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Investments in Pharmaceuticals Before and After TRIPS

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This paper explores whether the 1994 TRIPS agreement was associated with changes in the level, character and location of projects dedicated to the development of new pharmaceuticals. In theory, the implementation of patent protections increases expected profits from new-drug development. Because the TRIPS agreement strengthened patent protection on pharmaceuticals in developing and least-developed countries, the change in expected profits may have been particularly strong for diseases that are prevalent in these countries. In this research, we distinguish between "neglected diseases," which are prominent in less wealthy nations, and "global diseases," which are present in both wealthy and less wealthy countries. The heart of the analysis is an investigation into how pharmaceutical research organizations responded as TRIPS was implemented across these two categories of disease. We also evaluate whether the harmonization of patent rights across countries that occurred with TRIPS fostered local pharmaceutical activity within developing and least-developed countries as well as partnerships between local and established foreign firms. Using a dataset on drug development projects from 1990-2006, we find evidence of more research on diseases in TRIPS-compliant countries as patent protections were implemented than on diseases in non-TRIPS-compliant countries. However, our results suggest that, while TRIPS may have induced additional pharmaceutical research, the implementation of patent protections was not associated with extensive new research on neglected diseases. The analysis of the location of new research activity yields weak evidence of increased local research and collaboration outside of advanced countries. Thus, the impact of TRIPS is not discernible. Although TRIPS appears to have stimulated a modest amount of drug development on diseases prevalent in TRIPS-compliant countries, this effect was relatively weaker for neglected diseases than global diseases.

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In 1994, the Uruguay Round of GATT negotiations dissolved GATT and established, in its stead, the World Trade Organization (WTO). A condition of membership in the WTO was the implementation of an agreement entitled the "Trade-Related Aspects of Intellectual Property Rights," commonly known as the "TRIPS Agreement." TRIPS required that member nations enact laws on copyrights, trademarks and patents to protect and enforce many forms of intellectual property including trademarks, computer software, publications of various types, and pharmaceuticals. The rationale was that the extension of intellectual-property rights would integrate developing and least-developed countries into the global economy both by reducing the risks to established multinational corporations of operating in these economies and by enhancing the incentives for developing goods with proprietary intellectual content for sale in these markets. The overarching argument for TRIPS was that a unifying set of policies, applicable globally, would promote economic activity.

In particular, the extension of patent protection over pharmaceuticals under TRIPS was intended to protect pharmaceutical companies from the copying, re-exportation, or inappropriate use of existing drugs. The policy was controversial because it was implemented at a time when the prices of life-extending therapies for HIV were high in advanced countries, causing concern that TRIPS would also lead to high prices for such therapies in developing and least-developed countries. Arguments against the TRIPS policy emphasized that the agreement would create strong benefits for pharmaceutical firms in advanced countries. Critics expressed concern that temporary patent monopolies would not be effective at stimulating technology transfer or inducing research on diseases that were relevant to patients in developing and least-developed countries for a range of reasons, including the inability of the poor to pay the prices charged by leading pharmaceutical firms.

Proponents of the TRIPS policy responded by noting that the prospect of higher profits would induce additional research on neglected diseases (which are defined by the World Health Organization as afflictions from which more than 90% of deaths annually occur in poorer countries). 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 purpose of this paper is to evaluate how drug development activities worldwide adjusted in response to the incentives created by TRIPS. The goal is to assess how pharmaceutical research changed in response to the introduction and/or strengthening of patent protection in developing and least-developed countries. The analysis examines how the portfolio of research projects adjusted

across diseases, across countries, and over time. Specifically, we examine whether (1) research activity changed to reflect the composition of diseases in the population of patients that lived in countries that had adopted patent protection under TRIPS, (2) drug development projects involving researchers from newly TRIPS-compliant countries expanded, and (3) new institutions for conducting pharmaceutical research emerged in countries as they became TRIPS-compliant. To address these questions, we use detailed project-level information about pharmaceutical research and development from 1990 through 2006. This data is complemented by disease information from the World Health Organization and by TRIPS-compliance dates from the WTO and the Ginarte-Park index of IP protection.

The results demonstrate that, worldwide and across a broad range of pharmaceutical research organizations, the portfolio of development projects responded to the implementation of patent protections under TRIPS. Projects adjusted to reflect the distribution of diseases among patients that lived in newly TRIPS-compliant countries. However, the adjustment did not occur in proportion to the prevalence of diseases among patients. Proportionately more research occurred on "global diseases" such as cancer and diabetes, which are prevalent in both wealthy and less wealthy countries, than on neglected diseases such as tuberculosis and malaria, which are concentrated in less wealthy countries. This finding is robust across all stages of drug development, different measures of patent protection, and varied definitions of neglected diseases. Possible explanations include that (a) even with patent protection, the expected revenues associated with drugs sold in poorer countries may be insufficient to cover the fixed costs of research and development and/or (b) the research required on some neglected diseases is either too expensive, intractable, or pharmacologically inappropriate to justify even with patent protection and/or (c) the absence of complementary institutions, systems and processes such as clinical diagnostic services and pharmacies for neglected diseases may make distribution difficult. The significant results on global diseases follows the prediction that profits in wealthier countries cover the fixed costs of research, and thus the marginal profits associated with the additional sales into newly TRIPS-compliant countries makes additional research projects worthwhile.

The results on changes in the geography of research suggest that patent protection may yield other types of impact in developing countries. In countries that are TRIPS compliant, the number of drug development projects involving researchers from less wealthy countries, the number of partnerships between firms in advanced and developing countries, and the number of new domestic firms in developing countries that are active in drug development are each higher than in countries that are not TRIPS compliant, although this difference is not robustly significant. This analysis suggests that the implementation of patent protections under TRIPS had heterogeneous effects across countries during the period we study.

The results reported here complement the findings of recent papers in international trade and business. The main antecedent to this analysis, Lanjouw & Cockburn (2001) concluded that in 2001, "It [was] too early to tell…" the effect of TRIPS on "new pills for poor people" (p. 287). It is important to note that this paper examines only the net *gains* from TRIPS for developing and least-developed countries rather than the complex, embedded benefits and costs of the policies. The principal reasons for this are the absence of available information and an appetite in the research and policy communities for broad information about the efficacy of the policy. Several papers highlight the costs in the pharmaceutical and other sectors of implementing TRIPS in developing countries (Chaudhuri et al (2006), McCalman (2004)). Allred & Park (2007) show that the effects of patent protection on research and development differed in developing and developed countries. Generally, this body of work together with the findings here suggest that the extension of patent protections under TRIPS has had nuanced effects that varied by firms, disease category, country, and development level.

Background and Prior Literature

The TRIPS agreement has been controversial since negotiations over it began. Critics argued that the true purpose of the extension of patent rights in developing countries was the generation of monopolistic profits for pharmaceutical companies at the expense of the poor (Westerhaus and Castro (2006)). Proponents responded by observing that patent protection is essential for new drug development by for-profit corporations on any disease (Pollack (2001)).

Recognizing the potential impact of patent monopolies, the WTO later adapted the TRIPS Agreement in five major ways. First, developing countries and countries in transition from central planning could delay the implementation of TRIPS until January 1, 2000, and some won concessions to delay until January 1, 2005 (permitted under Article 65.4 of the WTO). Least-developed countries were initially given until January 1, 2006 to comply, but this deadline was extended in 2005 during the Doha Round to January 1, 2016.

Second, TRIPS allowed several exemptions under which countries could deny patents: (1) if the invention's commercialization would harm human, animal or plant life or health; (2) if the patent covered a specific method for treating humans or animals; and (3) for certain plant and animal inventions (WHO Fact Sheet (2006)).

Third, TRIPS included an exemption called the Bolar provision that allowed 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 exploited by advanced countries (such as Canada), as well as by developing and least-developed countries.

Fourth, the Doha Declaration in 2002 included another important adjustment: A country would be allowed to evoke a "compulsory license" during a period of national health emergency. This meant that a country could require a pharmaceutical company in another WTO country to provide a local manufacturer with a license under emergency circumstances as long as the manufacturer (or the country) compensated the patent holder with a "reasonable" payment (Loff (2002)). This provision was criticized by representatives from least-developed countries as ineffective because of the absence of indigenous manufacturers to which a license could be assigned (Westerhaus and Castro (2006)). It was also criticized by leading pharmaceutical companies for creating an environment that discouraged exports to least-developed countries because the administration of a compulsory license with a reasonable payment could be construed as an attractive alternative to direct export. Compulsory licenses have been rare, with only five issued on drugs for treating HIV (in Brazil,[1] Malaysia, Indonesia, Zambia and Mozambique) despite the health emergencies associated with the HIV epidemic in other countries of sub-Saharan Africa in particular. The discussion over compulsory licenses highlighted the role of absent, complementary institutions such as clinics and pharmacies for administering pharmaceuticals in less wealthy countries.

Fifth, in 2003, the rights of countries in national health emergencies were further strengthened under Paragraph 6 of TRIPS, which allowed "parallel imports" from generic manufacturers and other firms into a country suffering a health emergency if the country did not have the capacity to manufacture indigenously (Khor (2005)). Both of these updates were designed to preserve incentives under the patent system while simultaneously providing options for access by impoverished patients.

The effect of the WTO and TRIPS on trade, welfare and innovation is the subject of many recent papers in the international trade and business literatures. McCalman (2001) estimates that the US benefited more than other countries from the harmonization of patent protection required by TRIPS. Kanwar and Evenson (2003) found evidence that IP rights spurred innovation (or at least investment in research and development) in a sample of 29 countries from 1981-1995. Allred and Park (2007) study innovative activity in a panel of countries and find that while IP rights in developed countries are positively associated with R&D spending and patent applications, these relationships are not evident in developing countries. Qian (2007) finds heterogeneous effects of IP protection in her study of pharmaceutical R&D activities across countries. She demonstrates that patent protection alone does not increase various measures of domestic innovation, and that increasing patent protection beyond a threshold level actually may decrease innovation. In an empirical study, Chaudhuri, Goldberg and Jia (2006) find that the introduction of TRIPS would lead

[1] The Brazil compulsory license was issued in May, 2007.

to a social welfare loss in India because domestic producers, previously making generic versions of drugs under patent outside of India, would be forced to withdraw from the India market.

The available evidence on the efficacy of TRIPS at inducing pharmaceutical innovation on poverty diseases is inconclusive or mixed (Chen and Puttitanun (2002), Chien (2003), Jack and Lanjouw (2003)). Lanjouw and Cockburn (2001) conducted a careful statistical analysis complemented by interviews of pharmaceutical executives in several countries before concluding that the TRIPS policy had not yet yielded demonstrable effects on new-drug development. Lanjouw (2005) reported evidence of a positive relationship between patent protection and drug availability in a country, but against a backdrop of relatively limited distribution of many drugs even in wealthy countries where patent protection has long been established. Delgado, Kyle and McGahan (2008) found little evidence of increased pharmaceutical exports from advanced to least-developed countries after TRIPS implementation.

No prior study of which we are aware has yet examined the research projects of the world's leading pharmaceutical manufacturers directly for evidence of an increased emphasis on poverty diseases after the implementation of TRIPS. Thus, this study's contribution is a complement to prior theoretical and empirical studies that have focused on the incentives in TRIPS (leading examples include Glennerster and Kremer (2000) and Kremer and Glennerster (2004)). We rely on especially detailed data on R&D activity in a particular industry. Unlike most previous papers, we examine not only the level of R&D effort, but its aim by diseases and its composition (i.e., by whether it involves domestic firms and foreign partnerships).

Theory

The effect of TRIPS on the level and direction of pharmaceutical research

The theoretical rationale for conferring a temporary monopoly through patent protection is to create an ex ante incentive for firms to undertake risky research projects on new drug molecules. In theory, profit-seeking firms cannot justify to shareholders the expenditure of research and development resources if the resulting inventions can be imitated easily and if the returns on investment are projected as absent or negative. While firms in other industries may rely on other means to appropriate the profits from their innovations (such as trade secrets or early mover advantage), patents are critical in the pharmaceutical industry (Cohen et al (2000)).

There is substantial evidence that the fixed costs of pharmaceutical research are significant. DiMasi et al. (2004) estimate that developing a new drug requires about $400-500 million, and the time required from project inception to the commercial introduction of a new drug is 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. The existence of substantial fixed costs implies that if expected market size is very small (or, more precisely, if expected revenues are low due either to small quantities or low prices), drug development within profit-seeking enterprises will not take place.

There are a number of studies that find a positive response of pharmaceutical research to an improvement in the expected profits from drug commercialization. For example, Ward and Dranove (1995) find that a 10 percent increase in demand for care in a therapeutic area is associated with a 5-8 percent increase in R&D spending. Finkelstein (2004) examines the response of pharmaceutical firms to the implementation of US federal policies that required childhood vaccination against six diseases. She found that research firms responded to the dramatic increase in forecasted demand by doubling the number of drugs in clinical trial. Acemoglu and Linn (2004) study the relationship between market size, a crude measure of demand, 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. Lichtenberg and Waldfogel (2003) also document the strong relationship between market size and the number of drugs developed for a disease, and find 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 "small market" drugs.

Projected Revenues from Research on Global vs. Neglected Diseases

Patent protection essentially bars imitation during the patent term, and, as a result, generally increases the expected price a patent holder may charge for a successfully commercialized product. Even without any increase in projected prices, the elimination of a threat of imitation may increase the attractiveness of a development project on a disease. The implementation of patent protections under TRIPS in a country also potentially puts the population into "higher price" categories for relevant drugs, with relevance dependant on the disease profile of the country's population. Thus, if a drug is successfully developed, then increases in projected revenue before and after the implementation of patent protection may occur because of greater projected volumes of sales (with the elimination of imitation) or higher projected prices. .

The likelihood of higher projected prices is greater for global than neglected diseases because of changes in the composition of demand. Because wealth differs substantially across countries and the need for particular disease treatments also varies across countries, the expected average price for treatments sold primarily in poor countries is likely to be lower than for drug regimens that are also sold in wealthy countries. In addition, the use of price controls on pharmaceuticals is widespread in both developed and developing countries. If price controls are binding (in that the regulated price is lower than the level preferred by profit-maximizing firm), then expectations of profits will be lower despite patent protections.

Larger projected volumes may be greater for global than neglected diseases even in less wealthy countries because of country-level differences in the infrastructure investment required to deliver pharmaceuticals effectively. Many neglected diseases are particularly prevalent in the most impoverished areas and sub-populations of less-wealthy countries. In these communities, the infrastructure for distributing and administering pharmaceuticals may be ineffective (e.g. a shortage of trained physicians in these communities is a major impediment to treatment). By contrast, many global diseases are diagnosed even in less wealthy countries among a more accessible population of patients. Thus, the projected volume of sales associated with the extension of patent protections in less-wealthy countries may be systematically greater for global than neglected diseases.

Under these conditions, even if patent protection removes the threat of imitation and there is a large population of potential patients for a new drug for a neglected disease, the projected volume of sales may nonetheless be insufficient to justify the fixed costs of development for the treatment. The lower incentive may be exacerbated if the per-pill price of the treatment is also lower. Figure 1 illustrates this idea. For global diseases, with large numbers of deaths and higher expected revenue per patient, projected revenues likely exceed development costs and an increase in patent-protected deaths may induce more R&D investment. For neglected diseases, an expansion in the number of covered deaths may not be sufficient to allow for recovery of development costs.

Projected Fixed Costs of Research on Global vs. Neglected Diseases

Projected profits from research on global and neglected diseases also may differ even after the implementation of TRIPS because of asymmetries associated with the fixed costs of development. This may occur for two reasons. First, for global diseases, much of the fixed costs associated with development may be sunk by the time that decisions are made based on the larger numbers of patients in TRIPS-compliant countries: firms may have employed scientists with expertise in that disease area and set up laboratories dedicated to research in the disease area. By contrast, the fixed costs of new research on neglected diseases may not be either sunk or committed prior to the implementation of TRIPS.

The fixed costs of research on neglected diseases also may be assessed on scientific grounds as pharmacologically inappropriate or simply higher than for global diseases. Table 1 lists the diseases that fall into each category as of this writing.[2] The list of neglected diseases includes afflictions such as leprosy, maternal conditions and Vitamin A deficiency. For some of these

[2] Note that HIV/AIDS is on the borderline of the "neglected" and "global" disease categories because about 90% of worldwide deaths now occur in less wealthy countries. For the period of this study HIV/AIDS was considered a neglected disease and thus we report results with HIV/AIDS in the neglected category, but conduct sensitivity analyses in which the drug is classified in the global category. The results are sensitive to this reclassification as HIV/AIDS accounts for a large portion of research on neglected diseases.

conditions (e.g. Vitamin A deficiency), there may be established effective treatments (e.g., the administration of Vitamin A) and additional R&D is not required. For others (e.g., leprosy), drug therapies may be more expensive to develop than usual because of the demands on basic science; i.e., because little pharmacological research on leprosy has been conducted, the demands for drug discovery are extensive. Thus, the fixed costs of research and/or the relevance of pharmacological solutions may be systematically different for neglected than global diseases, and thus influence projected profits from drug research in each area.[3]

Projected profits

For our empirical analysis, we assume that a pharmaceutical firm invests in a drug development project if it expects positive profits, which depend on patient deaths (the total number of potential patients for the drug, which we measure by the number of deaths per year in a country as identified by the Global Burden of Disease project), the average price per patient, and the expected costs of development. The average price per patient is a function of the number of competing treatments, the number of imitators, the resources and availability of potential payers. Additional costs of delivering treatments to patients may depend on the location of potential patients within the target countries and the presence of complementary institutions. The data required to estimate a sophisticated model of these complex, interacting factors are not available. In particular, we have no direct measure of price, but stipulate that the expected average price is higher for diseases that are common in relatively wealthy countries than for diseases whose burden is concentrated in poor countries, and test for evidence consistent with this prediction. We also lack information on organizational expenditures on variable costs and on development by project, product, and disease. As a result, we estimate a simple, reduced-form model of entry into drug development for disease d in year t where "deaths" is the WHO's estimate of annual deaths from disease d in logs. We use the number of deaths as an approximation of potential market size or demand, consistent with earlier work such as Acemoglu and Linn (2004) and Finkelstein (2005).

Our empirical strategy is to conduct a differences-in-differences analysis in which we compare changes in the response before and after TRIPS across the two categories of disease to draw broad conclusions about the evidence on the response in each category. There are limitations of this approach. Ideally, we would have data on disease severity over time in each country as an additional source of variance. We instead rely on changes related to the adoption of IP protection that occurred in different years and in countries with different disease profiles. Consider the hypothetical case of only two countries and two diseases in the world where neither country has patent protection. One country has 1000 deaths per year from disease 1 and no deaths per year from

[3] The list of global diseases in Table 1also includes several categories for which pharmacological research may not be appropriate, e.g., "dental disorders" and "violent injuries and war."

disease 2. The other country has the opposite pattern of illness: it has no deaths per year from disease 1 and 1000 deaths per year from disease 2. Thus, the total number of deaths in countries without IP protection is 2000, and the total number of deaths in countries with IP protection is 0. Suppose the first country then adopts patent protection and becomes TRIPS compliant. The total number of deaths from disease 1 in countries without IP protection is now 0, and the total number of deaths from disease 2 in countries without IP protection continues at 1000. The total number of deaths from disease 1 in countries with IP protection is 1000, and the total number of deaths from disease 2 in countries with IP protection is 0. If patent protection raises the expected profits associated with drug development, then we should see an increase in the number of new drug development projects for disease 1 relative to disease 2, because disease 1 is disproportionately patent-protected.

Our empirical specification is:

$$Y_{dt} = \beta_0 + \beta_1(\text{Neglected}_d * IP_t) + \beta_2(\text{Global}_d * IP_t) + \beta_3(\text{Neglected}_d * \text{no } IP_t) + \beta_4(\text{Global}_d * \text{no } IP_t) + \text{controls} + \varepsilon_{dt}$$

where Y_{dt} is the count of drug development projects initiated in year *t*, targeted at disease *d*. (The unit of observation is a disease-year.) Neglected_d*IP_t is the log of the number of deaths in disease *d* in countries with IP protection in year *t*, if *d* is a neglected disease; Global_d*IP_t is the (log of) deaths in disease d in countries with IP protection in year *t*, if *d* is a global disease; $\text{Neglected}_d*\text{no } IP_t$ is the log of the number of deaths in disease d in countries without IP protection in year *t*, if *d* is a neglected disease; and $\text{Global}_d*\text{no } IP_t$ is the log of the number of deaths in disease d in countries without IP protection in year *t*, if *d* is a global disease. As is standard in the literature, these variables are taken in logs to account for potential non-linearities in the relationships between marginal projected revenues and the incentive to undertake a research project. Control variables include the number of established drug treatments for disease d in 1990 (the first year of our study) and year fixed effects. Because the dependent variable is a count of projects, we estimate Poisson and negative binomial models.

The hypotheses:

H1: $\beta_1 > \beta_3$ and H2: $\beta_2 > \beta_4$

The implementation of IP protection under TRIPS puts the country's population with a specific disease into a higher-priced category of potential patients for newly developed, relevant drugs. Thus, we hypothesize a greater sensitivity in the number of research projects to the patient population in TRIPS-compliant countries than in non-compliant countries. We expect this relationship for both neglected and global diseases.

H3: $\beta_1 < \beta_2$

We expect the sensitivity of new research projects in TRIPS-compliant countries to be greater for global than neglected diseases because of a larger volume of patients in high-priced categories for global diseases.

H4: $\beta_3 = 0$ and H5: $\beta_4 = 0$

If a drug is easily imitated in the absence of patent protection, then an increase in deaths without patent protection should not induce significant additional development effort. This should be true for both global and neglected diseases.

We exploit one additional feature of research efforts in this setting. Drug development has several distinct phases: preclinical work, followed by Phase 1, Phase 2 and Phase 3 clinical trials. The costs of research and development through these successive phases are fixed and sunk before revenues are realized. However, costs increase at each development phase, and decisions to continue occur between stages. Increases in projected profits influence decisions by a firm to continue or stop development after each phase. Imagine a marginal project that might be terminated before expensive Phase 3 trials due to expectations of low sales. If the projected demand for patent-protected sales for the project's target drug were to increase unexpectedly due to TRIPS implementation during the clinical phase, then the sponsoring organization may elect to continue investing rather than to terminate. Since we observe the decision to begin clinical trials as well as to continue at each phase, we can examine the effect of TRIPS on not only new drug development projects (those that enter Phase 1 trials), but existing trials as well (those that progress to Phase 2 and 3). Our empirical analysis tests our hypotheses for all three phases.[4]

The effect of TRIPS on pharmaceutical discovery activity by country

TRIPS and the introduction of formal IP protection may have other effects on developing and least-developed countries such as stimulation of a domestic, research-intensive pharmaceutical industry. This could occur because patent protection increases the returns to R&D investment for the domestic market, and because membership in the WTO facilitates the exportation of drugs from the country. Arora et al. (2008) provide compelling evidence of such a response by domestic Indian firms after 1995, when India began to implement patent reform in anticipation of TRIPS compliance. In addition, the 2002 Doha Declaration provided other motivations for least-developed and developing countries to develop local research and manufacturing capacity to facilitate the effectiveness of compulsory licenses should they become necessary. Jump-starting the development of local capabilities also created marginal incentives for the development of clinical, pharmacy, and other systems for effective drug distribution. Limitations on data availability prevent us from

[4] We analyze the entire portfolio of worldwide projects conducted in each phase in parallel models; in other words, we do not track specific projects through successive phases of development.

modeling all elements of the system, although we can identify the initial instance of drug development activity by an organization, which we roughly construe as "entry" into drug research. Similarly we can identify the number of drug research projects in which a domestic firm participates, and thus can evaluate increases in the levels of domestic research activity to in countries that become TRIPS-compliant during the period of study.

Available data also allow us to study a third element of local systems in newly TRIPS-compliant countries for conducting pharmaceutical research: partnerships involving researchers in both wealthy and less wealthy countries. The objectives of TRIPS include the transfer of knowledge from developed to developing countries. Firms outside the newly compliant country may be motivated to collaborate in research, distribution, or other activities with locally based companies that must conform to enforceable local patent requirements. Patent protection is generally understood as essential for the effective functioning of "markets for technology" (Arora et al. (2001)). Branstetter et al. (2006) and Park and Lippoldt (2003) document that foreign direct investment (FDI) is positively associated with the introduction of IP protection in a country. While we lack detailed information on each firm's direct investment by target country, we observe joint drug development efforts (i.e., research alliances) and the location of each firm in the alliance, which allows identification of a foreign organization's activity in target countries.

Using this available information about pharmaceutical activity in each country, we explore the impact of IP rights in three ways. First, we analyze the number of new domestic firms in pharmaceutical research and development in country *c* in year *t*. Second, we examine the number of research projects with participation by domestic firms in country *c* in year *t*. Finally, we look at the number of research projects in which domestic firms in country *c* and firms in developed countries are partners in year *t*. For this analysis, our unit of observation is a country-year, and our empirical specification is:

$$Y_{ct} = \sum_{i=1}^{4} \beta_i IP_{ct} * \text{Income\_level}_c + \text{controls} + \varepsilon_{ct}$$

where Y_{ct} is one of the three measures defined above. IP_{ct} is a dummy variable capturing whether country *c* had pharmaceutical IP protection or was TRIPS-compliant in year *t*. Income_level is a dummy variable corresponding to whether country c is categorized as high income, upper middle income, lower middle income, or low income; our specification allows for the effect of IP to differ by country income level. Controls include year effects and country population. Because the dependent variable is a count, we estimate negative binomial models.

Based on the above discussion, we hypothesize that $\beta_i > 0$ for each specification of the dependent variable, i.e.:

H6: Within an income group, the number of domestic pharmaceutical firms new to research is higher in countries with IP protection.

H7: Within an income group, the number of research projects involving domestic firms is higher in countries with IP protection.

H8: Within an income group, the number of research projects involving both domestic firms and firms from high-income countries is higher in countries with IP protection.

Data

Pharmaceutical research projects

The primary source of information on pharmaceutical research is the IMS R&D Focus dataset. Typically used by pharmaceutical firms to monitor the research activities of competitors, it 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. For every organization that participates in a drug's development, the country of headquarters is reported. Thus, from the IMS R&D Focus reports, we construct a rich dataset on diseases by year that describes the total number of projects at each phase of development, the number of projects in which firms headquartered in a particular country are participating, and the number of firms headquartered in a country that are newly active in drug development.

Table 2 shows the number of projects during the period 1990-2006. Because a project may target more than one disease, we treat each project-disease as a separate observation. Projects in active development are defined as those that have entered Phase 1 trials but have not launched or been discontinued. The chart demonstrates that both the number of projects in development and R&D spending grew during this period. The number of research projects on neglected diseases grew at a lower rate than research projects on global diseases.

Over 4500 individual organizations were active in drug development between 1990 and 2006 and are represented in the dataset. About 17% of these are universities, foundations, or other non-profit organizations. On average, the organizations were involved in 25 projects over the period, although this figure varies substantially as several firms were active in more than 2000 projects. Table 3 shows the number of for-profit firms headquartered in each country and the average number of projects in which those firms participated for countries that had at least 10 for-profit firms. The

US is the country of headquarters for more than 40% of the firms and accounts for about 50% of worldwide expenditures on pharmaceutical research.

Disease data

We use the World Heath Organization's 2003 estimates of deaths by disease and country to identify the potential patients that would be eligible to receive treatment from a successful drug for the disease. Ideally, the WHO would report estimates of deaths by disease and country for every year, but, because of resource constraints, data collection takes place at irregular intervals and inconsistently. As a result, analysis of changes within a country over time is unreliable. The count of deaths is also not an ideal measure of the number of potential patients for a variety of reasons. For example, two countries may have identical prevalence of a disease, but a country with available treatments and a good health infrastructure may have fewer deaths from that disease. Despite these limitations, we believe this dataset to be the best available for the large number of countries we examine here.

There is substantial debate regarding the precise definition of a neglected disease, and in particular whether a disease for which an effective treatment exists should be considered neglected. Lanjouw and Cockburn (2000) focused on those diseases for which 99% of the burden falls on developing or least-developed countries. The World Health Organization (WHO) explicitly lists neglected tropical diseases on its website. Our categorization of diseases is described in Table 1, and includes all conditions labeled by the WHO as communicable, maternal, perinatal and nutritional conditions. These conditions are also those for which more than 90% of diagnosed deaths occur in developing or least-developed countries over the period of our study. The list includes HIV, tuberculosis, malaria, river blindness, and leprosy. This categorization includes all the neglected tropical diseases identified by the WHO and those considered by Lanjouw and Cockburn (2000).

Global diseases may be prevalent in least-developed countries but also arise in developing and high-income countries, and include cardiovascular disease, neurological disorders, and cancer. Because a high proportion of deaths from HIV (relative to other neglected diseases) occurs outside of least-developed countries, we conducted sensitivity analyses to analyze whether our results turn on the classification of HIV as a neglected disease (as noted earlier, HIV was reclassified in 2008 by the World Health Organization as a global disease because of changes in the pattern of deaths). Figure 2 compares development efforts in HIV to other neglected diseases over our sample period.

Implementation of the analysis requires matching the project-level research areas in the IMS R&D Focus dataset to the disease categories used by the WHO. This is generally straightforward and was validated by physician review: a project whose indication is "bladder cancer" would be assigned to the WHO category "cancer."

TRIPS compliance and other measures of IP protection

The World Trade Organization's rules for TRIPS compliance depend on the standing of a country as least-developed, developing or advanced. Least-developed countries are those defined by the United Nations. All other WTO members defined themselves as either developing or advanced at the time of membership application.[5].

At the time of TRIPS ratification in 1994 and adoption at the beginning of 1995, the WTO announced a number of rules for compliance among member countries. We use these rules to estimate the dates of compliance for every country. We also researched every country for a history of disputes, and adjusted the estimated date of compliance if the country was identified through the WTO dispute-resolution process as non-compliant in TRIPS in violation of the rules. In these instances, we inspected the details of the documents in the dispute resolution process to estimate the ultimate date of compliance. Some countries were not compliant during the entire period under study.

The rules for compliance declared by the WTO in 1994 were subsequently updated for least-developed and developing countries (as noted earlier), but were consistent over time for developed countries. Countries that identified themselves as "developed" had a year to comply with the patent-protection requirements under TRIPS. For these countries, we estimated compliance at 1995. A country that was developed or advanced and joined the WTO subsequent to 1995 was assumed as compliant 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. Thus, for countries that were least-developed members on January 1, 1995, we estimate the date of compliance as January 1, 2006. Under the Doha round, the date for compliance was further extended until 2016. Thus, for countries that were least-developed and became members during or after the Doha round, we assume that compliance will occur only in 2016.

WTO member countries identified as "developing" were required to comply by January 1, 2000. We estimate compliance as of this date for countries that were WTO members at the time of TRIPS adoption in 1995. Generally, the WTO allowed developing countries to comply within three years of ascendancy to membership. Therefore we estimate the dates of compliance as the dates of membership plus three years for developing countries that joined after 1995.

Measuring TRIPS compliance using the WTO rules has many drawbacks. First among them is that while a country may claim to comply with TRIPS, its enforcement of patent and other IP

[5] For a description, see http://www.wto.org/english/theWTO_e/whatis_e/tif_e/org7_e.htm

protection generally and of pharmaceutical patent protection in particular may be in doubt. While it is difficult for us to measure expectations about enforcement or compulsory licensing, we experiment with alternative measures of patent protection. In particular, we use Ginarte-Park index of IP protection generously provided to us by Walter Park. The Ginarte-Park index measures the strength of IP protection and enforcement in 121 countries at 5 year intervals as described in Ginarte and Park (1997) and updated through 2005. From their data, we create a dummy variable indicating whether a country has chemical/pharmaceutical patent protection and enforces patent laws.[6] Countries that did not have pharmaceutical patent protection before implementing TRIPS would move from a "0" to a "1" after implementation. Countries for which TRIPS implementation did not involve a major change in pharmaceutical patent law are coded as a "1" both before and after implementation. This measure is therefore more nuanced than our TRIPS dummy variable, but it is missing for 40 countries in our dataset. We report results using both the measure based on WTO rules and the Ginarte-Park index.

A limitation to both measures is that they do not capture expectations that firms may have about the state of patent protection in a country in the future. Since drug development is a lengthy process, firms may make investment decisions based on whether they believe a country will have adopted patent protection some years in the future. In other words, the most influential factor in firm decisions about project support may be a country's intention to adopt patent protection as a condition of WTO membership, rather than the precise timing of compliance. If firms indeed made decisions based on projections of compliance, then our results would be biased as we examine how their decisions changed based on the date on which compliance actually occurred, but the direction of the bias would be against a significant finding. Note that we also explored other sources of data on IP laws and enforcement such as the US Trade Representative's Watch List and Priority Watch List. This alternative source was also unsatisfactory as it was unavailable prior to 2000 and is skewed towards countries engaged in significant trade with the US (so that Canada and Italy, for example, appear on the Watch List in some years). Thus we proceed with caution despite this limitation of the required assumptions about compliance.

Country controls

The World Bank's World Development Indicators dataset provides annual observations of GDP (measured in millions of constant 2000 US$), population (in thousands), health expenditures per capita, and a host of other potential controls. Unfortunately, many of the data series are incomplete for a large number of countries, particularly developing and least-developed. Since we

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

are especially interested in these countries, our empirical analysis does not exploit many of the potential controls as doing so would reduce our sample of countries significantly.

We collected information from globalhealthfacts.org, a website created by the Kaiser Family Foundation, on donations and disbursements for health from foreign governments and foundations and other non-governmental organizations such as the Gates Foundation. These variables also are not available by year (they are reported for the most recent year available, which is typically 2006).

Results

The effect of TRIPS on the level and direction of pharmaceutical research

Tables 4-6 present the results of tests on hypotheses 1 through 5. Each column represents the results of negative binomial estimation on a model of the number of projects starts for a disease in a particular year for a phase of research. Year effects are included in all specifications. Standard errors are clustered by disease. Table 4 presents results of models that treat HIV as a neglected disease. Table 5 reports the results of models in which HIV is re-classified as a global disease. Table 6 shows models that include only the drug development efforts of for-profit firms,[7] where HIV is classified as a global disease. Each table contains results where the TRIPS compliance of a country was measured first by the rules stipulated by the WTO, and second by the Ginarte-Park index of pharmaceutical patent protection and enforcement.

Hypotheses 1 and 2 predict that drug development efforts respond to increases in patent-protected deaths to a greater extent than to increases in the potential demand for a treatment in markets where TRIPS is not implemented. These hypotheses receive strong support across all phases, disease categorizations, and measures of IP protection, with the exception of Phase 2 starts for neglected diseases by for-profit firms. (Recall that our modeling approach treats projects at each stage as evaluated in parallel rather than sequentially; in other words, we do not model the succession of projects through each stage of development.) Thus, similar to the prior research described earlier on market size and innovation, our results suggest that patent protection stimulates drug development, although the nature of the relationship depends on the disease category.

Hypothesis 3 reflects the idea that the projected profits associated with neglected diseases may be lower than for global diseases despite large volumes of patients and despite patent protection. With the exception of Phase 1 starts in the model using the Ginarte-Park index of pharmaceutical patent protection, our results indicate that pharmaceutical research activity responded to TRIPS implementation more sensitively for global diseases than for neglected diseases. This is illustrated in Figure 2, which charts the predicted number of Phase 1 starts as a function of patient population (log

[7] Projects with any participation by a research foundation, government agency, or university are categorized as "nonprofit."

of deaths) in TRIPS-compliant countries for global and neglected diseases using the results from the first column of Table 4. Figure 3 shows that the number of development projects for any disease is not sensitive to the size of the patient pool when the pool is small, which is consistent with the idea that (a) the potential profits in poorer countries may not allow firms to recover the large fixed costs of development, (b) the tractability and/or pharmaceutical appropriateness of research may be lower for neglected than global diseases, and/or (c) patients may hard to be reach because of their location and the absence of complementary infrastructure. This figure also indicates that once the number of patient deaths reaches a threshold size, the number of projects related to global diseases increase faster than the number related to neglected diseases.

Hypotheses 4 and 5 concern the responsiveness of drug development efforts to deaths in countries without IP protection. They affirm that the number of project starts for both neglected and global diseases is ***not*** sensitive to deaths in countries that had not extended patent protections either because of a waiver from the WTO the country did not belong to the WTO, or the country was not yet required to comply with TRIPS even as a WTO member. These hypotheses are affirmed across most specifications: the number of project starts did not increase in response to deaths in non-TRIPS compliant countries. In fact, both β_3 and β_4 are negative and statistically significant in almost all instances reported in the table. Our results are statistically weaker using the Ginarte-Park measure of IP because the analysis based on the measure excludes many countries that are very poor and particularly affected by neglected diseases. The results validate that IP protection is directly relevant to projected profits from drug development.

Overall, the results reported in Tables 4-6 are consistent with predictions that reflect the profit-maximizing incentives of pharmaceutical firms.. Yet it is also possible that the results would be even stronger if only for-profit organizations were considered in the analysis, as these organizations are expressly responsible for profits to shareholders. The results when non-profit entities are excluded are similar to those in the main analysis. Tables 4-6 also show that the results are not sensitive to whether compliance is assessed using the algorithm based on the WTO rules or the Ginarte-Park index. The significance is maintained when HIV is reclassified, but the sizes of the estimated coefficients change. The difference suggests that HIV accounted for a large portion of research on neglected diseases over the period under study.

The robustness of the difference in findings for global and neglected diseases raises important questions for further research. While patent protection may be necessary for drug development, it may not provide sufficient incentives for the development of treatments for neglected diseases, eg "new pills for poor people," to borrow a phrase from Lanjouw and Cockburn (2001). The absence of complementary, systemic resources may be pivotal. Decisions about research projects appear to have been responsive to projections about patient volume, but only when

per-patient profits were sufficient to justify investment. The absence of complementary infrastructure may have prevented investment in research on neglected diseases despite the projections of large volumes of potential patients because the absent infrastructure drove up the costs of drug distribution to levels that dramatically damaged projected profit. Additional study is needed to validate whether this explanation accounts for the findings we obtain on the relationship between patent protection and research on neglected diseases.

Other potential explanations also arise for our results. It may be that the fixed costs of research on neglected diseases are large relative to those for global diseases, perhaps because research projects on global diseases build marginally and incrementally on an established body of knowledge while research projects on neglected diseases require greater investment in basic science. Yet another potential explanation is that projected profits are lower because firms expect governments to issue stringent price controls or compulsory licenses for important, life-saving drugs. This expectation has a precedent as the Canadian government once extensively issued compulsory licenses (although prior to and separately from TRIPS implementation), Brazil has recently issued compulsory licenses for certain HIV drugs; and even in the US, proposals were raised in 2001 to issue compulsory licenses on Cipro, a treatment for anthrax, and in 2005 on Tamiflu, a treatment for avian influenza.[8] If research organizations project that such action is more likely for drug treatments on neglected diseases than on global diseases, the decrease in expected profits from compulsory licensing could explain the differences we obtain for global and neglected diseases. Additional research is needed to explore this possibility.

The effect of TRIPS on domestic innovation in pharmaceuticals

The controversy at the adoption of TRIPS in part reflected concerns about the repatriation of profits from least-developed to high-income countries by first-world pharmaceutical companies. The Doha Declaration and Paragraph 6 adjustments were accompanied by an increasing sensitivity to the fact that many least-developed and developing countries do not host large numbers of pharmaceutical research institutions. The TRIPS adjustments were designed in part to support local researchers in these countries. As a result, we complemented our investigation of project starts with an analysis of the locations of research over the period of TRIPS implementation. Our purpose was to investigate for evidence that TRIPS may have cultivated the emergence of national innovation systems for pharmaceuticals in less wealthy countries.

Table 7 reports the results on Hypotheses 6-8. We examine the effect of IP protection on three measures of domestic innovative activity: the number of new domestic firms in pharmaceutical

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

development in country *c* in year *t*, the number of research projects with participation by domestic firms in country *c* in year *t*, and the number of research projects in which domestic firms in country *c* and firms in developed countries are partners in year *t*. All specifications exploit cross-sectional variation across countries, i.e. we do not estimate the within-country effect of the adoption of IP protection. (Including country fixed effects creates technical problems for model convergence.) Since the dependent variable is a count, we estimate the models as negative binomials. As in the prior analysis, we measure IP protection in two ways: by using the WTO rules and by restricting the same and implementing the Ginarte-Park index of pharmaceutical patent protection by country. In order to keep the sample of countries as large as possible, we include only minimal control variables (population and year fixed effects) as most other desired controls were not available for the entire time period of interest for many countries.

In this analysis, our results are sensitive to the set of countries we consider as well as the measure of IP protection. The difference in results using the two measures of IP protection is partly due to a difference in coverage: the Ginarte-Park index is not available for all countries in our dataset and is available only at 5 year intervals, which means that the estimates in intervening years may be inaccurate (we assume that any change in the index applies starting in the year of the index, when in fact the law could have changed at any point in the previous 5 years). On the other hand, the Ginarte-Park index is a more precise measure of the level of "true" patent protection and enforcement in the years and countries for which it is available than the WTO-rule based dummy.

We find that while IP protection is strongly and positively associated with increased pharmaceutical activity in high-income countries; the effect in countries with other income levels is weaker although significant. In general, lower-income countries have lower R&D activity across all measures. However, Wald tests comparing countries with and without IP protection by income group do not reject equality of the coefficients in most specifications. IP protection does not appear to be associated with higher levels of R&D activity within an income category at conventional levels of statistical significance (though in general, the difference is of the expected sign). The one exception is a specification using the Ginarte-Park index on the number of domestic research projects conducted in TRIPS-compliant versus non-compliant countries. Overall, this finding can be reconciled with results reported by Allred and Park (2007) and Qian (2007), who found that patent protection did not affect all countries in the same way. However, other explanations also arise: first, the establishment of a domestic research base may take more time than elapsed after many patent protection as implemented in least-developed countries; second, the firms engaged in R&D may have developed strategies to overcome weak IP protection in some non-compliant countries.

Taken together, these results support for hypotheses 6-8 although the level of support is lower than for prior hypotheses. Formal IP protection on pharmaceuticals in poorer countries may

have facilitated the establishment and development activity of domestic firms as well as collaborations between researchers in domestic and high-income countries. TRIPS may therefore have an indirect effect on innovation for poorer countries by enabling technology transfer and by facilitating domestic research, but this impact is confounded with the direct effects of country wealth (and other related, unmodeled factors). These interrelationships and the low level of significance on the results may mean that patent protection is insufficient to foster a local research base in poor countries. This issue certainly should be explored in future work.

Conclusion

This research examines the response of pharmaceutical research organizations – principally firms -- to the extension of patent protection under the TRIPS agreement. In particular, we look at the effect of IP protection on the level, character and location of drug development for global and neglected diseases. We find evidence that the level of drug-development effort increased as patent protections were implemented in countries that included greater numbers of potential patients for drug regimens. The relationship between patent protection and drug development is stronger for global than neglected diseases. We conjecture that this may occur because (a) revenue expectations for neglected diseases may continue to be low even after patent protection diminishes the threat of imitation, (b) the fixed costs of development for neglected diseases may be disproportionately high, or regimens may not be pharmacologically appropriate, and/or (c) the variable costs of distributing drugs for neglected diseases may be disproportionately high because of absent complementary infrastructure and activities. Finally, patent protection may foster the development of local firms in developing countries as well as partnerships between local and foreign firms from wealthier countries, thus promoting technology transfer and the dissemination of research. We find suggestive rather than conclusive evidence that domestic research activity is higher in countries with IP protection than those that are not TRIPS compliant. The benefits of increased research activity may be concentrated in "upper middle income" countries. The introduction of patent rights has heterogeneous impacts on the type of research conducted as well as the countries in which such research is carried out. The broadest implication is that public policies such as TRIPS intended to induce long-term investments in research & development may instead induce more nuanced responses from the private sector than anticipated.

Our most important finding is that, while TRIPS may have induced pharmaceutical research, patent protection may be insufficient to induce the development of drugs for neglected diseases, which are defined as illnesses that disproportionately affect patients in poor countries. This stands in contrast to work showing the responsiveness of drug development for orphan diseases in the US after an extension of the term of patent protection, as in Lichtenberg and Waldfogel (2003) or Yin

(2007). The critical differences may be that (a) firms are able to charge relatively high prices for orphan drug treatments in the US, and thus an extension of patent terms increases their expected profits, and (b) infrastructure is available in the US for distributing drug regimens. In the case of neglected diseases, high prices may not be possible with or without patent protection, and projected volumes may be relatively low because affected patients are difficult to reach, diagnose, and treat..

The analysis also considers how the TRIPS policy influenced development activities by indigenous researchers in the countries that implemented patent protections. Upper-middle-income countries may have responded to TRIPS implementation with the development of a local research base, but we find little evidence of this response in lower-income or lower-middle-income countries. Additional research is needed to identify other mechanisms that may be more potent for inducing research on neglected diseases. Proposals such as advanced commitments (Kremer and Glennester (2004)) or the use of vouchers (Ridley et al. (2006)), which provide alternative mechanisms for inducing drug discovery in the private sector, are examples. Maurer (2006) discusses these and other approaches for stimulating research on neglected diseases. These mechanisms are crucial subjects for further study, as the extension of patent protection under TRIPS did not stimulate research on neglected diseases. Additional investment in complementary institutions – such as clinics, pharmacies, and educational institutions for training medical practitioners – may also be essential next steps.

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Table 1: Categorization of Diseases

Neglected	**Global (or "Non-neglected")**
Tuberculosis	Cancers (all types)
STDs excluding HIV	Other neoplasms
HIV/AIDS	Diabetes mellitus
Diarrhoeal diseases	Endocrine disorders
Childhood-cluster diseases	Neuropsychological disorders (all types)
Meningitis	Glaucoma
Hepatitis B and C	Cataracts
Malaria	Vision disorders, age-related
Tropical-cluster diseases	Hearing loss, adult onset
Leprosy	Cardiovascular disorders (all types)
Dengue	Chronic obstructive pulmonary disease
Japanese encephalitis	Asthma
Trachoma	Peptic ulcer disease
Intestinal nematode infections	Cirrhosis of the liver
Lower respiratory infections	Appendicitis
Upper respiratory infections	Nephritis and nephrosis
Otitis media	Benign prostate hypertrophy
Maternal conditions	Skin diseases
Low birth weight	Rheumatoid arthritis
Birth asphyxia and birth trauma	Osteoarthritis
Protein-energy malnutrition	Congenital anomalies
Iodine deficiency	Dental disorders (all types)
Vitamin A deficiency	Unintentional injuries and accidents
Iron-deficiency anaemia	Violent injuries and war

Sources: World Health Organization, authors' definition.

Table 2: Characteristics of Research by Disease

Year	Total projects	Avg projects/disease	Neglected-disease projects	Avg projects/ neglected disease	Global projects	Avg projects/ global disease
1990	29195	436	3654	261	25541	482
1991	29640	442	3709	265	25931	489
1992	30373	453	3757	268	26616	502
1993	31282	460	3894	278	27388	507
1994	32280	475	4007	286	28273	524
1995	33045	486	4104	293	28941	536
1996	33808	497	4164	297	29644	549
1997	34665	510	4235	303	30430	564
1998	35567	515	4322	309	31245	568
1999	36501	521	4418	316	32083	573
2000	37555	537	4519	323	33036	590
2001	38572	551	4622	330	33950	606
2002	39556	565	4705	336	34851	622
2003	40760	582	4828	345	35932	642
2004	42021	600	4957	354	37064	662
2005	43282	618	5101	364	38181	682
2006	44279	624	5188	371	39091	686

Sources: IMS R&D Focus; author analysis. Each observation is a project-disease indication active in development during the year (projects are often under development for multiple disease indications).

Table 3: Characteristics of Firms and Projects by Country

Country	# firms	# projects	Country	# firms	# projects
USA	1661	15966	INDIA	36	182
UK	255	3462	AUSTRIA	35	117
JAPAN	223	3395	BELGIUM	34	614
CANADA	221	1128	TAIWAN	27	81
GERMANY	197	2265	ARGENTINA	21	54
FRANCE	136	2008	RUSSIAN FEDERATION	18	55
ITALY	107	731	FINLAND	17	107
AUSTRALIA	106	563	PORTUGAL	17	44
SOUTH KOREA	89	534	NORWAY	15	54
ISRAEL	83	376	BRAZIL	13	27
SWITZERLAND	78	2003	HUNGARY	13	81
NETHERLANDS	58	576	IRELAND	13	185
DENMARK	53	654	NEW ZEALAND	12	51
SWEDEN	52	260	SINGAPORE	12	71
CHINA	48	79	GREECE	11	26

Note: The dataset covers all WTO member and observer countries, most of which have little or no pharmaceutical development activity. This table includes countries with more than 10 firms active in drug development. Appendix A contains the complete list of countries.

Table 4: Effect of patent protection on research efforts for all organizations, HIV classified as a neglected disease+

	TRIPs-compliant measure of IP			Ginarte-Park measure of pharma IP		
	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts
Beta0: Intercept	-1.3292**	-1.0754**	-1.4170**	-1.6757**	-1.3251**	-1.5495**
	(0.21895)	(0.20000)	(0.21548)	(0.21437)	(0.19808)	(0.21004)
Beta1: Log(Deaths in countries with IP)*Neglected disease	0.38829**	0.35703**	0.29426**	0.83408**	0.58025**	0.49671**
	(0.06094)	(0.06438)	(0.06901)	(0.13561)	(0.12777)	(0.13277)
Beta2: Log(Deaths in countries with IP)*Global disease	0.87116**	0.87889**	0.84492**	0.83677**	0.79362**	0.86097**
	(0.05205)	(0.05236)	(0.05965)	(0.05207)	(0.05090)	(0.05875)
Beta3: Log(Deaths in countries without IP)*Neglected disease	-0.16878**	-0.19067**	-0.14055**	-0.78977**	-0.54556**	-0.43889**
	(0.04893)	(0.05092)	(0.05372)	(0.15583)	(0.14601)	(0.15060)
Beta4: Log(Deaths in countries without IP)*Global disease	-0.59537**	-0.64149**	-0.64449**	-0.69943**	-0.70452**	-0.82570**
	(0.04921)	(0.04935)	(0.05529)	(0.05622)	(0.05556)	(0.06376)
Beta5: Number of drugs available for disease in 1995	0.28186**	0.27670**	0.24283**	0.29790**	0.28981**	0.25382**
	(0.01128)	(0.01066)	(0.01040)	(0.01186)	(0.01116)	(0.01045)
Year effects	included	included	included	included	included	included
Dispersion	1.33638**	1.15972**	1.03494**	1.42068**	1.23103**	0.98484**
	(0.08673)	(0.07926)	(0.08839)	(0.09154)	(0.08510)	(0.08872)
Number of Observations	1513	1513	1513	1513	1513	1513
Log Likelihood	7100.7199	4817.8125	531.4960	7073.1405	4780.6018	526.5181
Chi-sq for Wald test of Beta1 = Beta3	11.801**	16.836**	13.764**	18.381**	10.004**	12.110**
Chi-sq for Wald test of Beta2 = Beta4	34.464**	29.490**	33.435**	29.157**	20.032**	30.818**
Chi-sq for Wald test of Beta1 < Beta2	6.028**	13.160**	16.066**	0.000	1.826	4.621**

+Models estimated are negative binomial where the dependent variable is the number of project starts at the relevant phase for a disease in a specific year; standard errors are clustered by disease and reported in parentheses.

** Significant at the 10% level, * = significant at the 10% level.

Table 5: Effect of patent protection on research efforts for all organizations, HIV classified as a global disease+

	TRIPs-compliant measure of IP			Ginarte-Park measure of pharma IP		
	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts
Beta0: Intercept	-1.3622**	-1.0892**	-1.4257**	-1.6280**	-1.2900**	-1.5241**
	(0.21777)	(0.19917)	(0.21442)	(0.21290)	(0.19701)	(0.20888)
Beta1: Log(Deaths in countries with IP)*Neglected disease	0.34265**	0.32552**	0.27581**	0.74269**	0.50380**	0.43359**
	(0.06630)	(0.07085)	(0.07758)	(0.13512)	(0.13060)	(0.13991)
Beta2: Log(Deaths in countries with IP)*Global disease	0.84315**	0.85746**	0.83681**	0.81744**	0.77832**	0.85687**
	(0.05263)	(0.05282)	(0.06019)	(0.05194)	(0.05091)	(0.05881)
Beta3: Log(Deaths in countries without IP)*Neglected disease	-0.16270**	-0.18591**	-0.13124**	-0.73369**	-0.49441**	-0.38596**
	(0.04942)	(0.05180)	(0.05486)	(0.15209)	(0.14570)	(0.15455)
Beta4: Log(Deaths in countries without IP)*Global disease	-0.56294**	-0.61803**	-0.63238**	-0.68573**	-0.69556**	-0.82589**
	(0.04891)	(0.04906)	(0.05504)	(0.05620)	(0.05564)	(0.06390)
Beta5: Number of drugs available for disease in 1995	0.28344**	0.27740**	0.24360**	0.29276**	0.28545**	0.25175**
	(0.01125)	(0.01064)	(0.01041)	(0.01159)	(0.01095)	(0.01036)
Year effects	included	included	included	included	included	included
Dispersion	1.35239**	1.17316**	1.04475**	1.39839**	1.21794**	0.97546**
	(0.08721)	(0.07975)	(0.08882)	(0.09083)	(0.08470)	(0.08848)
Number of Observations	1513	1513	1513	1513	1513	1513
Log Likelihood	7098.1450	4815.1965	530.0381	7076.5537	4782.4429	527.3226
Chi-sq for Wald test of Beta1 = Beta3	3.995	8.653**	5.892*	15.136**	7.854**	8.501**
Chi-sq for Wald test of Beta2 = Beta4	36.351**	29.634**	33.498**	31.033**	20.712**	31.644**
Chi-sq for Wald test of Beta1 < Beta2	4.911**	11.620**	15.002**	0.161	3.126*	7.839**

+The dependent variable is the number of project starts at the relevant phase for a disease in a specific year; standard errors are clustered by disease and are reported in parentheses.
* Significant at the 10% level, ** Significant at the 5% level

Table 6: Effect of patent protection on research efforts of for-profit firms only, HIV classified as a global disease+

	TRIPs-compliant measure of IP			Ginarte-Park measure of pharma IP		
	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts	Phase 1 Starts	Phase 2 Starts	Phase 3 Starts
Beta0: Intercept	-1.7627**	-1.1795**	-1.6914**	-2.0735**	-1.3792**	-1.7955**
	(0.23175)	(0.20210)	(0.22914)	(0.22945)	(0.20010)	(0.22329)
Beta1: Log(Deaths in countries with IP)*Neglected disease	0.36677**	0.35095**	0.23934**	0.55284**	0.36561**	0.31511**
	(0.07592)	(0.07639)	(0.08236)	(0.13681)	(0.13550)	(0.14826)
Beta2: Log(Deaths in countries with IP)*Global disease	0.78885**	0.77121**	0.75839**	0.74088**	0.68497**	0.79956**
	(0.05362)	(0.05373)	(0.06253)	(0.05200)	(0.05154)	(0.06091)
Beta3: Log(Deaths in countries without IP)*Neglected disease	-0.22563**	-0.22899**	-0.12437**	-0.56482**	-0.36843**	-0.27615*
	(0.05664)	(0.05625)	(0.05815)	(0.15358)	(0.15060)	(0.16329)
Beta4: Log(Deaths in countries without IP)*Global disease	-0.53947**	-0.56402**	-0.59079**	-0.63200**	-0.61926**	-0.79806**
	(0.04982)	(0.05007)	(0.05749)	(0.05674)	(0.05672)	(0.06685)
Beta5: Number of drugs available for disease in 1995	0.29131**	0.27830**	0.24844**	0.29974**	0.28639**	0.25593**
	(0.01117)	(0.01061)	(0.01055)	(0.01143)	(0.01087)	(0.01040)
Year effects	included	included	included	included	included	included
Dispersion	1.24059**	1.11243**	0.98274**	1.27898**	1.14592**	0.88894**
	(0.08631)	(0.08169)	(0.09219)	(0.09034)	(0.08617)	(0.08982)
Number of Observations	1513	1513	1513	1513	1513	1513
Log Likelihood	4766.0449	3081.8169	47.2534	4742.7265	3053.4114	52.1438
Chi-sq for Wald test of Beta1 = Beta3	4.999*	9.925**	3.730	4.909*	2.234	2.335
Chi-sq for Wald test of Beta2 = Beta4	29.542**	24.785**	27.522**	23.530**	16.135**	28.798**
Chi-sq for Wald test of Beta1 < Beta2	4.143**	7.405**	12.107**	0.515	2.007	4.417**

+The dependent variable is the number of project starts at the relevant phase for a disease in a specific year; standard errors are clustered by disease and are reported in parentheses.
* Significant at the 10% level, ** Significant at the 5% level.

Table 7: Domestic research activities

	TRIPs-compliant measure of IP			Ginarte-Park measure of pharma IP		
Dependent Variable	# firms	# projects	# partnerships	# firms	# projects	# partnerships
IP *High income country	2.33516**	2.37311**	2.38449**	2.37872**	2.63297**	2.63365**
	(0.23033)	(0.19137)	(0.19832)	(0.28848)	(0.20432)	(0.21188)
No IP *High income country	-2.2125**	0.78361**	0.95933**	-2.1286**	0.93138**	0.98101**
	(0.35247)	(0.27118)	(0.31943)	(0.38381)	(0.27097)	(0.31061)
IP *Upper middle income country	-0.68526*	-1.5748**	-2.6723**	-0.29922	-1.2252**	-2.4955**
	(0.36527)	(0.24605)	(0.30164)	(0.35607)	(0.23395)	(0.28245)
No IP *Upper middle income country	-0.58698**	-2.1979**	-3.3481**	-0.59930	-2.3939**	-3.5700**
	(0.29330)	(0.21145)	(0.26645)	(0.38266)	(0.25126)	(0.35000)
IP *Lower middle income country	-2.4843**	-3.7999**	-6.3186**	-2.2582**	-3.3769**	-7.4331**
	(0.68421)	(0.42887)	(1.17827)	(0.55045)	(0.32558)	(0.99882)
No IP *Lower middle income country	-2.5492**	-4.2383**	-7.3128**	-3.0712**	-5.8602**	-7.1513**
	(0.43233)	(0.27607)	(0.84637)	(0.58257)	(0.64549)	(0.90393)
IP *Low income country	-3.6627**	-5.2559**	-6.3731**	-3.1398**	-4.4854**	-5.2777**
	(1.07777)	(1.03205)	(1.26756)	(0.77923)	(0.52471)	(0.74998)
No IP *Low income country	-3.3394**	-5.9403**	-6.6095**	-3.1480**	-5.4362**	-6.7940**
	(0.49915)	(0.49232)	(0.61672)	(0.50755)	(0.44711)	(0.67487)
Population	0.00533**	0.00794**	0.00677**	0.00482**	0.00678**	0.00649**
	(0.00047)	(0.00069)	(0.00067)	(0.00040)	(0.00048)	(0.00065)
Dispersion	2.49206**	4.44075**	4.53375**	1.38806**	2.19343**	2.18305**
	(0.28063)	(0.26258)	(0.28918)	(0.17469)	(0.14382)	(0.15301)
# Observations	2745	2745	2745	1795	1795	1795
Log Likelihood	-383.7259	35074.7839	32694.7111	-238.5813	35424.7964	32975.5542
Chi-sq for Wald test of IP for upper middle income	0.029	0.716	0.741	0.389	5.155**	2.040
Chi-sq for Wald test of IP for lower middle income	0.007	0.426	5.544**	2.139	7.384**	0.135
Chi-sq for Wald test of IP for low income	0.509	0.899	0.106	0.000	2.896*	2.926*

All regressions estimated as negative binomials. Standard errors are clustered by country. Year effects are included.
* Significant at the 10% level, ** Significant at the 5% level.

Figure 1

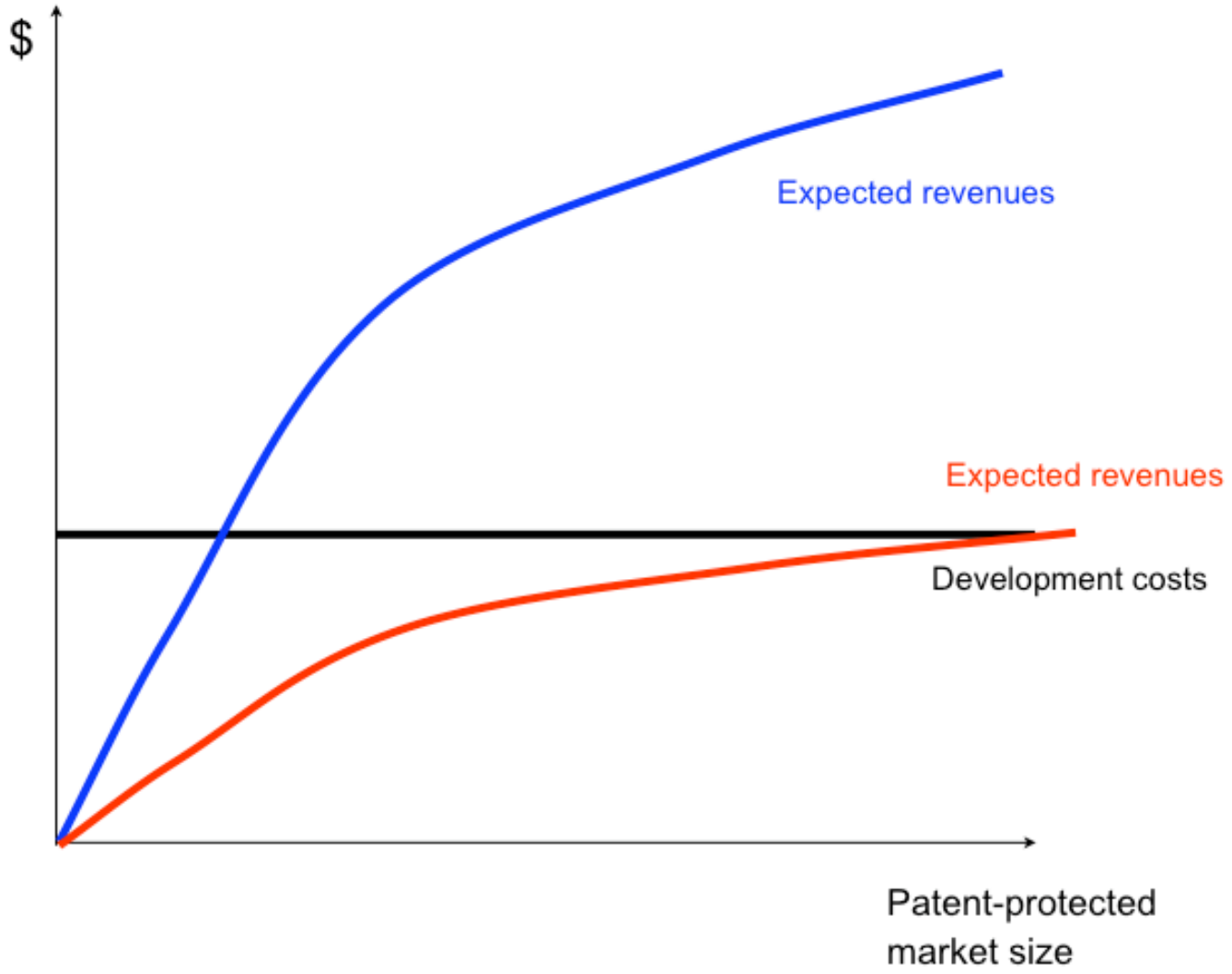
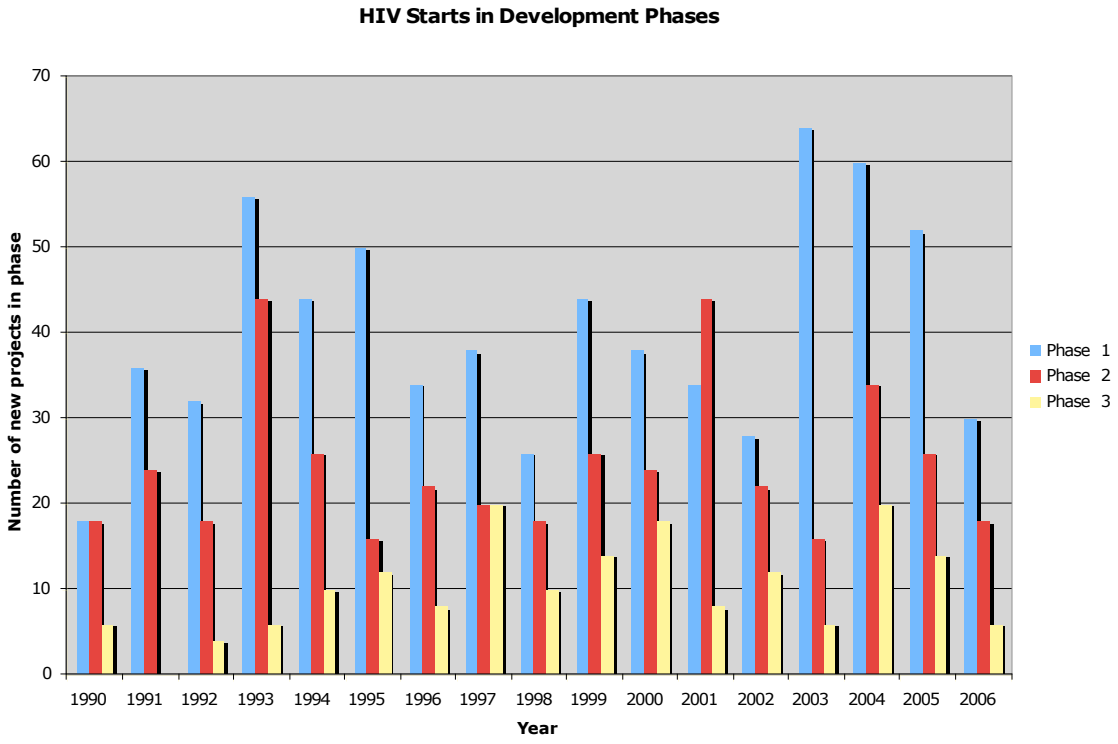

$
Expected revenues
Expected revenues
Development costs
Patent-protected
market size

Figure 2: Project starts in HIV and neglected diseases



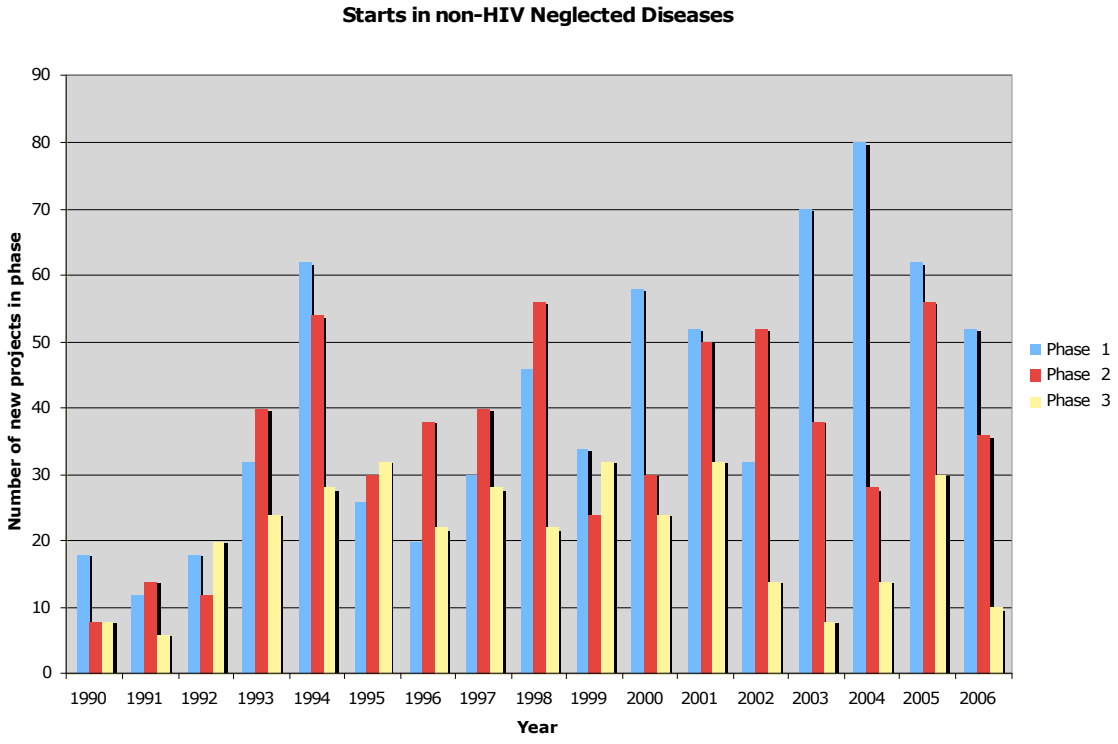
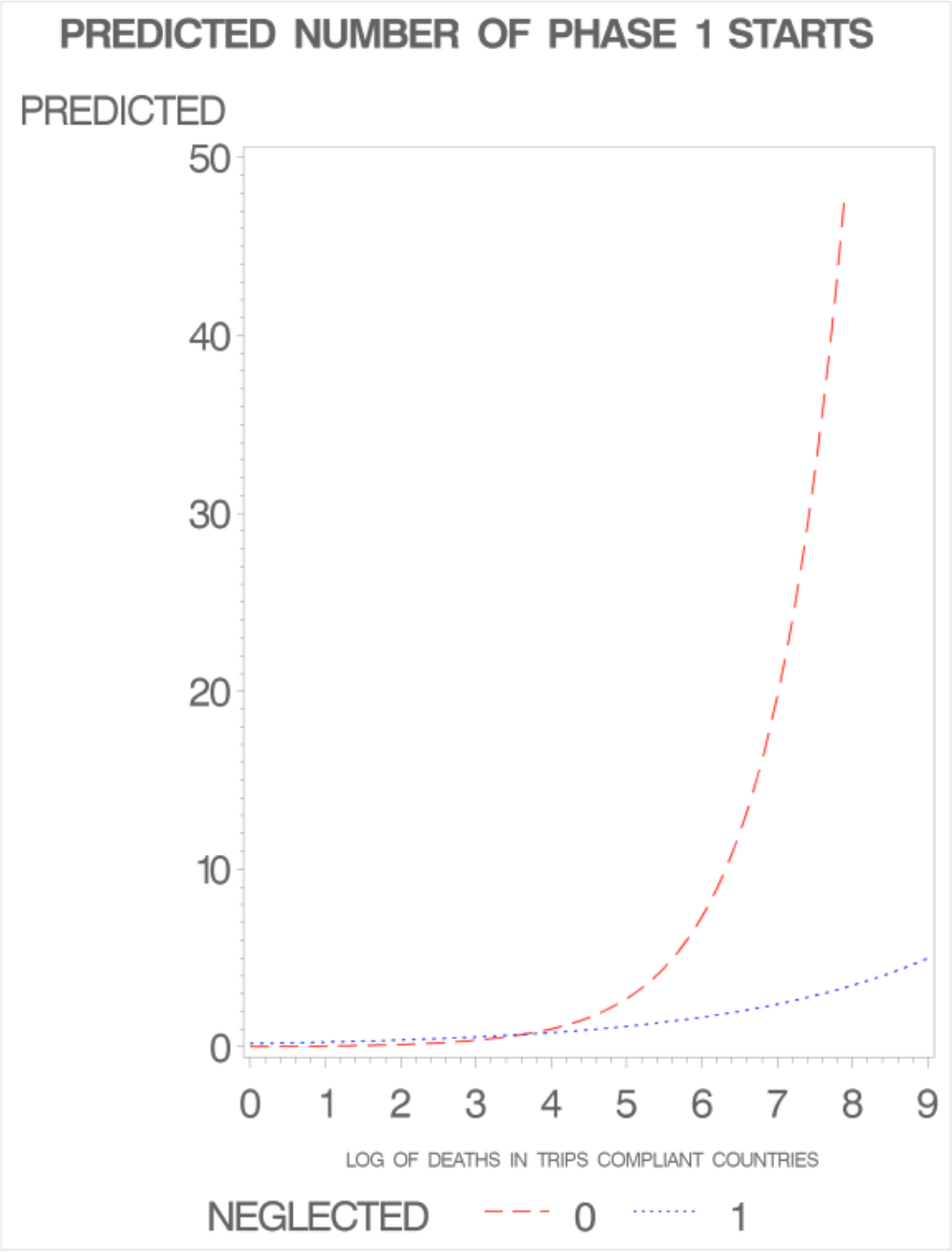


Figure 3


PREDICTED NUMBER OF PHASE 1 STARTS
PREDICTED
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9
LOG OF DEATHS IN TRIPS COMPLIANT COUNTRIES
NEGLECTED
0
1

Appendix A: Countries in dataset (with year of WTO membership).
Note: Disease data is not available for all countries in this list, nor is the Ginarte-Park index of IP protection. This list includes all WTO member and observer countries.

Developed countries			
ANDORRA	FRANCE (1995)	JAPAN (1995)	ST. PIERRE & MIQUELON
AUSTRALIA (1995)	GERMANY (1995)	LATVIA (1999)	SAN_MARINO
AUSTRIA (1995)	GIBRALTAR	LIECHTENSTEIN (1995)	SINGAPORE (1995)*
BELGIUM (1995)	GREECE (1995)	LITHUANIA (2001)	SLOVAKIA (1995)
BERMUDA	GREENLAND	LUXEMBOURG (1995)	SLOVENIA (1995)
CANADA (1995)	HOLY SEE (VATICAN)	MALTA (1995)*	SOUTH_AFRICA (1995)
CYPRUS (1995)*	HONG KONG (1995)*	MONACO	SOUTH_KOREA (1995)*
CZECH_REPUBLIC (1995)	HUNGARY (1995)	NETHERLANDS (1995)	SPAIN (1995)
DENMARK (1995)	ICELAND (1995)	NEW_ZEALAND (1995)	SWEDEN (1995)
ESTONIA (1999)*	IRELAND (1995)	NORWAY (1995)	SWITZERLAND (1995)
FAROE ISLANDS	ISRAEL (1995)*	POLAND (1995)*	UK (1995)
FINLAND (1995)	ITALY (1995)	PORTUGAL (1995)	USA (1995)

Least-developed countries			
AFGHANISTAN	DJIBOUTI (1995)	MALAWI (1995)	SOLOMON_ISLANDS (1996)
ANGOLA (1996)	EQUATORIAL_GUINEA	MALDIVES (1995)	SOMALIA
BANGLADESH (1995)	ERITREA	MALI (1995)	SUDAN
BENIN (1996)	ETHIOPIA	MAURITANIA (1995)	TANZANIA (1995)
BHUTAN	GAMBIA (1996)	MOZAMBIQUE (1995)	TIMOR-LESTE
BURKINA_FASO (1995)	GUINEA (1995)	MYANMAR (1995)	TOGO (1995)
BURUNDI (1995)	GUINEA-BISSAU (1995)	NEPAL (2004)	TUVALU
CAMBODIA (2004)	HAITI (1996)	NIGER (1996)	UGANDA (1995)
CAPE_VERDE	KIRIBATI	RWANDA (1996)	VANUATU
CENT_AFRICAN_REP (1995)	LAOS	SAMOA	YEMEN
CHAD (1996)	LESOTHO (1995)	SAO_TOME_PRINCIPE	ZAMBIA (1995)
COMOROS	LIBERIA	SENEGAL (1995)	
CONGO (1997)	MADAGASCAR (1995)	SIERRA_LEONE (1995)	

Developing countries			
ALBANIA (2000)	BRUNEI_DARUSSALAM (1995)*	ECUADOR (1996)	INDIA (1995)*
ALGERIA	BULGARIA (1996)	EGYPT (1995)*	INDONESIA (1995)*
ANGUILLA	BURMA	EL_SALVADOR (1995)*	IRAN
ANTIGUA_BARBUDA (1995)*	CAMEROON*	FALKLAND ISLANDS	IRAQ
ARGENTINA (1995)*	CAYMAN ISLANDS	FIJI (1996)*	ISLE OF MAN
ARMENIA (2003)	CHILE (1995)*	FRENCH GUIANA	JAMAICA (1995)*
ARUBA	CHINA (2001)*	FRENCH POLYNESIA	JERSEY
AZERBAIJAN	CHRISTMAS ISLAND	GABON (1995)*	JORDAN (2000)
BAHAMAS	COCOS ISLANDS	GAZA STRIP	KAZAKHSTAN
BAHRAIN (1995)*	COLOMBIA (1995)*	GEORGIA (2000)	KENYA (1995)*
BARBADOS (1995)*	COOK_ISLANDS	GHANA (1995)*	KUWAIT (1995)*
BELARUS	COSTA_RICA (1995)*	GRENADA (1996)*	KYRGYZSTAN (1998)
BELIZE (1995)*	CÔTE_D'IVOIRE (1995)*	GUADELOUPE	LEBANON
BOLIVIA (1995)*	CROATIA (2000)	GUAM	LIBYA
BOSNIA_HERZEGOVINA	CUBA (1995)*	GUATEMALA (1995)*	MACAO (1995)*
BOTSWANA (1995)*	DEM_REP_CONGO (1997)*	GUERNSEY	MACEDONIA (2003)
BRAZIL (1995)*	DOMINICA (1995)*	GUYANA (1995)*	MALAYSIA (1995)*
BRITISH VIRGIN ISLANDS	DOMINICAN_REPUBLIC (1995)*	HONDURAS (1995)*	MARSHALL_ISLANDS

MARTINIQUE	NORTHERN MARIANA ISLANDS	ST_VINCENT (1995)*	UKRAINE
MAURITIUS (1995)*	OMAN (2000)	SAUDI_ARABIA (2005)	UAE (1996)*
MAYOTTE	PAKISTAN (1995)*	SERBIA_MONTENEGRO	URUGUAY (1995)*
MEXICO (1995)*	PALAU	SEYCHELLES	UZBEKISTAN
MICRONESIA	PANAMA (1997)	SRI_LANKA (1995)*	VENEZUELA (1995)*
MOLDOVA (2001)	PAPUA_NEW_GUINEA (1996)*	SURINAME (1995)*	VIET_NAM (2007)
MONGOLIA (1997)	PARAGUAY (1995)*	SWAZILAND (1995)*	VIRGIN ISLANDS
MONTENEGRO	PERU (1995)*	SYRIA	WALLIS AND FUTUNA
MONTSERRAT	PHILIPPINES (1995)*	TAIWAN (2002)	WEST BANK
MOROCCO (1995)*	PITCAIRN ISLANDS	TAJIKISTAN	WESTERN SAHARA
NAMIBIA (1995)*	PUERTO RICO	THAILAND (1995)*	ZIMBABWE (1995)*
NAURU	QATAR (1996)*	TOKELAU	
NEW CALEDONIA	REUNION ISLANDS	TONGA (2007)	
NICARAGUA (1995)*	ROMANIA (1995)	TRINIDAD_TOBAGO (1995)*	
NIGERIA (1995)*	RUSSIAN_FEDERATION	TUNISIA (1995)*	
NIUE	SAINT HELENA	TURKEY (1995)*	
NORFOLK ISLAND	SAINT_KITTS_NEVIS (1996)*	TURKMENISTAN	
NORTH_KOREA	SAINT_LUCIA (1995)*	TURKS & CAICOS ISLANDS	