R&D Incentives for Neglected Diseases

--- The impact of firm characteristics on new product development

Chen Ni

Professor David B. Ridley, Faculty Advisor

Professor Kent Kimbrough, Advisor of the Honors Seminar

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Abstract

Although neglected diseases of developing countries are beginning to receive more attention from companies because of rising interest in corporate social responsibility and government incentive policies, the allocation of research funding to these diseases still remains extremely low. In this study, an ordinary least square regression methodology is used to decipher the impacts of firm-level characteristics such as revenue volume, headquarter location, pipeline size and business structure on R&D incentives for neglected diseases. Findings reveal that, research on neglected diseases by top 20 pharmaceutical firms is positively correlated with spillovers from other research (including animal health) and with European headquarters. Research on neglected diseases with greater burdens, e.g. Malaria and TB, tends to be done by firms with the greater revenue size; and research on the neglected diseases with smaller burdens, e.g. Dengue and Typhoid, tends to be done by firms with somewhat smaller revenue size. Based on these findings, appropriate policy implications are then drawn.

Key words: neglected diseases, firm characteristics, revenue size, headquarter, pipeline volume, animal health

JEL code: I

1. INTRODUCTION

Diseases can be classified as Type I diseases, which are incident in both rich and poor countries; Type II diseases, which are incident in both rich and poor countries but with a substantial proportion in poor countries, such as Tuberculosis (TB) and Malaria; and Type III diseases, which are overwhelmingly or exclusively incident in poor countries, such as Typhoid and Chagas. Type II diseases are often termed neglected diseases and Type III very neglected diseases[1]. These diseases appear on the left half of Figure 1, where the horizontal axis corresponds to a scale of the share of burdens in developed nations, and the vertical axis is a log scale of global burdens inflicted by the diseases. Typically, Type II and Type III diseases may not be the ones that inflict the heaviest global burdens in terms of Disability-Adjusted Life Years (DALYs)[2], but their impacts on low-income countries are often disproportionally large. This is illustrated in Table 1, which shows a comparison of leading causes of disease burdens globally versus in low-income countries. For instance, vascular diseases are more prevalent in the developed world. Infectious and parasitic diseases cause enormous health problems in the developing world whereas they leave the developed ones relatively unscathed. In particular, Malaria represents a substantial disease burden, being at 10^{th} place globally and 4^{th} place in low-income countries, while the same case applies to TB, which appears at 9^{th} place globally and 10^{th} place in low-income countries. Also noteworthy is that some of the leading causes of health burdens in low-income countries, although not explicitly stated as neglected diseases, are in fact highly correlated with the occurrences of neglected diseases. For instance, Premature and Low

[1] World Health Organization

[2] DALYs = Disability Adjusted Life Years i.e. The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. Hence, WHO Definition. *http://www.who.int/mental_health/management/depression/daly/en/* Assessed on March 19, 2011.

Birth Weight, as well as Birth Asphxia and Birth Trauma in African countries are often caused by Malaria contacted during pregnancy.

The barrier to treatments development for neglected diseases can be mainly attributed to the shortage of financing resources in developing countries. For instance, the average spending on health services in low-income countries was about $29 per capita in 2004[3]. Although many biopharmaceutical companies are beginning to allocate more R&D resources to neglected diseases due to the rising of corporate social responsibility and the emergence of incentive policies such as Product Development Partnerships and Priority Review Vouchers, Ridley et al (2006), Grabowski et al (2008), funding for anti-neglected diseases R&D projects remains disproportionally low. A case to point would be that in 2008, R&D funding for HIV/AIDS was more than twice of that for Malaria and was approximately ten times of that for diarrhea diseases, grossly out of proportion of the global burdens inflicted by the diseases, Moran et al (2009).

However, one has to note that the lack of private profitability of developing drugs for neglected diseases may not reflect low social benefits. From an economic perspective, the extremely low level of resource allocation to combat neglected diseases can be attributed to the presence of substantial positive externalities. On the supplier side, R&D on one neglected disease treatment will lead to a larger pool of knowledge for future R&Ds on related pathologies. However, the associated social surplus is generally not captured by for-profit pharmaceutical companies due to the low returns on treatments for neglected diseases. On the demand side, first, externalities can stem from the infectiousness of neglected tropical diseases, since an infected person can unintentionally infect others. Consequently, it is unlikely that individual patients would fully incorporate the externalities in terms of the health of others in their drug purchase

[3] World Health Organization data on health care spending in 2003

decisions, implying lower than optimal demand curve. Second, there are important altruism externalities in markets for such drugs. The demand curve of very poor, sick individuals for drugs may be extremely low because of budget constraints. From the perspective of potential wealthy donors, the value of a patient's life may be far above his ability to pay for the drugs, which is the "market" value of his life. In these circumstances, there is a positive externality from consumption of the product on the potential donor, Hollis (2005). However, since transaction costs of aiding poverty-stricken patients are very high due to moral hazard concerns such as embezzlement and inefficient allocation, a simple transfer of cash to patients in developing nations is impractical.

Given the neglected nature and high level of social benefits of anti-neglected diseases treatments, a key research question to be addressed would be, which firms develop drugs for neglected diseases and why? A good understanding of this question would allow future policy makers to devise more relevant and effective incentive programs to encourage the development of anti-neglected diseases treatments. Hence, in order to answer the research question, focus of this study is placed on the supplier side to investigate the impacts of various firm-level characteristics on research decisions for anti-neglected diseases treatments. In order to do so, parameters measuring firm characteristics such as financial power, headquarter location, pipeline size and business structure are collected and used as predictor variables for the number of drugs that a company develops for neglected diseases in a year. This way, differential impacts of firm characteristics on R&D incentives for neglected diseases can be deciphered, which will, highly probably shed light on and enhance the effectiveness of future push and pull incentives, Ridley et al. (2010)

Section 2 below presents some relevant existing studies that inspired and motivated the current research. These are existing literatures on the effects of firm characteristics on drug-related parameters, and some of the pertinent methodologies are therefore drawn and modified to fit the current research. This is then be followed by Section 3 --- discussion on model selection and section 4 --- results interpretations, which we believe will not only be applicable to the development of anti-neglected diseases treatments, but also shed light on R&D decision-making in industries characterized by large development costs, relatively low probability of product development success, small market size and large public interest. One such example would be medical countermeasures to combat bioterrorism.

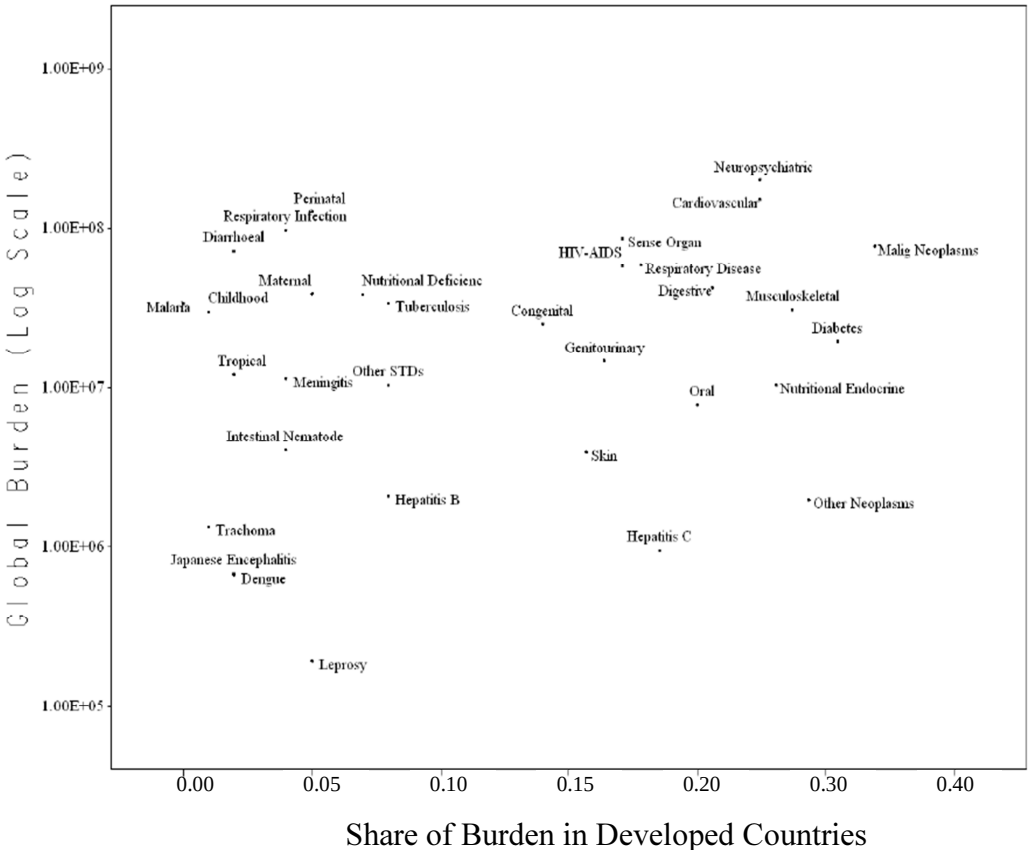

Figure 1: Disease burden in terms of disability-adjusted life years lost in developed countries relative to the rest of the world, adopted from Grabowski et al (2008)

Table 1.1 Leading Causes of Burden of Disease/Injuries (DALYs)
World, 2004

	Disease/Injury	DALYS (Millions)	Percent of total DALYS
1	Lower Respiratory infections	94.5	6.2
2	Diarrhoeal Diseases	72.8	4.8
3	Unipolar Depressive Disorders	65.5	4.3
4	Ischaemic Heart Diseases	62.6	4.1
5	HIV/AIDS	58.5	3.8
6	Birth Asphyxia and Birth Trauma	41.7	2.7
7	Road Traffic Accidents	41.2	2.7
8	Neonatal Infections and Others	40.4	2.7
9	Tuberculosis	34.2	2.2
10	Malaria	34.0	2.2
11	Hearing Loss (adult onset)	27.4	1.8
12	Congenital Abnomilities	25.3	1.7
13	Alcohol Use Disorders	23.7	1.6
14	Violence	21.7	1.4
15	Diabetes	19.7	1.3

Table 1.2 Leading Causes of Burden of Disease/Injuries (DALYs)
Low-income Countries, 2004

	Disease/Injury	DALYS (Millions)	Percent of total DALYS
1	Lower Respiratory infections	76.9	9.3
2	Diarrhoeal Diseases	59.2	7.2
3	HIV/AIDS	42.9	5.2
4	Malaria	32.8	4.1
5	Premature and Low Birth Weight	32.1	3.9
6	Neonatal Infections and Others	31.4	3.8
7	Birth Asphxia anf Birth Trauma	29.8	3.6
8	Uniploar Depressive Disorders	26.5	3.2
9	Ischaemic Heart Disease	26.1	3.1
10	Tuberculosis	22.4	2.7

2. LITERATURE REVIEW

Virtually no existing studies have been conducted to investigate firm-specific characteristics on R&D and clinical trial decisions for neglected diseases treatments. A few studies in the field of Health Economics, however, have been conducted to investigate the impacts of firm-level characteristics on various aspects of firm encounters and decisions such as FDA review time, Olson (1997), choice of R&D processes, Rodriguez (1998) and drug launches, Kyle (2006).

In Olson (1997), the author used a linear regression model to empirically examine the impacts of firm characteristics on review time length by FDA to approve drug applications between 1990 and 1992. The study treated regulatory decisions as endogenous and explains the variation in regulatory behavior as a function of firm and drug characteristics. Some of the firm characteristics considered were research intensity of the firm (constructed as the ratio of aggregate R&D spending to aggregate sales for a firm), firm's current experience with the FDA (constructed as the number of a firm's drugs that are submitted to the FDA at the time of drug of interest's approval), and a dummy variable for whether a firm is a US-registered entity or not. The result showed that, controlling of drug-specific factors, firms that were more research-intensive and had more contact with the regulators generally received faster reviews from the FDA. Moreover, US firms are not advantaged in the FDA regulatory process.

In Rodriguez (1998), the author examined the new product development decisions of pharmaceutical and biotechnology firms over the period of 1985 to 1996. Firms choose their R&D mode from a variety of development alternatives such as 1) the in-house development, (2) development via a merger or acquisition, (3) joint venture or strategic alliance, and (4) co-development with a patent license. Results showed that a firm's patent stock, number of previous approved drugs and the complexity of the disease target significantly affect the decision process.

In Kyle (2006), the author examined the determinants of new pharmaceutical launches since 1980 in G7 nations, taking market structure, firm, and product characteristics as sources of influences. The key result of the paper lies in that firm-level characteristics and their interaction with other variables are at least as important in deciphering drug launching decisions as market size and regulatory environment. More specifically, market characteristics alone correctly predict entry for only about 30% of the sample. Including firm characteristics improves this prediction substantially.

Methodology-wise, Kyle used a discrete-time hazard model with the following set up to regress a logistic of the probability of a drug's launch P(t) on various market and firm-level characteristics:

$$\log\left(\frac{P(t)}{1-P(t)}\right) = a(t) + N_{k\ell t}\delta + M_{k\ell t}\theta + X_{k\ell t}\beta + Z_{jk\ell t}\gamma + W_{ikt}\alpha.$$

Where l index drugs, j index firms, k index therapeutic classes, and i index countries. To clearlyt define the dependent variable, an important piece of assumption made is that a drug is "at risk" of entering into all other countries since the start of the year of its first launch into any market. On the right-hand side of the equation, N_{klt} is a vector of drug characteristics such as drug importance (drug's share of medicine citation within a therapeutic class), drug age (number of years since drug's first launch anywhere) and the number of countries that a drug is launched in; M_{klt} is a vector of market structure related variables such as the number of old drugs (of the same therapeutic class) in the market, the number of potential competitors and the number of domestic and foreign drugs in the market; X_{klt} is a vector of country-specific variables such as GDP per capita, population and the existence of price control policies; Z_{jklt} is a vector of firm-level characteristics such as total number of drugs in a firm's research pipeline, whether the firm is a

domestic country with regard to the target country of drug launch, whether the country of headquarter shares common languages, common borders or common regulations with the target country and whether a firm is multinational or not. Moreover, firms' experience in a country is defined as the number of drugs it launches in that country. The inclusion of this continuous independent variable is meant to capture firm's experience with the regulator, firm reputation, and the presence of a detailing force and distribution channels may be spread across all a firm's products within a particular country; and W_{klt} is vector denoting the interaction between domestic and foreign competition, for instance, terms under consideration include number of domestic incumbents*domestic entrant and number of foreign incumbents*domestic entrant.

Data-wise, Kyle used information in the the Pharma projects database, which keeps track of all drugs developed between 1980 and 2000. The database is maintained by the U.K. consulting firm PJB Publications. This dataset includes the drug's chemical and brand names, the name and nationality of the firm that developed it, the identity of licensees, the country and year in which it was patented, its status (in clinical trials, registered, or launched) in the various counties, and the year of launch etc.

Given the scarcity of existing literatures on the relationship between firm-specific characteristics and R&D/clinical trial decisions on treatments for neglected diseases, the current study uses Kyle (2006) as a starting point for future analysis. In her paper, Kyle mentioned that "economic theory suggests that entry decisions depend on market size, the level of competition, and the fixed costs associated with product launch. Strategic management and marketing suggests that firms are heterogeneous in nature: some are better suited, hence more willing to launch a particular product to a particular market than others. Joint testing of economic and strategic hypotheses is rare, largely because it requires a setting with cross-sectional data sets on

market, product and firm, and disentangling these various effects is an empirical challenge." This was exactly what Kyle achieved in her study by defining a market as a drug-country-year triple, hence capturing market-wide, product-level, as well as firm-specific characters. In the current study, a few simplifications to the model can be made without compromising its validity. First of all, the market landscape of drugs for neglected diseases is not a particularly important factor due to the financial constraints of patients. Hence, the decisions to launch clinical trial for anti-neglected diseases treatments are often not motivated by country-level factors such as market size and demand force in terms of GDP. On top of this, drug-level variables such as drug age and the number of markets a drug already exists in can be assumed to be homogenously zero since consideration is placed on anti-neglected diseases molecules in firms' pipelines undergoing clinical trials and FDA reviews. Taking all these proposed simplifications into account, Kyle's model can be modified into a regression model that considers only the effects on company-level factors on their R&D decisions for neglected diseases. In other words, among all the market-level, drug-level and firm-level factors that can potentially impact a firm's incentives to conduct R&D for neglected diseases, firm-level factors are the most important and relevant due to the specific nature of these anti-neglected diseases treatments.

3. METHOD/REGRESSION FRAMWORK

Following this line of reasoning, the dependent variable in the current regression should serve of measure a firm's level of commitment to the development of neglected diseases treatments, which can be modeled either as the monetary amount that a company spends annually on clinical trials, or as the number of relevant drugs that a company has in its pipeline in a particular year. Due to data availability, we adopt the second alternative of modeling dependent variable. This

way of modeling can potentially introduce bias since a firm may have very few R&D projects on neglected diseases while spending huge amounts on them. However, since the regression analysis is conducted by diseases, the bias can be expected to be minimal as R&D costs tend to remain fairly constant for a given disease. Therefore, the following model is used which treats the number of drugs for neglected diseases as an endogenous variable associated with a consortium of exogenous firm-level variables:

$$N_{ikt} = \alpha + \beta X_{ikt} + \delta Y_{ik} + \gamma Z_{ik} + \varepsilon_{ikt}$$

Where i index diseases, k index firms and t index years. Hence, N_{ikt} stands for the R&D decision variable quantified by the number of drugs for disease i developed by firm k in year t.

On the independent variable side, the vector of firm-level financial-related characteristics X_{ikt} consists of one variable, $Log\_Revenue_{kt}$, which measures company k's log revenue in 2000 real dollars in year t. Large firms have larger pools of resources to draw from when contemplating on R&D decisions, so $Log\_Revenue_{kt}$ is very likely to have a positive coefficient.

The vector Y_k for headquarters related characteristics includes the dummy variable $European\_Firm_k$, which equals to 1 if firm k is headquartered in Europe, and equals to 0 if firm k is headquartered in other continents. The majority of firms that fall under the 0 category are based in the US[4]. This dummy variable is set to capture the inter-continental differences in firms' willingness to invest in drugs for neglected diseases. For instance, European colonizing powers

[4] The original thought to include two dummy variables, $European\_Firm_k$ and US_Firm_k under Y_k is forgone on the basis of the highly negatively correlated nature of these two variables. 17 out of 20 firms in our data set are headquartered in US or Europe. For a detailed breakdown of headquarter locations, refer to Table 2 below. As a result, decision was made to include only the indicator variable $European\_Firm_k$ in the final analysis to avoid any confounding statistical issues due to multicollinearity.

such as Britain and France have tighter historical ties (in terms of language, number of immigrants and common legal origins) with target countries which neglected tropical diseases are prevalent in, hence, British firms such as GlaxoSmithKline might be more involved in certain development projects than some US firms, given the headquarter country's strong colonial ties with Southeast Asian and African countries.

Z_{kt} is a vector for portfolio-related firm characteristics. In particular, a firm's R&D pipeline would foreseeably provide predictive power on how willing and able it is to commit to the development of drugs for neglected diseases. For instance, a firm with substantial experience with Class P (Parasitic) diseases may have spillover advantages in developing drugs for neglected tropical diseases. To capture the spillover effects, $Pipeline_{kt}$ is modeled as a continuous variable for firm k' Class P pipeline size net of those for the neglected diseases under consideration in a given year t. Other than this, $Animal\_Health_{kt}$ is a measure of the percentage of firm k's revenue from animal health products, which may serve as a proxy for spillover effects onto drugs for neglected diseases, since most of animal health products are targeted at parasitic diseases. Taking all the factors into account, a linear regression model as the following may be constructed,

$$N_{ikt} = \alpha + \beta_1 Log\_Revenue_{kt} + \delta_1 Europe_k + \gamma_1 \, Pipeline_{kt} + \gamma_2 Animal\_Health_{kt} + \epsilon_{ikt}$$

TABLE 2
TOP 20 PHARMACEUTICAL COMPANIES BY 2009 PRESCRIPTION SALES

Company	Country of Headquarter	Sales (billion USD)
Pfizer	USA	41.7
Novartis	Switzerland	36.7
Sanofi-Aventis	France	35.1
GlaxoSmithKline	UK	34.3
AstraZeneca	UK	33.2
Roche	Switzerland	31.3
Johnson & Johnson	USA	26.9
Merck & Co	USA	25.0
Eli Lilly	USA	19.6
Abbott	USA	19.4
Teva	Israel	15.7
Bayer	Germany	15.4
Wyeth	USA	14.8
Amgen	USA	14.8
Boehringer	Germany	14.6
Takeda	Japan	14.4
Bristol-Myers	USA	14.2
Schering-Plough	USA	13.1
Daiichi Sankyo	Japan	8.5
Novo Nordisk	Denmark	8.2

There are two major assumptions in the definition of the dependent variable. First, only top 20 pharmaceutical companies ranked by 2009 global prescription drug sales are included in the analysis (Table 2). In this way, firm-level financial data can be easily collected from public sources such as Bloomberg and DataStream. Moreover, since some large firms had zero investment in drugs for neglected diseases, conditioning the analysis on the top 20 companies therefore captures important information carried by zero points. Consequently, the objective of this empirical analysis is to shed light on different factors that impact the decision-making outcome of the largest players in the pharmaceutical industry. However, by doing so, important information carried by small firms' R&D decisions may be neglected. More specifically, small

pharmaceutical firms tend to have higher levels of engagements in earlier stages of R&D such as Discovery, Preclinical and earlier parts of Phase I. Once these molecules reach later stages of clinical trials, large pharmaceutical companies often license them over to conduct the more costly Phase I, II and III clinical trials. The second assumption is, drugs under active research program are defined as drugs in Phase I, Phase II or Phase III of the R&D process[5]. Therefore, molecules in Discovery and Preclinical phases are excluded from the regression analysis. There are reasons behind this decision. First, clinical and human testing occurs through Phase I to Phase III, while Discovery and Preclinical phases are mainly concerned with in vitro and at most, animal studies. Consequently, R&D costs are driven heavily by human trials rather than animal testing in the Discovery and Preclinical phases. Second, using data in the Tufts CSDD database of approved drugs, DiMasi et al (2003), estimated the average time from synthesis of a compound to initial human testing for self-originated drugs to be 52.0 months, while phase lengths of Phase I to Phase III are about 2 years each, Adams et al (2006). Therefore, Discovery and Preclinical phases on average cost less but last longer than human trials. As a result, inclusion of molecules in these earlier phases may lead to an upward bias in measuring firm's willingness to conduct research for drugs for neglected diseases.

[5] "In Phase I, a small number of healthy volunteers are tested to establish safe dosages and to gather information on the absorption, metabolic effects, excretion and toxicity of the compound. To conduct clinical testing in the US, a manufacturer must file an investigational new drug application (IND) with the FDA. Phase II trials are conducted with subjects who have the targeted disease and are designed to obtain evidence on safety and preliminary data on efficacy. The number of subjects tested in this phase may be in the hundreds. The final pre-approval clinical testing phase, Phase III, typically consists of a number of large-scale (often multi-center) trials that are designed to firmly establish efficacy and to uncover side-effects that occur infrequently. The number of subjects in phase III trials for a compound can total in the thousands". Source: DiMasi J.A., Hansen R.W., Grabowski H.G. The price of innovation: new estimates of drug development costs. *Journal of Health Economics 22 (2003) 151–185*

4. RESULTS

Professor David B. Ridley of Duke University's Fuqua School of Business has very kindly provided a clinical trial dataset purchased from IMS Health[6], which includes a comprehensive list of research projects that span all classes of drugs undertaken by pharmaceutical companies around the world from 1994 to 2010. To suite the purpose of the current study, the original data set was trimmed down to include only projects conducted by the top 20 pharmaceutical companies listed in Table 2. Table 3 below shows summary statistics for all the dependent and independent variables in this study. Total number of observations in the dataset is 263, with data points from 20 pharmaceutical companies collected over a 16-year period (1994-2000). The actual number of data points falls short of the theoretical 20*16=320, as some data points are missing due to changes in company status after mergers and acquisitions. Financial-related data such as gross revenue and revenue generated from animal health business are gathered from Bloomberg, company websites or annual reports on Edgar[7]. Drug and pipeline-related data such as numbers of various drugs and Class P pipeline sizes are calculated based on the IMS dataset. Note that in the data set, revenue ranges from USD$ 685m to USD$ 50,978m (2000 dollars) with a mean of USD$ 19,830m. 49% of the data points come from US-based pharmaceutical companies, while about 43% come from European firms. The average number of Class P drugs that each company has in its pipeline is about 0.63, and on average, approximately 1.77% of

[6] IMS Health is an international company that supplies the pharmaceutical industry with sales data and consulting services. It collects pharmaceutical sales and prescription data from markets across the world. As of January 2007, they collect sales data from 75% of prescriptions in 100 countries. In the U.S. it is able to cover 90% of pharmaceutical sales. This allows IMS to cover over one million pharmaceutical products from over 3,000 companies. Website: *http://www.imshealth.com/portal/site/imshealth* Accessed on March 23, 2011

[7] EDGAR, the Electronic Data-Gathering, Analysis, and Retrieval system, performs automated collection, validation, indexing, acceptance, and forwarding of submissions by companies and others who are required by law to file forms with the U.S. Securities and Exchange Commission (the "SEC"). The database is freely available to the public via the Internet.

company's annual gross revenue is generated from animal health business. Reference to the summary statistics will be frequently made throughout the results discussion sections for various neglected diseases.

TABLE 3
SUMMARY DATA

Variable	Mean	Standard Deviation	Minimum	Maximum
Number_MalariaDrugs	1.01	1.42	0	8
Number_TBDrugs	0.26	0.45	0	2
Number_DengueDrugs	0.08	0.29	0	2
Number_TyphoidDrugs	0.12	0.43	0	3
Revenue[8]	19830	11372	685	50978
Revenue (log)	9.65	0.86	6.53	10.84
US_Firm	0.49	0.50	0	1
European_Firm	0.43	0.50	0	1
Pipeline	0.63	0.95	0	4
Animal_Health	1.77	0.03	0	12.16

Based on the data, four separate regressions were performed to investigate the impacts of firm level characteristics on anti-Malaria, anti-TB, anti-Dengue and anti-Typhoid drugs. Results are arranged in order of increasing level of negligence with respect to diseases. In other words, Typhoid is the most neglected disease among the four. To illustrate this point, Table 4 below shows the number of clinical trials in each disease category conducted by the above-mentioned top-20 pharmaceutical companies, as well as by all pharmaceutical companies and non-profit research institutions globally from 1994 to 2009.

[8] Expressed in constant 2000 US Dollars.

TABLE 4
NUMBER OF CLINICAL TRIALS BY DISEASES

Drug	Number Among Top 20 Pharmaceutical Companies	Total Number
Anti-Malaria	36	198
Anti-TB	24	108
Anti-Dengue	7	31
Anti-Typhoid	8	18

4.1 Malaria

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. In 2008, there were 247 million cases of malaria and nearly one million deaths, mostly among children living in Africa[9]. In the same year, only about USD$566m was spent on R&D projects for Malaria drugs, less than half of that for HIV/AIDS. Globally from 1994-2009, there are altogether 198 active or inactive anti-malaria drug research projects, with 362 participating companies or research institutions. In the trimmed data set under consideration, mean number of anti-Malaria research projects conducted by the Top 20 pharmaceutical companies in a given year is approximately 1 with a standard deviation of 1.42 (Table 3). The regression output is given in Table 5 below.

[9] WHO Fact Sheet on Malaria *http://www.who.int/mediacentre/factsheets/fs094/en/* Accessed on 20 March, 2011

TABLE 5
ESTIMATES OF THE IMPACT OF FIRM CHARATERISTICS ON ANTI-MALARIA R&D PROJECTS[10]

Variable	Coefficient	Robust t-Statistic	P-Value	
Log_Revenue	0.280	2.016	0.045	*
European_Firm	0.846	3.157	0.002	**
Pipeline	0.884	6.804	0.000	***
Animal_Health	0.043	0.971	0.333	

It is worth noting that all the coefficients have the expected signs stated in Section 3. That is, positive associations are observed between the number of anti-Malaria drugs that company k has in its pipeline in year t and company k's revenue volume, pipeline size and proportion of revenue derived from its animal health business. Moreover, if company k is headquartered in Europe, it is likely to have more R&D incentives for anti-Malaria drugs than other firms. On top of this, all coefficients, but that of Animal_Health, have statistically significant p-values.

First and foremost, the regression output reveals a positive correlation between Log_Revenue and the number of anti-malaria drugs that a firm invests in a particular year. A coefficient of 0.280 means that 1% a change in a firm's revenue is associated with an increase of 0.0028[11] in the number of active anti-Malaria drug R&D programs, which can be translated to a revenue elasticity of 0.28 at the mean. Given the range (from USD$ 50978m to USD$ 685m) and standard deviation of revenue (USD$ 11372m) under consideration and the highly statistically significant p-value, it is very likely that revenue size among large pharmaceutical companies has a considerable positive impact on their willingness to invest in anti-Malaria drugs.

[10] In all the output tables, "." – statistically significant at 0.1 level, "*"— statistically significant at 0.05 significance level, "**" -- statistically significant at 0.01 level, "***" -- statistically significant at levels below 0.001. Note that all the statistical significance is with reference to a 2-tailed test.

[11] For linear-log regression, 1% change in X is associated with a change in Y of 0.01*coefficient of X

Second, in line with our earlier prediction, a positive association between the dummy variable European_Firm and the dependent variable is identified. A coefficient of 0.846 means that European firms on average have 0.846 (84.6% of the grand mean of the independent variable) more anti-Malaria molecules in their pipelines than firms based in other continents, predominantly US firms. This difference, put into the context of the mean of the dependent variable, represents a large discrepancy between the willingness of US and European firms to invest in anti-Malaria drugs. The difference can be attributed to a consortium of factors. As mentioned before, European countries such as Britain and France has close colonial ties with countries where Malaria is prevalent in, and therefore companies based in these countries may show heightened corporate social responsibilities towards Malaria-riddled countries. Furthermore, other factors such as review regimes, general trend in corporate strategies and corporate cultures may potentially contribute to the coefficient as well.

Third, a positive association of coefficient 0.884 between the independent variable Pipeline and the dependent variable is identified. This essentially reveals that on average, for every 1 increase in the number of Class P projects in a company's pipeline, the spillover effect of R&D knowledge leads to a 0.884 increase in the number of anti-Malaria research projects. Taking the mean of $Pipeline_{kt}$ into account, the Pipeline-elasticity of number of anti-Malaria R&D projects at mean is approximately 0.56. In other words, 1% increase in a company's pipeline volume for Class P drugs is correlated with a 0.56% increase in its pipeline volume for anti-Malaria drugs. This piece of result, coupled with the highly statistically significant p-value, reveals a high importance of spillover effects for anti-Malaria research, which may be due to the highly established nature of Malaria pathology, hence relevant knowledge from R&D of other diseases can be easily identified and assimilated.

Finally, a positive association between a company's percentage of revenue from animal health business and the dependent variable is seen. More specifically, 1% increase in revenue generated from a company's animal health business segment is associated with an increase of 0.043 in the number of anti-malaria drugs in the company's pipeline. However, p-value for this coefficient is as large as 0.3. Hence, the positive spillover effect from R&D of animal health products into anti-Malaria research may not be justified on statistical ground.

4.2 TB

TB is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years. Moreover, TB is often co-morbid with HIV/AIDS. In 2009, 1.7 million people died from TB, including 380 000 people with HIV/AIDS. TB is still considered a disease of poverty, affecting mostly young adults in their most productive years[12]. In 2008, only USD$470m was spent on R&D for anti-TB drugs, again less than half of that for HIV/AIDS. Although the co-morbid nature of the two diseases may suggest that investments in anti-HIV/AIDS research projects may serve to lower TB incidence, this level of level of spending, given the current level of global burden inflicted by TB, is still considered to be disproportionally low. In the data set, average number of anti-TB research projects conducted by the top 20 pharmaceutical companies is approximately 0.26 (Table 3). The regression output is given in Table 6 below.

[12] WHO Fact Sheet on TB *http://www.who.int/mediacentre/factsheets/fs104/en/* Accessed on 20 March, 2011

TABLE 6
ESTIMATES OF THE IMPACT OF FIRM CHARATERISTICS ON ANTI-TB R&D PROJECTS

Variable	Coefficient	Robust t-Statistic	P-Value	
Log_Revenue	0.154	4.200	0.000	***
European_Firm	0.099	1.399	0.164	
Pipeline	0.054	1.561	0.120	
Animal_Health	0.020	1.719	0.087	.

In accordance with earlier predictions, all independent variables, as expected, have positive associations with the dependent variable. Only the coefficients for Log_Revenue and Anmial_Health have statistically significant p-values at 0.1 level. However, one has to note that the coefficients for European_Firm and Pipeline can in fact achieve statistical significance at 0.1 level if one-tailed t-tests are performed instead of the default two-tailed t-tests.

For more specific interpretations, first, a statistically significant positive association between Log_Revenue and the dependent variable can be easily discerned. A coefficient of 0.154 implies that for 1% increase in a firm's annual revenue, the number of anti-TB drugs in its portfolio for that year increases by approximately 0.00154. Calculation reveals revenue-elasticity of anti-TB research programs to be 0.59 at the mean. This value is considerably larger than that for anti-Malaria research programs due to the fact that anti-TB research projects are are more concentrated among companies with larger revenue volumes.

Second, the coefficient of the dummy variable European_Firm is 0.099, which means that, on average, European registered firms have 0.099 (38% of the grand mean of the dependent variable) more pipeline anti-TB drugs than non-European firms in a given year. However, from a statistical perspective, the coefficient is not significant (p-value=0.164). Therefore, unlike the case for anti-Malaria drugs, the developmental incentives for anti-TB drugs are not as clustered among European firms. This can be attributed to be fact that TB, due to its highly co-morbid

nature with HIV/AIDS, has an incidence distribution that is not as concentrated in developing nations that have colonial ties with European countries.

Third, a positive association of coefficient 0.054 between the independent variable Pipeline and the dependent variable is identified. This essentially reveals that on average, for every 1 increase in the number of Class P projects in a company's pipeline, the spillover effect of R&D knowledge leads to a 0.054 increase in the number of anti-TB research projects. Therefore, the Pipeline-elasticity of number of anti-TB R&D projects at mean is approximately 0.13. In other words, 1% increase in a company's pipeline volume for Class P drugs is correlated with a 0.13% increase in its pipeline volume for anti-TB drugs, which is indeed a much lower level of spillover effect than that for anti-Malaria drugs. This, and the fact that the coefficient is not statistically significant (p-value=0.120), can be attributed to the highly drug and vaccine resistant nature of TB, hence scientific knowledge pooled from R&D for other diseases may not be as readily applied to anti-TB research than to anti-Malaria research.

Last but not least, positive association between Animal_Health and the dependent variable is identified with a coefficient of 0.020. 1% increase in revenue from animal health business is associated with a 0.020 (7.7% of the grand mean for the grand mean of the dependent variable) increase in number of anti-TB molecules in a company's R&D pipeline. Although the coefficient is statistically significant at 0.10 level (p=0.087), given that the average percentage of revenue from animal health business across the sample is only about 1.77%, an increase of 1% represents a large deviation from the norm.

4.3 Dengue

Dengue is a mosquito-borne infection that causes a severe flu-like illness, and sometimes a potentially lethal complication called Dengue Haemorrhagic Fever. It is found in tropical and sub-tropical climates worldwide and about two fifths of the world's population is now at risk. Moreover, Dengue Haemorrhagic Fever is a leading cause of serious illness and death among children in some Asian countries. There is no specific direct anti-viral treatment for dengue, but appropriate medical care frequently saves the lives of patients with the more serious Dengue Haemorrhagic Fever[13]. In 2008, only USD$ 130m was spend on R&D programs for Dengue, about 1 tenth of that for HIV/AIDS. In our dataset, average number of anti-Dengue research projects conducted by the Top 20 pharmaceutical companies under consideration is approximately 0.08 (Table 4). The regression output is given in Table 7 below.

TABLE 7
ESTIMATES OF THE IMPACT OF FIRM CHARATERISTICS ON ANTI-DENGUE R&D PROJECTS

Variable	Coefficient	Robust t-Statistic	P-Value	
Log_Revenue	-0.040	-1.689	0.093	.
European_Firm	0.141	3.063	0.003	**
Pipeline	0.084	3.789	0.000	***
Animal_Health	0.004	0.500	0.618	

The coefficients of European_Firm, Pipeline and Animal_Health all have positive signs, as expected. However, the coefficient of Log_Revenue turns out to be negative, indicating a negative association between firm's financial power and willingness to invest in drugs of neglected diseases. Besides, all coefficients, but that for Animal_Health, are statistically

[13] WHO Fact Sheet on Dengue and Dengue Hemorrhagic Fever.
http://www.who.int/mediacentre/factsheets/fs117/en/index.html Accessed on 20 March, 2011.

significant at 0.1 level under two-tailed t-tests. Below is a more detailed discussion of the regression outputs.

First, in conflict with earlier predictions, there appears to be a negative association between Log_Revenue and the dependent variable. More specifically, a coefficient of -0.040 implies that for 1% increase in a firm's annual revenue, the number of anti-Dengue drugs in its portfolio in that year decreases by approximately 0.0004. The revenue-elasticity of anti-Dengue research programs is henceforth calculated to be -0.5 at the mean. This large negative revenue-elasticity shows that unlike the case for anti-Malaria and anti-TB drugs, larger companies are less willing than smaller companies to conduct research for anti-Dengue drugs.

Second, European registered firms have 0.141 (>100% of the grand mean of the dependent variable) more anti-Dengue drugs than non-European firms in pipeline in a given year. This, together with the statistically significant p-value (p-value=0.03), essentially means that almost all R&D projects for anti-Dengue drugs in our sample are conducted by European based pharmaceutical companies.

Third, every 1 unit increase in the number of Class P projects in a company's pipeline leads to a 0.084 increase in the number of anti-Dengue clinical trials. Translating into elasticity terms, 1% increase in a company's pipeline volume for Class P drugs is correlated with a 0.66% increase in its pipeline volume for anti-Dengue drugs, which is at least partially attributable to the spillover effects of research knowledge across related diseases.

Last but not least, the coefficient of the predictor variable Animal_Health equals 0.004. This fairly low magnitude of impact, coupled with low level of statistical significance (p-value=0.618), implies that spillover effects from animal health business is not as important as other factors in influencing a company's R&D decision in anti-Dengue drugs.

4.4 Typhoid

Typhoid fever is a bacterial disease that is commonly transmitted through the ingestion of food or drink contaminated by the faeces or urine of infected people. Typhoid fever is characterized by the sudden onset of sustained fever, severe headache, nausea, severe loss of appetite and diarrhoea. As a direct consequence, Typhoid is often classified under the broader umbrella of Diarrhoea Diseases. According to WHO website, the very conservative annual number of typhoid cases for the year 2000 is estimated at 17 million with 600 000 deaths[14]. Moreover, with the advent of proper sanitary facilities, Typhoid fever has been eliminated in almost all developed nations.

TABLE 8
ESTIMATES OF THE IMPACT OF FIRM CHARATERISTICS ON ANTI-TYPHOID R&D PROJECTS

Variable	Coefficient	Robust t-Statistic	P-Value	
Log_Revenue	-0.112	-3.214	0.002	**
European_Firm	0.161	2.396	0.018	*
Pipeline	0.139	4.240	0.000	***
Animal_Health	-0.004	-0.379	0.705	

In opposition to earlier predictions, negative associations are identified between the dependent variable, which captures a firm's willingness to invest in anti-Typhoid R&D projects, and the predictors Log_Revenue and Animal_Health. Moreover, statistically significant p-values for the coefficients are found for the variables Log_Revenue, European_Firm and Pipeline. Hence, Animal_Health may not add statistically significant predictive power to the overall model.

[14] WHO Fact Sheet on Typhoid Fever. *http://www.who.int/vaccine_research/diseases/typhoid/en/* Accessed on 25 March, 2011.

The paragraphs below offer more detailed interpretations of the regression output. First of all, perhaps due to the highly neglected nature of Typhoid fever, a negative correlation, quantified by a coefficient of -0.112, between Log Revenue and the dependent variable is revealed by the regression analysis. Calculation yields a revenue-elasticity of -0.95 at the mean, which is the strongest negative elasticity among the four diseases. In a direct sense, this means that the distribution of clinical trials for anti-Typhoid drugs is highly skewed towards companies with smaller revenue sizes in the data set.

Second, European-based firms again have more incentives to develop drugs for Typhoid. A coefficient of 0.161 implies almost all anti-Typhoid research projects are conducted by European firms.

Third, coefficient for $Pipeline_{kt}$ is 0.139 (equivalent to a pipeline-elasticity of 0.72), is the highest among the four diseases under investigation. Again, this can be due to the fact that the disease pathology of Typhoid is highly established, and hence, spillover R&D knowledge or expertise from other clinical trials can be readily assimilated.

Last, the statistically insignificant (p-value= 0.705) coefficient of Animal_Health is -0.004, again implying that the percentage of revenue that a company derives from its animal health business segment is not a powerful predictor of its R&D decisions for drugs for neglected diseases.

5. CONCLUSION

Taking all four regressions into account, differential impacts of firm-level characteristics on R&D decisions for different disease categories are clearly revealed. The results, to a certain extent, serve to answer the research question stated at the beginning of the paper, “which firms

develop drugs for neglected diseases, and why"? It is found that, research on neglected diseases with greater burdens, such as Malaria and TB, tends to be done by firms with the greater revenue sizes; and research on neglected diseases with smaller burdens, such as Dengue and Typhoid, tends to be done by firms with somewhat smaller revenue size. Moreover, research on neglected diseases by top 20 firms is also correlated with spillovers from other research (including animal health) and with European headquarters. Based on these findings, appropriate policy implications can then be drawn.

Table 9 summarizes the processed regression outputs from each disease category for comparison purpose. More specifically, anti-TB drugs exhibit the highest level of positive revenue-elasticity, followed by anti-Malaria drugs, while anti-Dengue drugs exhibit a moderate negative revenue-elasticity, and anti-Typhoid drugs exhibit a high level of negative revenue-elasticity. In a direct sense, a firm's revenue can serve as a proxy for its financial size, so large firms are more willing to invest in widespread diseases such as Malaria and TB, while less willing to invest in more neglected diseases such as Dengue and Typhoid. Moreover, and perhaps in a less direct sense, measuring revenue-elasticity can serve as a remote proxy for measuring the extent to which monetary incentives can impact on R&D decisions. Based on the regression results, monetary-related incentive programs such as tax breaks and R&D grants may be postulated to have the highest impact on anti-TB drugs. On top of this, the regression results also reveal that European headquartered firms are, in general, more willing to invest in drugs for neglected than US based firms. The differential effect is the largest for anti-Typhoid and anti-Dengue drugs, followed by anti-Malaria drugs and then anti-TB drugs. This piece of result implies that European-based companies are more willing to conduct clinical trials targeting at diseases that are more disproportionally rampant in developing nations. Therefore, when

devising incentive program, US-based firms may represent better targets, since drugs for neglected diseases already occupy a more significant portion of European pharmaceutical companies' risk portfolio. Furthermore, positive spillover effects from R&D on anti-parasitic diseases are observed across all four disease categories under investigation. Anti-Typhoid, anti-Dengue and anti-Malaria all exhibit relatively higher level of pipeline elasticity as compared to that of anti-TB drugs. This falls in line with the general knowledge that the pathology of TB, being highly drug and vaccine resistant in nature, is harder to be scientifically established than that of Dengue and Malaria. Therefore, to encourage future R&D for anti-TB drugs, a potential measure would be for government and non-profit organizations to promote more primary research programs on the disease mechanism and pathology of TB. This way, more meaningful spillover effects can be captured for anti-TB drugs by pharmaceutical firms. Last but not least, a positive association between the share of animal health in a company's business model and its willingness to invest in neglected diseases is observed across all but one disease types, although the impact is rather small and the only case of statistical significance is observed for anti-TB drugs.

TABLE 9
COMPARING THE IMPACT OF FIRM CHARATERISTICS ON ANTI-MALARIA, ANTI-TB AND ANTI-DENGUE R&D PROJECTS

Drug	Revenue-Elasticity	European_Firm Coefficient (% of grand mean)	Pipeline-Elasticity	Animal_Health Coefficient (% of grand mean)
Anti-Malaria	0.28*	0.864 (84.6%)**	0.56***	0.043 (4.3%)
Anti-TB	0.59***	0.099 (38%)	0.13	0.020 (7.7%)`
Anti-Dengue	-0.50`	0.141 (>100%)**	0.66***	0.004 (5.0%)
Anti-Typhoid	-0.95**	0.16 (>100%)*	0.72***	-0.004

In conclusion, firm-level characteristics can have very different magnitude and direction of impacts on R&D decisions for different categories of diseases. The differential impacts or associations can be attributed to a host of factors such as the current understanding of disease pathologies, regions of prevalence of diseases, and availability of alternative treatments etc. Therefore, when looking to device incentive programs to encourage R&D for neglected diseases, different impacts of firm-level characteristics should be taken into account. Future studies may need to gather a more comprehensive list of independent firm level characteristics to achieve a more accurate prediction of firms' willing to develop drugs for developing nations. For instance, to measure intercontinental or inter-country differences in firm's level of commitment to neglected diseases research, more specific parameters such number of immigrants, degree of similarities in regulatory regimes, and the use of common languages could be employed as predictor variables.

References

Ridley, David B., Henry G. Grabowski and Jeffrey Moe. 2006.Developing Drugs for Developing Countries. *Health Affairs Volume 25, Number 2, P313-323.*

Grabowski, Henry G., David B. Ridley and Jeffrey Moe. 2008. Encouraging Innovative Treatment of Neglected Diseases through Priority Review Vouchers. *Prescribing Cultures and Pharmaceutical Policy.*

Moran M., Guzman J., Ropars A.L., McDonald A., Jameson N., Omune B., Ryan S. and Wu L. 2009. Neglected Disease Research and Development: How Much Are We Really Spending? *PLoS Med 6(2): e1000030.*

Hollis, Aidan. 2005. An Optional Reward System for Neglected Disease Drugs.

Ridley, David B., Adrian Towse and Hannah Kettler. 2010. Drugs for Developing Countries. *Draft prepared for the Oxford Handbook of Pharmaceutical Economics*

Olson, M.K. 1997. Firm Characteristics and the Speed of FDA Approval. *Massachusetts Institute of Technology Journal of Economics & Management Strategy, Volume 6, Number 2, Summer 1997, 377–401.*

Rodriguez, Daniel. 1998. Decisions of Pharmaceutical Firms for New Product Development. *http://web.mit.edu/ipc/publications/pdf/Decisions.pdf.*

Kyle, Margaret K. 2006. The role of firm characteristics in pharmaceutical product launches. *RAND Journal of Economics Vol. 37, No. 3, Autumn 2006 pp. 602-618.*

DiMasi J.A., Hansen R.W., Grabowski H.G. The price of innovation: new estimates of drug development costs. *Journal of Health Economics 22 (2003) 151–185*

Adams C.P., Brantner V.V. Estimating The Cost Of New Drug Development: Is It Really $802 Million? *Health Affairs, 25, no. 2 (2006): 420-42*