 classifies HIV as global, and Column 3 excludes HIV from the analysis. Once again, we find the same pattern of coefficients across income types with one important difference. While the coefficients η_1 and η_2 (market size for the high income category for global and neglected diseases) are quite similar when HIV is defined as neglected, there is a wide gap between them in columns 2 and 3. This result arises from the fact that HIV is the most prevalent "neglected disease" in rich countries, which means that and significant R&D, both public and private, has been invested to address it. Unfortunately, available measures of R&D effort are not sufficiently nuanced to capture differences across projects in dosage formulations or combinations best suited to developing or least-developed countries (such as pediatric and heat-stable presentations), and thus we cannot test formally for differences in R&D investments for HIV targeted at higher and lower income countries.

To put our results into some perspective, we note that Acemoglu and Linn (2004) estimated that a 1% increase in potential market size in the US led to a 4% increase in the number of new drugs introduced. They remark in their paper that this estimate is quite large. However, our estimates are in line with more recent work by Dubois et al. (2011), although we are looking at new clinical trials (or drug candidates) rather than drug approvals, and our sample includes a much larger set of countries. Unlike these previous papers, we explicitly compare the elasticity of market size across countries and the presence of patent protection. Our findings indicate that for a neglected disease and with patent protection, R&D is roughly four times as responsive to an increase in log market size in a high-income country than to an upper middle-income country. The summary of tests of coefficient differences in Table 6 suggests that while there are statistically significant differences between IP and no-IP coefficients in high-income countries, this pattern does not appear for other

income levels. In addition, the difference between global and neglected diseases is not generally statistically significant. Indeed, for lower income levels without IP, R&D is sometimes estimated to be more responsive to neglected disease needs than to global, which could reflect the efforts of non-governmental organizations (NGOs) and others that are not profit-driven.

Although we have reported many robustness checks in this paper, it is important to qualify our findings in several ways. One concern is the potential endogeneity of IP protection and enforcement. It may be that countries only adopt and enforce patent laws when they have achieved a minimum level of income and development. Economic development may occur simultaneously with the implementation of patent protections (as was an objective of the WTO). In practice, developing and least-developed countries have often attempted to delay and weaken the requirements of TRIPS, and ultimately implemented the policy to achieve other benefits from WTO membership. We find only weak evidence that IP rights have an impact in developing and least-developed countries, but this may reflect an unwillingness to enforce these rights and understate the real effect of strong, enforceable patents.

More generally, expectations about future policies related to profitability and IP rights, which are not observed, are important to incentives. Price controls are an example of a policy (widespread in developed countries) that could dampen profits even in the presence of patents. The use of compulsory licensing is another, and this is not restricted to developing and least-developed countries. For example, the Canadian government once extensively issued compulsory licenses (although prior to TRIPS). Even in the US, in 2001 the government considered compulsory licenses for Cipro, a treatment for anthrax, and in 2005 on Tamiflu, a treatment for avian influenza.[18] If governments are expected to issue compulsory licenses for some drugs, R&D investment choices may reflect these expectations. As noted previously, few compulsory licenses were issued during our sample period. However, the option of compulsory licenses is an important aspect of how TRIPS

compliance affects R&D incentives, and the use of price regulation is not addressed by TRIPS at all. Thus, while we may underestimate the impact of "true" patent protection, our results should still accurately reflect the impact of TRIPS in particular.

Another concern is that our data source may not reflect all research activities. For example, IMS may focus on the activities of firms more intensively than on the activities of universities, foundations, and NGOs in assembling its R&D Focus data. If this bias in coverage exists, we would underestimate the number of projects underway. If universities and other nonprofits are more likely to focus on neglected diseases and are sensitive to the IP environment, then we might be biased towards finding less effort on such diseases. However, this is unlikely to be a major problem for several reasons. First, we compared the IMS R&D Focus coverage to two competing databases from PJB Publications and Thomson Scientific. The coverage of IMS included firms located in a larger set of countries than the other two. Second, about 17% of the organizations covered by IMS R&D Focus are universities, foundations, or other non-profit organizations. Third, the controversy over TRIPS and increased attention to the burden of disease in the developing world – through the Gates Foundation or the Clinton Health Initiative, for example – may have made all types of organizations more likely to "advertise" and disclose their R&D activities directed at neglected diseases, which may cause an upward bias in our estimate of the impact of patent protection. It should be noted that increased funding from these NGOs and others may also have stimulated additional R&D for neglected diseases, but this should be unrelated to the presence of patent protection (many NGOs oppose patent protection, in fact).

The WHO Mortality Data is a compilation of information provided by each member country, which may vary in quality. In particular, the prevalence of HIV appears to be understated in many developing and least-developed countries.[19] Omitting HIV from our sample does not change the qualitative results, however. In addition, an earlier version of this paper yielded similar findings

based on the WHO's Global Burden of Disease dataset. Ultimately, we used the WHO Mortality Data because it includes time-series variation as well as more specific disease categories.

VII. Conclusion

This paper examines how R&D investment in pharmaceuticals has changed with the adoption of the TRIPS Agreement. Particularly in the case of patents for pharmaceutical treatments, TRIPS involves a trade-off between dynamic efficiency, i.e. incentives for R&D investment, and static inefficiency, i.e. access to drugs. An important issue for developing and least-developed countries is whether the introduction of patent protection for drugs has led to dynamic benefits in the form of an increase in R&D effort to treat diseases that are especially prevalent there.

We conclude that patent protection in developing and least-developed countries does not appear to have induced investment in new treatments for diseases that primarily affect poorer countries. R&D on neglected diseases is not associated with increases in the potential market size in low-income countries, whether or not those markets provided patent protection. This is not to claim that patents are irrelevant: patent protection is associated with greater R&D investment in diseases that affect high income countries, and the treatments developed as a result may benefit people in poorer countries too. The existence of a market in rich countries allows firms to recover their R&D investments. Consequently, global diseases – those present in countries of all income levels – attract research effort. However, patent protection is not sufficient to induce R&D for diseases that have no significant potential market in high-income countries. If those affected, or their governments, lack the ability to pay prices much higher than the marginal cost of producing treatments, firms are unable to recoup the fixed costs of R&D regardless of the level of patent protection. This effect may arise both because revenues are projected to be low and because the costs of innovation are high, and our findings suggest the former is more likely.

Our study focuses on only one possible effect of the introduction of IP rights. Importantly, we do not tackle the issue of whether access to treatments in developing countries decreased, or how investments in health-delivery systems in developing countries may have changed in response to TRIPS implementation. Other possible effects include an increase in technology transfer to developing countries and greater incentives for domestic R&D activity. WTO membership, possible only with the adoption of TRIPS, may have provided other benefits to developing countries that we do not consider here.

The results of this research suggest that alternative mechanisms for inducing R&D effort on neglected diseases may be more effective than the extension of patent protection alone. Recently, such mechanisms have received increased attention from policy makers and other organizations. For example, the first advance market commitment for a pneumococcal vaccine was established in 2007 by GAVI. The US introduced a system of priority review vouchers targeted at neglected diseases in 2007. In 2008, UNITAID proposed the use of a patent pool for pediatric HIV treatments. We hope that such efforts will soon yield new treatments for diseases that principally affect patients in less wealthy countries.

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Table 1: Summary statistics

Number of countries	192				
Number of diseases	84				
Number of years	17				
	N	**Mean**	**Std Dev**	**Min**	**Max**
Phase I starts (all)	1428	8.086	17.704	0	229
Phase I starts (trimmed)	1428	7.386	12.479	0	75
Total deaths in disease/country/year (before imputation)	106952	2277.120	14036.820	0	824861
Total deaths in disease/country/year (after imputation)	648261	2352.310	16832.280	0	940496
Treatments in 1990	1428	9.89	16.99	0	83
Ln(Total Deaths)	1428	10.296	2.486	3.022	14.910
Ln(Deaths)*global disease	1428	9.141	3.810	2.079	14.910
Ln(Deaths)*neglected disease	1428	3.224	2.821	2.079	13.162
Ln(Deaths)*IP*global disease	1428	8.539	4.043	1.386	14.910
Ln(Deaths)*IP*neglected disease	1428	2.444	2.746	1.386	13.030
Ln(Deaths)*no IP*global disease	1428	6.389	3.941	1.386	14.358
Ln(Deaths)*no IP*neglected disease	1428	2.246	2.430	1.386	12.647
Ln(Deaths)*high income*IP*global	1428	7.716	4.464	0.000	13.980
Ln(Deaths)*high income*IP*neglected	1428	1.072	2.835	0.000	12.354
Ln(Deaths)*high income*no IP*global	1428	3.135	3.759	0.000	11.297
Ln(Deaths)*high income*no IP*neglected	1428	0.427	1.606	0.000	9.741

Ln(Deaths)*upper middle income*IP*global	1428	5.417	4.021	0.000	12.476
Ln(Deaths)*upper middle income*IP*neglected	1428	0.735	2.207	0.000	11.242
Ln(Deaths)*upper middle income*no IP*global	1428	4.074	4.485	0.000	12.284
Ln(Deaths)*upper middle income*no IP*neglected	1428	0.701	2.338	0.000	11.241
Ln(Deaths)*lower middle income*IP*global	1428	5.190	4.781	0.000	14.183
Ln(Deaths)*lower middle income*IP*neglected	1428	0.808	2.535	0.000	12.029
Ln(Deaths)*lower middle income*no IP*global	1428	5.061	4.396	0.000	14.055
Ln(Deaths)*lower middle income*no IP*neglected	1428	0.850	2.542	0.000	12.039
Ln(Deaths)*low income*IP*global	1428	3.669	3.754	0.000	12.523
Ln(Deaths)*low income*IP*neglected	1428	0.580	1.941	0.000	10.418
Ln(Deaths)*low income*no IP*global	1428	4.652	3.561	0.000	12.473
Ln(Deaths)*low income*no IP*neglected	1428	0.767	2.240	0.000	10.886

The unit of observation is a disease-year for all variables except total deaths in disease/country/year. Summary statistics are calculated for HIV defined as a neglected disease and IP protection as TRIPS compliant. Multiple imputation methods were used to complete missing observations on deaths, as described in the text.

Table 2: Negative binomial regressions of Y = number of new Phase I trials in disease-year

Variable	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Marginal Effect
Ln(Total Deaths)	0.035**				0.1330
	(0.003)				
Ln(Deaths)*global disease		0.034**			0.1296
		(0.003)			
Ln(Deaths)*neglected disease		0.029**			0.1094
		(0.004)			
Ln(Deaths)*IP*global disease			0.068**		0.2517
			(0.006)		
Ln(Deaths)*IP*neglected disease			0.057**		0.2124
			(0.008)		
Ln(Deaths)*no IP*global disease			-0.007		-0.0278
			(0.007)		
Ln(Deaths)*no IP*neglected disease			-0.005		-0.0198
			(0.009)		
Ln(Deaths)*high income*IP*global				0.357**	1.0791
				(0.030)	
Ln(Deaths)*high income*IP*neglected				0.294**	0.8902
				(0.049)	
Ln(Deaths)*high income*no IP*global				0.086*	0.2623
				(0.048)	

Ln(Deaths)*high income*no	-0.168**	-0.5073
IP*neglected	(0.076)	
Ln(Deaths)*upper middle	-0.050**	-0.1535
income*IP*global	(0.020)	
Ln(Deaths)*upper middle	0.074	0.2240
income*IP*neglected	(0.171)	
Ln(Deaths)*upper middle income*no	-0.111**	-0.3376
IP*global	(0.049)	
Ln(Deaths)*upper middle income*no	0.007	0.0229
IP*neglected	(0.089)	
Ln(Deaths)*lower middle	0.026	0.0802
income*IP*global	(0.045)	
Ln(Deaths)*lower middle	-0.000	-0.0004
income*IP*neglected	(0.218)	
Ln(Deaths)*lower middle income*no	-0.046	-0.1404
IP*global	(0.043)	
Ln(Deaths)*lower middle income*no	0.190*	0.5753
IP*neglected	(0.101)	
Ln(Deaths)*low income*IP*global	-0.048	-0.1462
	(0.034)	
Ln(Deaths)*low income*IP*neglected	-0.083	-0.2522
	(0.129)	
Ln(Deaths)*low income*no IP*global	-0.031	-0.0955
	(0.025)	

Ln(Deaths)*low income*no IP*neglected				-0.230**	-0.6952
				(0.056)	
Treatments in 1990	0.056**	0.056**	0.058**	0.051**	
	(0.002)	(0.002)	(0.002)	(0.002)	
Intercept			-		
	-1.57**	-1.50**	0.601**	-2.20**	
	(0.217)	(0.220)	(0.259)	(0.316)	
Number of Observations Used	1428	1428	1428	1428	
Log likelihood	19218.1	19220.1	19241.5	19387.4	

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 3: Robustness to lagged measures of market size

Variable	Eq. 1	Eq. 2	Eq. 3	Eq. 4	Marginal Effect
Ln(Total Deaths)	0.057**				0.1321
	(0.002)				
Ln(Deaths)*global disease		0.034**			0.1284
		(0.002)			
Ln(Deaths)*neglected disease		0.028**			0.1069
		(0.004)			
Ln(Deaths)*IP*global disease			0.065**		0.2421
			(0.006)		
Ln(Deaths)*IP*neglected disease			0.055**		0.2055
			(0.009)		
Ln(Deaths)*no IP*global disease			0.003		0.0143
			(0.006)		
Ln(Deaths)*no IP*neglected disease			0.002		0.0109
			(0.009)		
Ln(Deaths)*high income*IP*global				0.353**	1.0422
				(0.033)	
Ln(Deaths)*high income*IP*neglected				0.342**	1.0098
				(0.060)	
Ln(Deaths)*high income*no IP*global				0.145**	0.4289
				(0.043)	

Ln(Deaths)*high income*no	-0.142*	-.4208
IP*neglected	(0.073)	
Ln(Deaths)*upper middle	-0.019	-.0578
income*IP*global	(0.016)	
Ln(Deaths)*upper middle	-0.042	-.1254
income*IP*neglected	(0.176)	
Ln(Deaths)*upper middle income*no	-0.162**	-.4797
IP*global	(0.045)	
Ln(Deaths)*upper middle income*no	-0.207**	-.6117
IP*neglected	(0.087)	
Ln(Deaths)*lower middle	0.024	0.0706
income*IP*global	(0.045)	
Ln(Deaths)*lower middle	0.088	0.2619
income*IP*neglected	(0.206)	
Ln(Deaths)*lower middle income*no	-0.078	-.2313
IP*global	(0.047)	
Ln(Deaths)*lower middle income*no	0.411**	1.2126
IP*neglected	(0.105)	
Ln(Deaths)*low income*IP*global	-0.037	-.1097
	(0.042)	
Ln(Deaths)*low income*IP*neglected	-0.113	-.3342
	(0.119)	
Ln(Deaths)*low income*no IP*global	-0.028	-.0845
	(0.023)	

Ln(Deaths)*low income*no IP*neglected				-0.349**	-1.030
				(0.058)	
Treatments in 1990	0.035**	0.057**	0.059**	0.049**	
	(0.002)	(0.002)	(0.002)	(0.002)	
Intercept	-1.58**	-1.52**	-0.936**	-2.01**	
	(0.213)	(0.216)	(0.246)	(0.291)	
Number of Observations Used	1428	1428	1428	1428	
Log likelihood	19222.9	19225.3	19237.8	19400.6	

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 4: Robustness to IP definition

Variable	TRIPS	Hamdan	Ginarte-Park
Ln(Deaths)*high income*IP*global	0.357**	0.481**	0.418**
	(0.030)	(0.051)	(0.033)
Ln(Deaths)*high income*IP*neglected	0.294**	0.224	0.223**
	(0.049)	(0.183)	(0.051)
Ln(Deaths)*high income*no IP*global	0.086*	0.145**	0.027
	(0.048)	(0.061)	(0.031)
Ln(Deaths)*high income*no IP*neglected	-0.168**	-0.101	-0.047
	(0.076)	(0.185)	(0.060)
Ln(Deaths)*upper middle income*IP*global	-0.050**	-0.051**	-0.058**
	(0.020)	(0.019)	(0.021)
Ln(Deaths)*upper middle income*IP*neglected	0.074	-0.016	0.049
	(0.171)	(0.084)	(0.139)
Ln(Deaths)*upper middle income*no IP*global	-0.111**	0.039	-0.038
	(0.049)	(0.052)	(0.040)
Ln(Deaths)*upper middle income*no	0.007	-0.086	-0.023
IP*neglected	(0.089)	(0.088)	(0.055)
Ln(Deaths)*lower middle income*IP*global	0.026	-0.009	0.015
	(0.045)	(0.033)	(0.058)
Ln(Deaths)*lower middle income*IP*neglected	-0.000	0.009	0.103
	(0.218)	(0.089)	(0.175)

Ln(Deaths)*lower middle income*no IP*global	-0.046	-0.468**	-0.140**
	(0.043)	(0.056)	(0.039)
Ln(Deaths)*lower middle income*no	0.190*	0.291*	0.160*
IP*neglected	(0.101)	(0.143)	(0.079)
Ln(Deaths)*low income*IP*global	-0.048	0.009	0.002
	(0.034)	(0.022)	(0.036)
Ln(Deaths)*low income*IP*neglected	-0.083	-0.063	-0.215**
	(0.129)	(0.051)	(0.075)
Ln(Deaths)*low income*no IP*global	-0.031	0.026	-0.029
	(0.025)	(0.028)	(0.024)
Ln(Deaths)*low income*no IP*neglected	-0.230**	-0.270**	-0.165*
	(0.056)	(0.072)	(0.077)
Treatments in 1990	0.051**	0.050**	0.052**
	(0.002)	(0.002)	(0.002)
Intercept	-2.20**	-1.62**	-2.11**
	(0.316)	(0.291)	(0.302)
Number of Observations Used	1428	1428	1428
Log likelihood	19387.4	19430.1	19394.9

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 5: Robustness to HIV classification

Variable	Neglected	Global	Omitted
Ln(Deaths)*high income*IP*global	0.357**	0.397**	0.380**
	(0.030)	(0.030)	(0.030)
Ln(Deaths)*high income*IP*neglected	0.294**	0.215**	0.218**
	(0.049)	(0.072)	(0.071)
Ln(Deaths)*high income*no IP*global	0.086*	0.035	0.069
	(0.048)	(0.043)	(0.048)
Ln(Deaths)*high income*no IP*neglected	-0.168**	-0.272**	-0.267**
	(0.076)	(0.095)	(0.095)
Ln(Deaths)*upper middle income*IP*global	-0.050**	-0.056**	-0.052**
	(0.020)	(0.020)	(0.020)
Ln(Deaths)*upper middle income*IP*neglected	0.074	0.087	0.086
	(0.171)	(0.178)	(0.176)
Ln(Deaths)*upper middle income*no IP*global	-0.111**	-0.051	-0.103**
	(0.049)	(0.045)	(0.050)
Ln(Deaths)*upper middle income*no	0.007	0.035	0.028
IP*neglected	(0.089)	(0.091)	(0.091)
Ln(Deaths)*lower middle income*IP*global	0.026	0.012	0.012
	(0.045)	(0.044)	(0.045)
Ln(Deaths)*lower middle income*IP*neglected	-0.000	0.090	0.090
	(0.218)	(0.260)	(0.257)
	-0.046	-0.048	-0.042

Ln(Deaths)*lower middle income*no IP*global	-0.046	-0.048	-0.042
	(0.043)	(0.042)	(0.043)
Ln(Deaths)*lower middle income*no	0.190*	0.145	0.135
IP*neglected	(0.101)	(0.115)	(0.116)
Ln(Deaths)*low income*IP*global	-0.048	-0.057*	-0.050
	(0.034)	(0.031)	(0.034)
Ln(Deaths)*low income*IP*neglected	-0.083	-0.209	-0.211
	(0.129)	(0.204)	(0.203)
Ln(Deaths)*low income*no IP*global	-0.031	-0.050**	-0.027
	(0.025)	(0.023)	(0.025)
Ln(Deaths)*low income*no IP*neglected	-0.230**	-0.022	-0.020
	(0.056)	(0.089)	(0.089)
Treatments in 1990	0.051**	0.051**	0.051**
	(0.002)	(0.002)	(0.002)
Intercept	-2.20**	-2.55**	-2.44**
	(0.316)	(0.323)	(0.330)
Number of Observations Used	1428	1428	1411
Log likelihood	19387.4	19392.0	18970.2

* = significant at 5%, ** = significant at 1%. Standard errors are clustered by disease and adjusted for use of multiple imputation. Year fixed effects are included in all specifications.

Table 6: Summary of tests of coefficients

	Baseline	Lagged market size	Ginarte-Park	Hamden	HIV as global	Excluding HIV
IP vs no IP, high income, neglected	0.47**	0.52**	0.21	0.33**	0.43**	0.43**
IP vs. no IP, high income, global	0.26**	0.21**	0.30**	0.42**	0.32**	0.29**
Global vs. neglected, high income, IP	0.04	-0.00	0.28*	0.18**	0.19**	0.18**
Global vs. neglected, high income, no IP	0.25**	0.30**	0.20	0.09	0.30**	0.31**
IP vs no IP, upper middle income, neglected	0.05	0.13	0.02	0.05	0.06	0.07
IP vs. no IP, upper middle income, global	0.09	0.16**	-0.11*	-0.05	0.04	0.07
Global vs. neglected, upper middle income, IP	-0.11	0.03	-0.01	-0.09	-0.13	-0.12
Global vs.	-0.14	0.00	0.12	0.01	-0.11	-0.13

neglected, upper middle income, no IP						
IP vs no IP, lower middle income, neglected	-0.16	-0.25	-0.16	-0.07	-0.05	-0.04
IP vs. no IP, lower middle income, global	0.06	0.13**	0.55**	0.19**	0.04	0.04
Global vs. neglected, lower middle income, IP	0.08	-0.00	-0.01	-0.01	0.01	0.01
Global vs. neglected, lower middle income, no IP	-0.14	-0.39**	-0.73**	-0.29**	-0.09	-0.08
IP vs. no IP, low income, neglected	0.15	0.24	0.23**	-0.00	-0.16	-0.17
IP vs. no IP, low income, global	0.01	0.01	0.00	0.04	0.02	0.00
Global vs. neglected, low income, IP	-0.03	-0.00	0.00	0.11	0.04	0.04

Global vs. neglected, low income, no IP	0.10	0.22**	0.24**	0.06	-0.14	-0.13

* = significant at 5%, ** = significant at 1%. Wald tests of coefficients corresponding to Equation 4 for various specifications.

Appendix A: Disease list; * indicates a neglected disease category

Cause of death		ICD10 codes
Certain infectious and parasitic diseases	Cholera*	A00
	Diarrhoea and gastroenteritis of presumed infectious origin	A09
	Other intestinal infectious diseases (includes typhoid)*	A01-A08
	Respiratory tuberculosis*	A15-A16
	Other tuberculosis*	A17-A19
	Plague	A20
	Tetanus	A33-A35
	Diphtheria	A36
	Whooping cough	A37
	Meningococcal infection	A39
	Septicaemia	A40-A41
	Infections with a predominantly sexual mode of transmission	A50-A64
	Acute poliomyelitis	A80
	Rabies	A82
	Yellow fever	A95
	Other arthropod-borne viral fevers and viral haemorrhagic fevers*	A90-A94, A96-A99

	Measles	B05
	Viral hepatitis	B15-B19
	Human immunodeficiency virus [HIV] disease*	B20-B24
	Malaria*	B50-B54
	Leishmaniasis*	B55
	Trypanosomiasis*	B56-B57
	Schistosomiasis	B65
	Remainder of certain infectious and parasitic diseases (includes leprosy, trachoma and Buruli ulcer)*	A21-A32, A38, A42-A49, A65-A79, A81, A83-A89, B00-B04, B06-B09, B25-B49, B58-B64, B66-B94, B99
Neoplasms	Malignant neoplasm of lip, oral cavity and pharynx	C00-C14
	Malignant neoplasm of oesophagus	C15
	Malignant neoplasm of stomach	C16
	Malignant neoplasm of colon, rectum and anus	C18-C21
	Malignant neoplasm of liver and intrahepatic bile ducts	C22
	Malignant neoplasm of pancreas	C25
	Malignant neoplasm of larynx	C32

Malignant neoplasm of trachea, bronchus and lung	C33-C34
Malignant melanoma of skin	C43
Malignant neoplasm of breast	C50
Malignant neoplasm of cervix uteri	C53
Malignant neoplasm of other and unspecified parts of uterus	C54-C55
Malignant neoplasm of ovary	C56
Malignant neoplasm of prostate	C61
Malignant neoplasm of bladder	C67
Malignant neoplasm of meninges, brain and other parts of central nervous system	C70-C72
Non-Hodgkin's lymphoma	C82-C85
Multiple myeloma and malignant plasma cell neoplasms	C90
Leukaemia	C91-C95
Remainder of malignant neoplasms	C17, C23-C24, C26-C31, C37-C41, C44-C49, C51-C52, C57-C60, C62-C66,C68-C69,C73-C81,C88,C96-C97
Remainder of neoplasms	D00-D48

Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Anaemias	D50-D64
	Remainder of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D65-D89
Endocrine, nutritional and metabolic diseases	Diabetes mellitus	E10-E14
	Malnutrition	E40-E46
	Remainder of endocrine, nutritional and metabolic diseases	E00-E07, E15-E34, E50-E88
	Mental and behavioural disorders	F01-F99
	Mental and behavioural disorders due to psychoactive substance use	F10-F19
	Remainder of mental and behavioural disorders	F20-F99
Diseases of the nervous system	Meningitis*	G00, G03
	Alzheimer's disease	G30
	Remainder of diseases of the nervous system	G04-G25, G31-G98
	Diseases of the eye and adnexa	H00-H57
	Diseases of the ear and mastoid process	H60-H93
Diseases of the		

circulatory system	Acute rheumatic fever and chronic rheumatic heart diseases*	I00-I09
	Hypertensive diseases	I10-I13
	Ischaemic heart diseases	I20-I25
	Other heart diseases	I26-I51
	Cerebrovascular diseases	I60-I69
	Atherosclerosis	I70
	Remainder of diseases of the circulatory system	I71-I99
Diseases of the respiratory system	Influenza	J10-J11
	Pneumonia*	J12-J18
	Other acute lower respiratory infections	J20-J22
	Chronic lower respiratory diseases	J40-J47
	Remainder of diseases of the respiratory system	J00-J06, J30-J39, J60-J98
Diseases of the digestive system	Gastric and duodenal ulcer	K25-K27
	Diseases of the liver	K70-K76
	Remainder of diseases of the digestive system	K00-K22, K28-K66, K80-K92
	Diseases of the skin and subcutaneous tissue	L00-L98
	Diseases of the musculoskeletal system and connective tissue	M00-M99

Diseases of the genitourinary system	Glomerular and renal tubulo-interstitial diseases	N00-N15
	Remainder of diseases of the genitourinary system	N17-N98
Pregnancy, childbirth and the puerperium	Pregnancy with abortive outcome	O00-O07
	Other direct obstetric deaths	O10-O92
	Indirect obstetric deaths	O98-O99
	Remainder of pregnancy, childbirth and the puerperium	O95-O97
	Certain conditions originating in the perinatal period	P00-P96
	Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99

Appendix B: Country list

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Afghanistan	Low	Least developed	Observer				
Albania	Low		Member	2000	2000		
	Lower						
Algeria	Middle		Observer				1985
Andorra	High		Observer				
Angola	Low	Least developed	Member	1996	2016		*
	Upper						
Antigua and Barbuda	Middle	Developing	Member	1995	2000		
	Upper						
Argentina	Middle	Developing	Member	1995	2000	1996	2000
Armenia	Low		Member	2003	2003		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Aruba	High						
Australia	High		Member	1995	1995		1990
Austria	High		Member	1995	1995		1985
Azerbaijan	Low		Observer				
Bahamas, The	High		Observer				
	Upper						
Bahrain	Middle	Developing	Member	1995	2000		*
Bangladesh	Low	Least developed	Member	1995	2016	*	
	Upper						
Barbados	Middle	Developing	Member	1995	2000		
	Lower						
Belarus	Middle		Observer				

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Belgium	High		Member	1995	1995		1985
	Lower						
Belize	Middle	Developing	Member	1995	2000	2000	
Benin	Low	Least developed	Member	1996	2016		*
Bermuda	High						
Bhutan	Low	Least developed	Observer				
	Lower						
Bolivia	Middle	Developing	Member	1995	2000	2000	1995
Bosnia and							
Herzegovina	Low		Observer				
	Lower						
Botswana	Middle	Developing	Member	1995	2000		2000

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Brazil	Upper Middle	Developing	Member	1995	2000	2001	2000
Brunei Darussalam	High	Developing	Member	1995	2000		
Bulgaria	Lower Middle		Member	1996	1996		2000
Burkina Faso	Low	Least developed	Member	1995	2016		*
Burundi	Low	Least developed	Member	1995	2016		*
Cambodia	Low	Least developed	Member	2004	2016		
Cameroon	Low	Developing	Member	1995	2000		*
Canada	High		Member	1995	1995		1990
Cape Verde	Lower Middle	Least developed	Member	2008	2016		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Cayman Islands	High						
Central African Republic	Low	Least developed	Member	1995	2016		*
Chad	Low	Least developed	Member	1996	2016		*
Chile	Upper Middle	Developing	Member	1995	2000	2005	2000
China	Low	Developing	Member	2001	2001		2005
Colombia	Lower Middle	Developing	Member	1995	2000	2000	1995
Comoros	Low	Least developed	Observer				
Congo, Dem. Rep.	Low	Least developed	Member	1997	2016		*
Congo, Rep.	Low	Developing	Member	1997	2000		*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Costa Rica	Lower Middle	Developing	Member	1995	2000	2000	*
Côte d'Ivoire	Low	Developing	Member	1995	2000	2000	*
Croatia	Upper Middle		Member	2000	2000		
Cuba	Lower Middle	Developing	Member	1995	2000		
Cyprus	High	Developing	Member	1995	2000		*
Czech Republic	Upper Middle		Member	1995	1995		*
Denmark	High		Member	1995	1995		1985
Djibouti	Lower	Least developed	Member	1995	2016		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
	Middle Lower						
Dominica	Middle Lower	Developing	Member	1995	2000	*	
Dominican Republic	Middle Lower	Developing	Member	1995	2000		*
Ecuador	Middle Lower		Member	1996	2000		1995
Egypt, Arab Rep.	Middle Lower	Developing	Member	1995	2000	2006	*
El Salvador	Middle	Developing	Member	1995	2000		1995
Equatorial Guinea	Low	Least developed	Observer				

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Eritrea	Low	Least developed					
	Lower						
Estonia	Middle	Developing	Member	1999	2000		
Ethiopia	Low	Least developed	Observer				*
	Lower						
Fiji	Middle	Developing	Member	1996	2000		*
Finland	High		Member	1995	1995		1995
France	High		Member	1995	1995		1985
	Upper						
Gabon	Middle	Developing	Member	1995	2000	*	*
Gambia, The	Low	Least developed	Member	1996	2016		
Georgia	Low		Member	2000	2000		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Germany	High		Member	1995	1995		1985
Ghana	Low	Developing	Member	1995	2000	2003	1995
Greece	Upper Middle		Member	1995	1995		1990
Grenada	Lower Middle	Developing	Member	1996	2000		*
Guatemala	Lower Middle	Developing	Member	1995	2000	2000	2005
Guinea	Low	Least developed	Member	1995	2016		
Guinea-Bissau	Low	Least developed	Member	1995	2016		
Guyana	Low	Developing	Member	1995	2000	*	*
Haiti	Low	Least developed	Member	1996	2016	1999	*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Honduras	Low	Developing	Member	1995	2000		2000
	Upper						
Hungary	Middle		Member	1995	1995		1995
Iceland	High		Member	1995	1995		*
					2000 (2005		
India	Low	Developing	Member	1995	for pharma)	2005	2005
	Lower						
Indonesia	Middle	Developing	Member	1995	2000	1997	2000
	Lower						
Iran, Islamic Rep.	Middle		Observer				
	Lower						
Iraq	Middle		Observer				

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Ireland	High		Member	1995	1995		1995
Israel	High	Developing	Member	1995	2000		1985
Italy	High		Member	1995	1995		1985
	Lower						
Jamaica	Middle	Developing	Member	1995	2000	*	*
Japan	High		Member	1995	1995		1985
	Lower						
Jordan	Middle		Member	2000	2000		2000
	Lower						
Kazakhstan	Middle		Observer				
Kenya	Low	Developing	Member	1995	2000	2001	2005
Kiribati	Lower	Least developed					

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
	Middle Lower						
Korea, Dem. Rep.	Middle						
Korea, Rep.	High	Developing	Member	1995	2000	1998	1985
Kuwait	High	Developing	Member	1995	2000		
Kyrgyz Republic	Low		Member	1998	1998		
Lao PDR	Low	Least developed	Observer				
Latvia	Lower Middle		Member	1999	1999		
Lebanon	Lower Middle		Observer				
Lesotho	Lower	Least developed	Member	1995	2016		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Liberia	Middle Low	Least developed					*
Libya	Upper Middle		Observer				
Lithuania	Lower Middle		Member	2001	2001		1995
Luxembourg	High		Member	1995	1995		1995
Macao, China	High	Developing	Member	1995	2000		
Macedonia, FYR	Lower Middle		Member	2003	2003		
Madagascar	Low	Least developed	Member	1995	2016	*	*
Malawi	Low	Least developed	Member	1995	2016	*	*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Malaysia	Upper Middle	Developing	Member	1995	2000	2000	1985
Maldives	Lower Middle	Least developed	Member	1995	2016		
Mali	Low	Least developed	Member	1995	2016		*
Malta	Upper Middle	Developing	Member	1995	2000		2000
Marshall Islands	Lower Middle						
Mauritania	Low	Least developed	Member	1995	2016		*
Mauritius	Upper Middle	Developing	Member	1995	2000	2002	*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Mexico	Upper Middle	Developing	Member	1995	2000	1995	2000
Micronesia, Fed. Sts.	Lower Middle						
Moldova	Lower Middle		Member	2001	2001		
Monaco	High						
Mongolia	Low		Member	1997	1997		
Morocco	Lower Middle	Developing	Member	1995	2000	2000	*
Mozambique	Low	Least developed	Member	1995	2016		
Myanmar	Low	Least developed	Member	1995	2016		

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Namibia	Lower Middle	Developing	Member	1995	2000	*	
Nepal	Lower	Least developed	Member	2004	2016		
Netherlands	High		Member	1995	1995		1985
New Zealand	High		Member	1995	1995		1985
Nicaragua	Low	Developing	Member	1995	2000	2000	*
Niger	Low	Least developed	Member	1996	2016		*
Nigeria	Low	Developing	Member	1995	2000	*	*
Norway	High		Member	1995	1995		*
Oman	Upper Middle		Member	2000	2000		
Pakistan	Low	Developing	Member	1995	2000	2005	*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Palau	Upper Middle Lower						
Panama	Middle		Member	1997	1997		2000
Papua New Guinea	Lower Middle	Developing	Member	1996	2000		*
Paraguay	Lower Middle	Developing	Member	1995	2000	2005	2005
Peru	Lower Middle	Developing	Member	1995	2000	1995	1995
Philippines	Lower Middle	Developing	Member	1995	2000	1997	2000

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Poland	Lower Middle	Developing	Member	1995	2000	2000	2000
Portugal	High		Member	1995	1995		*
Qatar	High	Developing	Member	1996	2000		
Romania	Lower Middle	Developing	Member	1995	2000	1995	1995
Russian Federation	Lower Middle		Observer				1995
Rwanda	Low	Least developed	Member	1996	2016		*
Samoa	Lower Middle	Least developed	Observer				
San Marino	High						

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
São Tomé and Principe	Low	Least developed	Observer				
	Upper						
Saudi Arabia	Middle		Member	2005	2005		*
Senegal	Low	Least developed	Member	1995	2016	2000	*
Serbia and Montenegro	Lower						
(former)	Middle		Observer				
	Upper						
Seychelles	Middle		Observer				
Sierra Leone	Low	Least developed	Member	1995	2016		*
Singapore	High	Developing	Member	1995	2000	1995	1990
	Lower						
Slovak Republic	Middle		Member	1995	1995	1995	1995

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Slovenia	Upper Middle		Member	1995	1995		
Solomon Islands	Lower Middle	Least developed	Member	1996	2016		
Somalia	Low	Least developed					*
South Africa	Upper Middle		Member	1995	1995	1997	1985
Spain	High		Member	1995	1995		1995
Sri Lanka	Low	Developing	Member	1995	2000	2003	*
St. Kitts and Nevis	Upper Middle	Developing	Member	1996	2000		
St. Lucia	Upper	Developing	Member	1995	2000	*	

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
	Middle						
St. Vincent and the	Lower						
Grenadines	Middle	Developing	Member	1995	2000	*	
Sudan	Low	Least developed	Observer				*
	Lower						
Suriname	Middle	Developing	Member	1995	2000	*	
	Lower						
Swaziland	Middle	Developing	Member	1995	2000	*	
Sweden	High		Member	1995	1995		1985
Switzerland	High		Member	1995	1995		1985
	Lower						
Syrian Arab Republic	Middle						*

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
Tajikistan	Low		Observer				
Tanzania	Low	Least developed	Member	1995	2016	*	*
	Lower						
Thailand	Middle	Developing	Member	1995	2000	1999	1995
Togo	Low	Least developed	Member	1995	2016		*
	Lower						
Tonga	Middle		Member	2007	2007		
	Upper						
Trinidad and Tobago	Middle	Developing	Member	1995	2000		2000
	Lower						
Tunisia	Middle	Developing	Member	1995	2000		
Turkey	Lower	Developing	Member	1995	2000	1999	1995

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
	Middle						
	Lower						
Turkmenistan	Middle						
Uganda	Low	Least developed	Member	1995	2016	*	*
	Lower						
Ukraine	Middle		Observer				1995
United Arab Emirates	High	Developing	Member	1996	2000		
United Kingdom	High		Member	1995	1995		1985
United States	High		Member	1995	1995		1985
	Upper						
Uruguay	Middle	Developing	Member	1995	2000	2001	2000
Uzbekistan	Lower		Observer				

Country name	1995 Income Level (World Bank)	Self-designation to WTO	WTO status	Year of WTO membership	Year of TRIPS compliance	Hamden Year	Ginarte-Park Year
	Middle Lower						
Vanuatu	Middle Lower	Least developed	Member	2007	2016		
Venezuela, RB	Middle	Developing	Member	1995	2000	1995	1995
Vietnam	Low		Observer		2008		1995
Virgin Islands (U.S.)	High						
Yemen, Rep.	Low	Least developed	Observer				
Zambia	Low	Least developed	Member	1995	2016	*	*
Zimbabwe	Low	Developing	Member	1995	2000		*

Figure 1: Adoption of TRIPS over time by income level

[1] Our definition of "neglected diseases" is described more precisely in Section V.

[2] Many other papers discuss aspects of this controversy. Among many others, these include Cohen and Illingworth (2003), Li (2008), Taubman (2008), Chaudhuri et al (2006) and Lanjouw (2003).

[3] For example, Brazil now requires issuance of a compulsory license prior to parallel importing (Oliveira et al (2004)).

[4] See "Declaration on the TRIPS Agreement and Public Health," available at http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

[5] Patents also may confer strategic advantages on firms by conferring control over a scientific area through 'prospecting' (Kitch 1977, Merges and Nelson 1994), by coordinating through licensing the R&D efforts of subsequent researchers (Arora, Fosfuri and Gambardella 2001, Arora and Gambardella 2010), and by shaping the direction of subsequent R&D effort (Cohen and Malerba 2001, Burt and Lemley 2009, Gambardella and McGahan 2010).

[6] In practice, there is mixed evidence that pharmaceutical firms charge substantially lower prices in developing countries (see Maskus (2001)). There are many possible explanations for this, which this paper does not address. However, differences in prices are an important element of the TRIPS debate because of concerns that high prices in developing countries are the result of patent protection.

[7] Other policies may, of course, also play a role. The use of price controls may constrain pricing and reduce expected profits, even for high-income countries. Stringent regulatory requirements for launching a drug may contribute to country-specific fixed costs.

[8] We have also performed the same analysis on later stages of clinical development and obtained similar results.

[9] Earlier versions of this paper used this single cross-section of DALYs to measure market size. While results presented here are largely consistent with our previous findings, we decided the advantages of the time variation provided in the mortality data outweighed those of DALYs.

[10] Additional details and SAS code are available from the authors. See Rubin (1987) for a complete discussion of methods.

[11] The WHO relies on reports of cause of death from each country. Countries report cause of death using either ICD9 or ICD10 codes during our sample period. However, the WHO cautions that due to differences in reporting across countries, it may not be appropriate to make inter-country comparisons. The WHO also provides data that has been corrected for use in such comparisons (the Global Burden of Disease data), but this is available for a single cross section only. Our results are robust to using this data.

[12] See H.R. 3580, Food and Drug Administration Amendments Act of 2007.

[13] The WTO lists a few countries that joined after 1995 with transition periods that expired in 1999. See http://www.wto.org/english/tratop_e/trips_e/tripfq_e.htm

[14] The results are robust to the use of other elements of the Ginarte-Park index.

[15] We researched the history of disputes for each WTO member and explored other sources of data on IP laws and enforcement such as the US Trade Representative's Watch List and Priority Watch List. We did not incorporate the ad hoc information we obtained about compliance and enforcement because the Watch List is available only after 2000 and the set of countries included is skewed towards those engaged in significant trade with the US (Canada and Italy, for example, appear on the Watch List in some years).

[16] This statement assumes that the revenues within a high-income market are also roughly the same for the two disease types. We lack the data to distinguish between disease revenues within a country income group.

[17] We experimented with different lags and found similar results.

[18] "Pressure Rises on Producer of a Flu Drug," *New York Times*, October 11, 2005.

[19] An AIDS-related death may be coded as a death from pneumonia, for example.