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The hope for neglected diseases: R&D incentives

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Neglected diseases are neglected because they cannot generate enough return on R&D to pharmaceutical firms. This paper analyzes and compares existing proposals for public intervention in R&D for neglected diseases. Incentives for neglected diseases are comprehensively evaluated based on seventeen selected criteria grouped into four categories: efficiency, feasibility, fairness, and sustainability. Our conclusion is that public-private partnerships coordinated through a centralized service platform have the highest potential to satisfy the criteria for the successful development.

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JEL classification: I12, I18, H41, H87

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1. Introduction

Neglected diseases (NDs) are so called because pharmaceutical firms cannot make an adequate return on research and development (R&D) into their prevention and cure. With the exception of tuberculosis, these diseases mainly occur in low income countries where patients have low purchasing power and which lack functioning healthcare systems. Approximately 2.5 million people die every year from NDs. Because NDs are parasitic and bacterial infections, they potentially put the majority of the human race at risk.

Tuberculosis, malaria, schistosomiasis, leishmaniasis and others as listed in Table 1 affect more than 1 billion people and yet less than 0.001% of the US$ 60–70 billion spent on new drug development is dedicated to ND treatments (WHO, 2009: 3). Few of the new chemical entities are drugs for tropical diseases (Pecoul, Chirac et al. 1999; Trouiller, Olliaro et al., 2002). Chirac and Torreele (2006) shows that out of 163 new chemical entities marketed between 2000 and 2004, four drugs (2.5%) were for NDs. Since then some progress has been noticed for tuberculosis, malaria and dengue, but other diseases have no new drug candidate registered in the US (Wolters Kluwer Health's Adis R&D Insight)[1]. Progress on tuberculosis, malaria and dengue may be explained by increased R&D spending (Moran, Guzman et al., 2008: 5).

Academic research is sparse: less than 2% of all citations on PubMed, the U.S. national digital archive of biomedical and life sciences journal literature, were attributed to tropical diseases for the period 1980-1999 (Lanjouw and Cockburn, 2001). And even when some progress is made with the development of drugs which could cure NDs,

[1] available at http://newmeds.phrma.org, accessed on 1 July 2010.

pharmaceutical companies are cautious in publishing the results for fear of increased public pressure (Moran, Ropars et al., 2005).

The burden of these diseases is heavy if measured by the disability-adjusted life year (DALY). DALY measures the time lost in being ill; it combines years of life lost due to premature mortality and years of life lost due to time spent being ill. One year of less than healthy live is equal to one DALY. Japanese having the longest life expectancy, premature mortality is measured against Japanese life expectancy. Various schemes have been put forward in an attempt to alleviate this burden by increasing pharmaceutical R&D related to NDs. This paper aims to describe these proposals and to assess their efficiency.

The next section reviews the burden of these diseases and ways in which that burden is exacerbated by conditions in low income countries; section III discusses disadvantages of the existing proposals to tackle the NDs problem; section IV compares existing proposals through a policy analysis framework followed by our recommendations and a conclusion.

2. Burden of neglected diseases

Some NDs, such as tuberculosis and malaria, have many sufferers and create a large health burden (table 1). Comparing the global burden of neglected diseases in 2004 with 2001, tuberculosis, malaria, and Chagas disease show modest progress (column 4) while mixed or no progress is observed for most of the other NDs during that period.

Table 1 - Major neglected diseases and their characteristics ranked by global burden

Disease (1)	People at risk in a year (2)	Regional concentration (3)	DALYs, thousand 2004/2001 (4)	Deaths, thousand 2004/2001 (5)	Major health damage (6)	Available medicine (7)
Tuberculosis (TB)	Over 2bn carry the bacterium; 2nd most dangerous infection after HIV	Mostly Africa and SE Asia	34,188/ 36,093	1,462.5/ 1,606	1.6 m deaths in 2005, with annual global damage of around US$12 bn, costing up to 7% of GDP in some countries.	Several months of intensive therapy with a variety of drugs; cure is not guaranteed; increasing resistance
Malaria	More than 0.5bn; 40% of the world's population are at risk; 2 children statistically die every minute	Mostly Africa and SE Asia; transmitted by mosquito	33,941/ 39,970	888.3/ 1,208	Over 1 m death every year, mostly children; costing about 1.3% of GDP in the affected countries	Combination of therapies; expensive for the poor, increasing resistance
Intestinal nematode infections (Ascariasis, Trichuriasis, Hookworm)	576-1,221 m infected, 4.2bn at risk	Worldwide in warm regions, especially in SS Africa, SE Asia and Central America	16,261/ 2,349	31.7/ 12	Nematodes (worms) live in human body causing pain, toxicity, cognitive delays, weight loss, and anaemia	Limited access to existing drugs, ineffective against adult worms
Lymphatic filariasis	120 m affected with 1.3 bn at risk	India and Africa; transmitted by mosquito	5,940/ 4,667	0.3/ 0	1/3 of patients are seriously incapacitated, causes adenolymphangitis and lymphedema	Limited access to drugs, which tend to be effective for early treatment
Leishmaniasis	About 350 m at risk in 88 countries	Africa and SE Asia, transmitted by parasites	1,973/ 1,762	46.8/ 51	Leads to scarring, damage to liver, anaemia	Drugs are either toxic or expensive
Schistosomiasis (bilharzia)	About 207 m in 74 countries	Mostly Africa and SE Asia; transmitted by parasites	1,706/ 1,526	41.1/ 14	Damage to the bladder and kidneys, liver fibrosis, cognitive backwardness	Limited access to drugs, drug resistance
Human African Trypanosomiasis	Around 60 m at risk	Sub-Saharan Africa	1,671/ 1,333	52.3/ 48	Sleeping sickness	Drugs are toxic and injectable only
Japanese encephalitis	Up to 50,000 cases a year	Asia	680/ 604	11.0/ 14	Mosquito-born virus, can lead to mortality and mental retardation	vaccine exists, but expensive
Dengue	About 1/3rd of the world's population	Most developing countries; transmitted by mosquito	669/ 529	18.1/ 19	Terrible flu-like symptoms	No effective specific drugs; mosquito nets
Chagas disease	25 m in 21 countries	South and Central America	426/ 585	11.3/ 14	Cardiomyopathy (heart damage), megacolon, megaesophagus	Available drugs have serious side effects
Onchocerciasis	90 m at risk	Tropical Africa; transmitted by parasitic worm	388/ 439	0.1/ 0	Serious vision impairment, can be transmitted by flies	An effective drug exists
Leprosy	2002: 650,000 2004: 410 000 new cases	Africa, SE Asia, Brazil, mainly concentrated in 9 countries	194/ 192	5.4/ 6	Might lead to permanent damage for skin, nerves, and eyes	Fully cured in most countries, effective drugs exist

					caused by bacillus	

Sources: Ford (2006: 112); http://www.who.int/tdr/svc/diseases (the WHO Program for Research and Training in Tropical Diseases); http://www.who.int/mediacentre/factsheets/, http://www.wpro.who.int/health_topics/schistosomiasis/; Deworming for health and development. Report of the third global meeting of the partners for parasite control, Geneva: World Health Organization, 2005. Data on tuberculosis is obtained from http://www.tballiance.org/why/tb-threat.php; columns (2), (6) and (7) are based on Hotez, Molyneux et al. (2007); column (7) is supplemented by data from Mrazek and Mossialos (2003). Columns (4) and (5) for 2004 are based on WHO (2008: 54-56); the data for 2001: Lopez, A. D. and Disease Control Priorities Project (2006: 174, 228, 452).

Using WHO (2008) data we estimated the median of DALYs lost to NDs was 13.1% in countries with GDP per capita below $1000 by purchasing power parity (PPP) in international dollars. Decreased workers' productivity due to neglected tropical diseases (excluding tuberculosis) causes losses of potential output worth billions dollars (Hotez, Molyneux et al., 2007: 1021). An economic cost of DALYs for malaria alone could be valued at 5.8 percent of the gross national product of sub-Saharan Africa if each DALY is valued conservatively as equal to per capita income (Report of the Commission on Macroeconomics and Health, 2001: 31). Using the same conservative evaluation and the WHO (2008) data for year 2004, we estimated the median share of GDP lost to neglected diseases was 7.25% for countries with GDP per capita less than $1000 by PPP.

Testing for causes

NDs might be labelled as diseases of poverty implying that rising income would eliminate most of the disease burden. However this is not the whole story. Poverty, lack of sanitation, lack of political commitment are all reasons that have been advocated in the literature to explain the burden of NDs (WHO, 2009:11). Preston (1975) finds a high positive correlation between the logarithm of national per capita income and life expectancy for low income countries. Research by Pritchett and Summers (1996) supports the hypothesis that economic growth reduces infant mortality. The causal

relation between health and poverty can run in both directions. Poverty significantly reduces access to proper nutrition and health care products and services, and, in turn, health problems can reduce productivity and corresponding labour compensations. Lorentzen, McMillan et al (2008) find that a greater risk of death discourages education, savings and investment and this largely explains poor growth performance of most African countries.

In most of the countries concerned, political commitment prioritizing healthcare is lacking as can be seen by the lack of access to basic infrastructure, taxes and non-tariff barriers for imported medicines, difficulties in contract enforcement, and bureaucratised patenting (Ahmed, Cudjoe et al., 2007). While some diseases could be treated easily and cheaply such as intestinal worms (treatments cost less than a dollar per year and only need to be taken once or twice per year with no side effect) little is done – despite one in four people being affected worldwide (Kremer, 2002: 68). The lack of governance in the health sector as reflected by absenteeism and corruption of health personnel and health care managers has been evidenced as being crucial (Lewis, 2006). Suspicion of corruption in Zambia (Mfula, 2010) translated in $33 million of health assistance being suspended in 2009 by Sweden and the Netherlands and another $300 million in 2010 by The Global Fund to Fight AIDS, Tuberculosis and Malaria.

According to the political economy literature (McCarty and Meirowitz, 2007), the lack of political commitment is explained by the relatively short political horizons of elected officials in comparison to long drug development cycles; by the diversion of funds to some “national pride” big investment projects; by a lack of qualified cost-benefit estimations of the impact of the disease burden on the economy that would enhance

political visibility of such diseases; and lastly because the people affected by these diseases have little political voice.

The data and estimation

We tested the hypothesis that sanitation, government commitments to health care and per capita income have a negative association with the burden of NDs. We use data for the year 2004 for which the recent disease burden estimations of the WHO (2008) are available. Unfortunately, methodological inconsistency in DALY estimates across time and countries provided by the WHO disables panel data analysis. The WHO report on global burden of diseases gives the most recent comparable cross-country estimates of DALYs (WHO, 2008). Other variables have been obtained from the World Bank web site of the World Development Indicators and The Worldwide Governance Indicators[2] for 188 countries (table 2). Commitment to health care is proxied by the share of public health expenditures in total government expenditures and by governance indicators.

Table 2 - Descriptive statistics

Variables	Observations	Mean	Std. Dev.	Min	Max
Lnurses	60	.2035	1.1211	-1.6607	2.6532
Lhlgov	187	2.2458	.5574	-.3567	3.5086
Lgdp	176	8.5512	1.2922	5.5281	11.1186
Lsanita	159	3.8141	.7722	1.0986	4.6052
Lwater	168	4.2428	.3939	2.3979	4.6052
Lrural	185	3.6403	.7339	.5423	4.5029
Ldalyn	188	5.6861	2.3121	.4947	9.2395
	The governance indicators of the World Bank:				
Va	188	-.06	1.02	-2.14	1.83
Gaf	188	-.06	1.00	-2.16	2.34
Cc	185	-.08	1.00	-1.79	2.43

[2] available at http://info.worldbank.org/governance/wgi/index.asp

With *ldalyn, lnurses, lhlgov, lgdp, lsanita, lwater, lrural* respectively logarithms of DALYs lost to neglected diseases, nurses per 1,000 people, public health expenditure in total government expenditures, GDP per capita by PPP, improved sanitation facilities, improved water source, and share of rural population; *va*, *gaf* and *cc* stand respectively for the governance indicators: voice and accountability, government effectiveness, and control of corruption.

There is a negative correlation between the logarithms of DALYs lost to NDs and access to water, numbers of nurses, and government efficiency (table 3).

Table 3 - Correlation between major regressors

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. *ldalyn*	1.00									
2. *lnurses*	-0.67	1.00								
3. *lhlgov*	-0.15	0.29	1.00							
4. *lgdp*	-0.67	0.79	0.25	1.00						
5. *lsanita*	-0.53	0.53	0.11	0.49	1.00					
6. *lwater*	-0.60	0.45	0.12	0.40	0.40	1.00				
7. *lrural*	0.45	-0.45	-0.25	0.55	-0.29	-0.20	1.00			
8. *va*	-0.47	0.51	0.45	0.47	0.30	0.38	-0.35	1.00		
9. *gaf*	-0.73	0.62	0.40	0.67	0.38	0.51	-0.48	0.77	1.00	
10. *cc*	-0.76	0.61	0.39	0.61	0.31	0.52	-0.50	0.77	0.93	1.00

We run the following simple cross section OLS (table 4) to see if sanitation and national income corresponds with the burden of diseases for NDs:

$$Ldalyn_i = \alpha_1 + \alpha_2 lgdp_i + \alpha_3 lsanita_i + \alpha_4 lwater_i + \alpha_5 lrural_i + \alpha_6 lhlgov_i + \alpha_7 lnurses_i + \alpha_8\ Governance\ indicator_i + \varepsilon_i$$

where the residuals follow a white noise process for a country i.

Table 4 - Regression results for logarithm of DALYs lost NDs per 100,000 population, 2004

	1	2	3	4	5	6
Lgdp	-1.031	-1.031	-.096	-.619	-.901	-.817
	(.203)***	(.207)***	(.158)	(.202)***	(.188)***	(.218)***
Lsanita	-.459	-.458	-.271	-.506	-.356	-.453

	(.166)***	(.168)***	(.183)	(.160)***	(.142)**	(.182)**
lwater	-1.131	-1.132	-1.001	-1.008	-.685	-1.037
	(.553)**	(.556)**	(.336)***	(.416)**	(.385)*	(.499)**
lrural	.104	.105	.269	.062	.140	.137
	(.265)	(.265)	(.362)	(224)	(.412)	(.239)
Lhlgov		.009	.475	.148	.150	.211
		(.164)	(.197)**	(124)	(.134)	(.147)
Lnurses			-.293			
			(.199)			
Gaf			-.944			
			(.276)***			
Cc				-.825	-.453	
				(167)***	(.268)*	
Va						-.493
						(.175)
Constant	20.877	20.862	10.826	16.771	16.960	18.026
	(1.955)***	(1.935)***	(2.782)***	(1.971)***	(2.893)***	(2.098)***
Observations	148	148	54	147	97	148
F-statistic	76.84	62.77	16.21	111.45	32.34	65.66
R^2	0.742	0.742	0.718	0.796	0.663	0.764

Note: heteroscedasticity robust t-statistics are in parentheses. Significance levels: *** - at the 1%, ** - at 5%, * - at 10%. The fifth regression estimates coefficients for low and lower-middle-income economies in the classification of the World Bank World Development Report (2005).

GDP per capita, improved access to sanitation, and water appear to be statistically significant across most specifications. Share of rural population or government expenditures on health are not robustly significant indicators for the burden of NDs. Using regression specification 4, elasticity of DALYs lost to NDs by sanitation facilities is -0.51, by access to water is -1.01, and a one unit improvement in the control of corruption index reduces the DALYs lost by 0.83%. A similar estimation for the low and lower-middle-income countries listed in the World Development Report (World Bank, 2005: 291) gives elasticity of DALYs lost to NDs by GDP per capita at -0.9, by sanitation facilities at -0.36, by access to water at -0.69, and one unit increase in the control of corruption decreases the DALYs by 0.45%. Improved access to water and control of corruption appear to have strong impact on the burden of NDs. It follows that more committed national policies in these areas could make a difference.

However, if that is a necessary condition for progress, it is not a sufficient one. Governments of low income countries still need efficient drugs to be available, and such countries lack the capacity to conduct modern pharmaceutical R&D, especially for pre-clinical research, which often requires sophisticated technologies and research skills.

Various reasons have been advanced in the literature explaining why the pharmaceutical industry has not been forthcoming in developing NDs drugs: the small size of the markets for pharmaceuticals; a significant mismatch of medical conditions between people in rich and affected countries, especially in infectious and parasitic diseases; the scarcity of qualified medics; the corruption of drug procurement and misuse of drugs leading to the building of drug resistance; the pharmaceutical regulation sometimes driven by political agenda rather than efficiency considerations; the limited intellectual property rights for pharmaceutical (Kremer, 2002); failures of social insurance markets in poor countries Farlow (2005); Berndt and Hurvitz (2005) also emphasize a free rider problem where countries expect other countries to take on the risks and costs of a breakthrough in R&D for the commonly experienced diseases; and once R&D costs are sunk, monopsonic powers are used by governments to set lower prices for drugs, which discourage pharmaceutical R&D from the outset. Therefore a typical prisoners' dilemma sets in where neither the pharmaceutical corporations nor the governments of the affected countries rush to develop new drugs.

3. A survey of the various schemes to stimulate R&D

Proposals can be broadly divided into three types of incentives – push, pull and mixed. Push incentives involve companies being paid in advance of drug discoveries, creating a supply-side incentive for R&D; pull incentives are the offer of various rewards for successful drug discoveries (such as prizes or patent buy-outs) in effect guaranteeing demand for the final product hence a positive return on the R&D investment. All these schemes face the problem of sustainable funding. The difficulty is to reduce barriers to a successful innovation process comprising risk management, integration of knowledge, and learning from past R&D project failures (Pisano, 2006).

3.1 Push schemes

Push schemes include R&D tax incentives, grants, direct public funding or services for pharmaceutical companies, non-profit public-private partnership, open-source R&D. All these schemes however have their limitations.

Most of the various R&D subsidy schemes suffer a moral hazard problem (Attaran and Granville, 2004: 187). R&D tax credits involve complicated administration, may stimulate creative accounting, and might be useless for biotechnology firms which while conducting innovative research often have no taxable accounting profit (Kremer and Glennerster, 2004: 53). Direct public involvement in the form of grants runs the risk of being exposed to moral hazard and adverse selection problems as donors cannot comprehensively monitor researchers and evaluate costs and the probability of success for mooted research projects. For example, Children's Vaccine Initiative founded in 1990/1991 closed down in 1999 without significant success; this ending did not come as a surprise given the bureaucracy and politicised conflicts engendered by the large number

of sponsors (Murashkin, 1996). Other examples include $60 million spent by the United States Agency for International Development (USAID) on malaria vaccine with little result except for some researchers being found guilty in the 1980s of having diverted grant funds (Kremer, 2002: 83). Aid inefficiency should not be attributed to the USAID as illustrated by Easterly and Pfutze (2008) who ranked 37 aid agencies by their transparency, selectivity, fragmentation of aid, overhead costs, and use of effective channels. USAID was ranked sixteenth while most UN Agencies were placed at the bottom of the rankings. This ranking exercise casts doubt on the idea of creating a global public organization – as has been proposed by the Commission on Macroeconomics and Health which supports the establishment of a new Global Health Research Fund (GHRF), with sufficient funding to disburse around $1.5 billion per year (Report of the Commission on Macroeconomics and Health, 2001: 14). Such an organization might merely add to the list of inefficient aid agencies. The low efficiency of bureaucrats in business and in correctly picking winners is well documented and raises doubt as their capacity to nurture efficient innovations (World Bank, 1995).

Of all the push incentives scheme *public-private partnerships* (PPPs) seems to be a better choice in terms of generating R&D as PPPs are seen as organizationally flexible and more cost efficient than government organizations (Light, 2009; Moran, Ropars et al., 2005; Munos, 2006). PPPs are non-for-profit project-based organizations which reduce the risks and costs of R&D by involving governments, private subcontractors like pharmaceutical firms or clinical research organizations (CRO) and philanthropic organizations. Philanthropic organizations such as the Bill and Melinda Gates Foundation, Médecins Sans Frontières, and the Rockefeller Foundation provided the bulk

of the funding for the period 2000-2004 with 79% of all funds compared to 16% by OECD governments and 3% by UN organizations excluding the WHO (Moran, Ropars et al., 2005: 34). The successful PPPs are characterized by effective governance, competent management and staff, and proper scientific external review (Mahoney, Krattiger et al., 2007: 4009). About half of drugs developed by PPPs are highly innovative and developed faster than the industry on its own. PPPs require less outside funding, entail lower risk and direct operational involvement of an outside donor, and can be adapted to the needs of specific developing countries. Most PPPs with small company partnerships cover direct costs of R&D and exclude interest payments and overheads. The PPPs which operate with large pharmaceutical companies often required the least outside funding (Moran, Ropars et al., 2005).

PPPs are not perfect, however. Faster drug development time may be explained not by superior organisation but simply because PPPs usually work with drug candidates at advanced phases of development and only for diseases with a large potential commercial patient base such as tuberculosis and malaria (Trouiller, Olliaro et al., 2002). When such base is lacking, PPPs may not be viable: Buruli ulcer, trachoma and rheumatic fever did not have any intermediaries or partnerships (Moran, Guzman et al. 2008:43). Some drug candidates may be revived projects previously declined by private firms for commercial reasons. Once such drug candidates are exhausted, R&D costs for PPPs might substantially increase (Munos, 2006). Patents on new products might be appropriated by pharmaceutical firms resulting in high prices being charged for middle-income countries and for poor people in high income countries (Sarewitz, Foladori et al., 2004).

PPPs also suffer from asymmetric information. A donor knows less than an actual drug developer about the real state of progress and its potential risks and costs (Ridley, Grabowski et al., 2006). Maurer (2006) suspects that PPPs maybe more willing to tolerate inefficient drug projects and tend to allocate patents to participating companies. This might compromise affordability of the resultant new drugs through patent protection. PPPs' staff often have no pharmaceutical industry experience and this can cause misunderstanding especially as regards the needs of small pharmaceutical companies (Moran, Ropars et al., 2005: 27); PPPs suffer from a lack of accountability, they often do not publish their budgets, outcomes, and governance structures and their priorities and selection criteria for research projects are not always clearly set; they tend to work in parallel rather than with proper collaboration resulting in fragmentation of efforts in relation to specific diseases though The Global Forum for Health research supports information exchange through networks (Mrazek and Mossialos, 2003); corporations participating in PPPs might be driven by marketing or public relations motivation without a hardened commitment to the real objective putting into question the financial sustainability of PPPs (Moran, Ropars et al, 2005). Moran, Ropars et al. (2005) also recognize that most PPPs experience funding shortfalls slowing down the R&D process. Moreover commercial firms might be tempted to channel public subsides or financing to other areas of their commercial research and can quite easily mislead their partners on the true costs of the research (Hollis, 2006: 128).

Another push scheme is *Open-source R&D* where contributions are made voluntarily by representatives from academia, public institutions, and pharmaceutical firms. Maurer, Rai et al. (2004) propose donations by companies, universities, and

individuals with subsequent free access to software, research tools, drug candidates, and databases based on licences that permit anyone to use information. Munos (2006) advocates an open-source component for knowledge-based work combined with a managed project approach and outsourcing for rule-based work. The best ideas are then selected and transformed into projects to be financed and outsourced with an open call for sponsors. Remuneration is mainly non monetary such as enhanced reputation. For Munos, the majority of PPPs already operate in this way managing a portfolio of drug discovery projects while outsourcing R&D. The most vivid example of this is the Medicines for Malaria Venture as well as the Institute for One World Health. These bodies openly call for drug project ideas and based on the scrutiny and recommendations of an external scientific committee select the best ones to be funded, and then outsource the relevant R&D. The crucial elements are the presence of committed partners, strong project leadership, and experience in drug discovery projects. Potential problems with this scheme include guessing costs of private companies-subcontractors, lack of upstream research as drug candidates are borrowed from elsewhere, and under funding (Maurer, Rai et al., 2004).

3.2 Pull schemes.

Patents are the most conventional pull factor but are not applicable on their own to NDs given the lack of purchasing power. Various schemes have therefore been designed to motivate pharmaceuticals to trade patent protection of drugs against various rewards.

Pogge (2006) proposes to establish a reward for new drugs in proportion to that particular drugs' contribution to the decrease in the global burden of disease. This scheme assumes a *global public good* strategy as a parallel alternative to the patent based approach to pharmaceutical innovation. In exchange for patents on life saving medicines put into public domain, firms will be rewarded from a global public fund in proportion to the realized impact on global health for the duration of what would have been the patent life. The idea is that firms would be stimulated to produce and sell cheap essential drugs widely to enhance the global health impact. Pogge assumes that this strategy will require US$45-90 billion of annual public contributions to the global fund. Hollis (2006, 2007) proposes an Optional Reward system, which foresees sponsors paying about $500 million for ND drugs annually based on estimations of the global therapeutic effectiveness of those drugs. A somewhat similar idea of an independent public non profit drug development corporation, which would largely finance drug R&D based on cost-effectiveness analysis in the US is proposed by Finkelstein (2008). The problem with these proposals involving a huge global public policy strategy is that they run the risk of encountering the same deficiencies found in government programmes: corruption and lobbyism, methodological problems of estimating the global disease burden reduction, difficulties with collection and assessment of information across countries, establishment of proper international controls, deficiency of expertise etc. It is not clear who, why, and how much should be contributed to the global fund and how the necessary volume of the fund should be estimated or optimized in the event of a budget deficit. As Pogge's strategy essentially amounts to the public in developed countries subsidising patients in low income countries, questions of political feasibility might legitimately be raised.

However, the idea of rewarding pharmaceutical innovators based on their realized contribution to the global health can set correct incentives for drug R&D.

Other pull schemes include extending the duration of intellectual property rights or fast track approval in exchange for NDs drugs and guaranteed advance market commitments (AMCs). The extension of patent rights on (some) drugs in exchange for drugs for NDs has been proposed by Jean-Paul Garnier, CEO of Glaxo (Hollis, 2006: 131). This scheme proposes large cross-subsidies indirectly paid by patients and health insurances from developed countries. Only a part of the lost consumer surplus due to higher drug prices is transferred into more R&D, including NDs, and increased companies' profits. However if the current level of efficient patent life is sufficient to encourage innovations, such cross-subsidies are likely to create large distortions and dead-weight losses. Hollis (2007) criticizes patent extensions as higher patent-protected drug prices will be imposed on sick people without giving additional incentives to develop the best drugs.

AMCs promise to buy a drug with some pre-specified standards, primarily vaccines, at a stipulated price and quantity (Kremer, M., O. Barder, et al, 2005). Although vaccines might be the most efficient medicine, saving millions every year – probably 4-5 times more than an average drug, many pharmaceutical firms have scaled back or shut down their vaccine operations even in developed countries. In 1997, only two out of the twenty top pharmaceutical companies produced vaccines (Bartfai and Lees, 2006: 198, 268). In the US the number of licensed vaccine manufacturers decreased from 26 in 1967 to 12 in 2004 with four dominant players (Milstein, Batson et al. 2005: 1).

In "Making Markets for Vaccines: Ideas to Action", a report produced by the Center for Global Development (CGD) Advance Market Commitment (AMC)[3] Working Group chaired by Michael Kremer, Ruth Levine, and Alice Albright (operational from 2003 to April 2005), an AMC plan for vaccines was put forward. The plan include establishing an independent adjudication committee (IAC) with the support of donors and the industry to identify medical parameters of a vaccine with a right to lower those parameters if necessary; sponsors would legally bind themselves to purchase the specified vaccine at some commercially attractive minimum price to immunize a fixed number of persons. The price is set per treated person and developing countries would pay an affordable co-payment. The proposed minimum amount of purchase set at $3.1 billion in net present value (in 2004 dollars) is estimated to represent adjusted revenue from a typically successful commercial new chemical entity drug; an inventor agreeing to this contract must also set a low price, close to the marginal cost, for additional units of the vaccine, or put a production license into a public domain. In order to match the supply of vaccines with demand from low income countries sponsors would subsidize purchases of the vaccine by qualifying countries up to the specified amount; the residual co-payments will be matched by the governments of the disease affected countries to ensure the commitment of recipients (Kremer, Barder et al. 2005). The APC reward could be adjusted to take into account direct funding already received by the inventor from other sources, the progress already achieved in vaccine development before launching the APC and the technological complexity of specific vaccine (Berndt, Glennerster et al., 2007). In

[3] Light (2009:5):"Up to the final editing by an outside political writer, Kremer always called it and advanced *purchase* commitment (APC), or agreement, because it is not a "market" but a single large purchase.[…] Thus, until the final draft of the CGD report, it was called and APC, not an AMC, and one can find on Google extensive literature and references to APCs."

2007, a pilot AMC was launched for a vaccine to be developed against pneumococcal viruses. It started with a $1.5 billion promise from five countries (Italy, the UK, Norway, Canada and Russia) and the Bill & Melinda Gates Foundation for a later stage of development of the vaccine, and a similar scheme was proposed for malaria[4]. For Light (2009:ii) this arrangement is actually an advance procurement commitment as it pays for already developed vaccines. An AMC to treat malaria is expected to begin after 2016 and last for 11 years with a purchase commitment of US$2.3 billion.

A number of objections have been raised against the CGD AMC Working Group report notably by one of its former members Donald Light already mentioned. Light (2005, 2009) is concerned that the IAC may lack transparency and independence from political pressures; he claims that the scheme neither guarantee a sustained market nor ensures sustainable growth of R&D arguing as well that R&D costs have not been estimated independently; and because patent rights are kept with the inventing companies access to new drugs may be reduced; he also worries that the AMC will damage the successful advancement made by PPPs and reduce pharmaceutical technology transfer to poor countries. Light (2005) stresses that stimulating R&D through a guaranteed purchase of a vaccine may be less efficient than directly financing R&D vaccine with the purchase money. He cites estimates of Finkelstein (2004: 543) for US vaccine trials that "for every $1 permanent increase in expected annual market revenue…, the pharmaceutical industry will spend an additional 6 cents annually in present discounted value on R&D". Indeed, in a broader perspective, Cameron (1996) summarizes a number of empirical studies on output elasticity of R&D conducted from 1980 to 1995 for several high-tech industries and reports the elasticity to be in the range of 0.06 to 0.45 at firm

[4] http://www.gavialliance.org/media_centre/press_releases/2010_03_23_amc_commitment.php

level. We estimated the elasticity of commercial R&D by cash flow at 0.36 for a dynamic panel of 482 pharmaceutical companies (available from the authors upon request).

Farlow (2005) doubts that the setting of the AMC prize will be optimal due to the difficulty of estimating future costs and technological changes resulting in either a too low prize which may fail to motivate companies or in a too high prize wasting resources. Maurer (2006) argues that the AMC may overpay companies because no good quality drugs may be developed in a specific time period and also because actual R&D may cost 20-30% less than the average targeted by the commitment. Moreover the cost-sharing mechanism implying co-payment by diseases affected countries might not be optimal. Cohen and Dupas (2010) have conducted an experiment in Kenya by distributing antimalarial insecticide-treated bed nets to pregnant women. They find no statistical evidence that cost-sharing affects nets usage; a dramatic demand reduction is however observed, they therefore argue that free distribution of the antimalarial nets might be more effective.

Another objection to the scheme raised by both Light (2005) and Farlow (2005) and supported by more than fifty pharmaceutical companies is that only large pharmaceutical corporations may have enough cash to finance R&D. Senior executives of the companies pointed out that venture capitalists are looking for a significant return in the medium run and that it can take time for big pharmaceutical companies to find and subcontract to a small biotech company. Small biotech firms find it too expensive to finance phases II and III of clinical trials; small firms need assistance in dealing with health authorities in developing countries and some guarantees for purchases of final products (Grace, 2006: 11, 15). The fear is also that the majority of the AMC prize will

be spent on capital costs rather than on R&D; companies especially small ones may be facing additional capital costs due to uncertainty and risks (Farlow, 2005:16-19).

This last set of issues affecting small companies matters given the role of small firms in developing new drugs. Villa, Compagni et al. (2009) calculated that the majority of new drugs approved under Orphan drug laws targeting diseases with small patient base have been developed and produced by small and medium sized pharmaceutical firms. Such drugs generate modest annual sales from US$50 to US$300 million and are less profitable than traditional blockbuster drugs. Love (2003: 10) cites the estimation of the Pharmaceutical Education and Research Institute for 117 drug development projects that it took just 7.1 years and $75.4 million in direct R&D costs per successful drug. This survey highlights that small firms spent less than half of the large firm costs per successful drug so that small firms tend to be more cost-efficient than larger one.

Berndt and Hurvitz (2005) suggest that milestone payments can be made within the AMC scheme, but if there is an efficient market for R&D contracts such payments are not necessary as proper subcontracts can be negotiated. The problem however is that R&D markets are not efficient, especially in the short run. R&D markets suffer from asymmetric information and require search and information processing costs making the cost of external capital for an R&D project higher, this is especially true for small firms (Hall, 2002). Asymmetric information is endemic in part because R&D projects have a low probability of financial success (Carpenter and Petersen, 2002). There are no financial standards to disclose and evaluate risks that relate to ongoing research meaning that new – and therefore financially constrained – biotech firms cannot straddle an optimal learning curve, as a few unsuccessful drug candidates result in the closing of the

small firm (Pisano, 2006). Asymmetric information is present between inventor and investor, as the inventor has more expertise in their own project or else hesitates to reveal all information; the situation is exacerbated by the high uncertainty of R&D projects that unevenly declines as a project progresses (Hall, 2002). Although many small firms in innovation-driven sectors may approach venture capitalists for finance, they may not be in position to do so as a drug project typically needs to generate a 25-35% annual return in order to attract investments from venture capitalists (Grabowski and Vernon, 2000).

To address the issue of cash flow, Brogan and Mossialos (2006) propose selling a call option, i.e. a right to buy a future drug at a pre-specified price in case of its successful development. The general problem of application of financial instruments to NDs is that the market is unlikely to work in determining the prices of such instruments given the extremely limited number of potential buyers and sellers. The high uncertainty surrounding early stage R&D and insufficient observations on success rates and the quality of ND research projects make it quite challenging to value such options.

3.3 Mixed schemes.

An example of a mixed scheme using both push and pull factors *is the Orphan (rare) drug scheme* adopted by the USA, Japan, EU, and Australia. The push incentives include protocol assistance, fast-track approval, tax credits on clinical research, research grants, while the pull factors include extending patent rights with up to 7 years market exclusivity (Villa, Compagni et al. 2009). The US Orphan drug program has been rather successful, 326 drugs received FDA approval and 41 of these drugs were supported by

program grants; the vast majority of drug candidates were sourced from academia and biotechnology companies (Cote 2008).

One criticism is that as Orphan drug incentives are effective only for drugs carrying very high prices affordable for health insurance systems in developed countries, no drug for neglected diseases was developed through this scheme (Trouiller, Olliaro et al., 2002). Moreover the risk is that with extended exclusivity periods, high prices for new drugs would reduce access and usage of such drugs in developing countries (Mrazek and Mossialos, 2003). This effect however could be compensated by granting orphan status to all NDs in the US and EU. This would bring additional incentives through high prices charged to developed countries consumers while charging more affordable prices to developing countries (Danzon, 2007). In addition, NDs seem to be spreading to rich countries, the US has more than 110,000 cases of dengue fever, over 3,000 cases of Chagas disease, and 8,000 schistosomiasis cases (Hotez, 2008). Many of these diseases are associated with US-Mexico border territories and African refugees. Malaria and human trypanosomiasis have already been given rare status (Villa, Compagni et al. 2009).

However, patients have differing nutrition, immunity, and cross-infection backgrounds according to whether they live in rich or poor countries and the difference may be such that drugs clinically tested on developed countries patients may not be effective for low-income countries patients. Another criticism of the scheme is that little competition seems to be encouraged facilitating first exclusive entry. For the period 1983-2005 only one percent of drugs were allowed as the second entrant for the same condition in the Orphan scheme (Berndt, Glennerster et al. 2007).

Other mixed schemes include granting to a pharmaceutical company a voucher for FDA priority review of any drug in exchange for that company developing an approved drug to treat a ND (Ridley, Grabowski et al. 2006). This scheme has been implemented into US policy with the Food and Drug Administration Amendments Act (FDAAA) of 2007. FDA review is guaranteed within 6 months of submission; this voucher is transferable and can be sold (Cote 2008). The scheme assumes that the approved drugs must be superior to existing analogues and that patent rights for such drugs will be allocated in a public domain. Such a voucher might be valued at about $300 million or more by a company with a potential blockbuster drug candidate and such voucher can be also auctioned to finance an R&D scheme. The assumption is that consumers in developed countries would benefit from accelerated approval of drugs without compromising safety as reducing review times by authorities does not increase drug market withdrawal (Berndt, Gottschalk et al. 2005); this scheme should not create congestion as firms will be paying a $1 million fee to the FDA for additional labour involved in the drug review. In short, the proceeds from selling one or two priority reviews together with the tax credits offered by the Orphan Drug Act should suffice to finance an ND drug (Ridley, Grabowski et al. 2006). Moran, Ropars et al. (2005) propose an auction of a right (options) for fast track priority reviews (fast track options – FTOs) of new commercial drugs by early involvement in monitoring and advising on clinical trials. FTOs allow greater flexibility in targeting the financing of R&D.

Both of these schemes - the vouchers and FTOs – seem to be the most politically feasible way to raise funds as this does not imply explicit public expenditures. The risk however is that close substitutes known as me-too imitative drugs be pushed through

these schemes distorting incentives for creation of pioneering and therapeutically advanced commercial drugs. The share of me-too drugs is already quite high. Only 14 percent of all new chemical entities were therapeutically superior to existing drugs for the period 1997-2006 (Prescrire International, 2007). Philipson and Dai (2003: 46) argue that competition with newly patented drugs in the US reduces the first innovator sales more than generic drugs. Bartfai and Lees (2006: 41-42,197) state that if a good drug target is found, other companies enter the market with their drugs addressing the same target often within a year. Often drugs that enter the market second or third in a new therapeutic class are better than the first and acquire a larger slice of the market than the original innovator's drug.

With the voucher and FTO schemes firms may be tempted to minimize the costs of developing medicine for NDs through me-too drugs with insignificant therapeutic advantage over existing products or by not paying enough attention to the difficulty of drug delivery and administration in the field conditions of low income countries. This seems to be confirmed historically as out of 13 drugs for NDs developed by the pharmaceutical industry for 1975-1999, "12 had a low overall health value to developing country patients" (Grace 2006: 19).

4. Designing the best scheme

Using an R&D option model Hsu and Schwartz (2008) evaluated some research incentives for developing countries' vaccines. Their criteria were expected R&D costs and price per treatment, probability of success, consumer surplus, expected vaccinations,

and expected cost per person successfully vaccinated. They concluded that (i) patent extension was not an effective incentive; (ii) fixed cost-sharing subsidy had a low expected cost to the sponsor, but generated lower consumer surplus if granted patents for new drugs increased prices; (iii) the AMC performed better than the cost-sharing subsidy; and (iv) a combination of an AMC and a cost-sharing subsidy may achieve the best results. However, the model did not take into account the conflict of interest between sponsors, consumers, and innovators, and assumed the quality of new vaccines to be impervious to the incentives in operation during the development process. Many schemes overcome participation constraint by implying some profitability to participating companies, but do not provide strong incentives to deliver quality drugs at the lowest cost.

From our review in section 3 we selected seventeen criteria grouped into four categories: efficiency, feasibility, fairness, and sustainability. Our results are reported in Table 5. Five criteria appear in the sub-group relating to efficiency: rewards based on cost-efficiency and adoptability of new drugs, facilitation of competition in R&D and subsequent production of drugs, risks of distortions created by cross-subsidies, risks of inflated costs, facilitation of information disclosure. Four criteria appear in the sub-group relating to feasibility: requirement for special binding international agreements, scale of required direct public/charity funding, scale of public contributions from low income countries, complexity of administration. Three criteria appear in the sub-group relating to fairness: tackling the free rider problem, stockholders from affected countries as decision makers, restraining product prices in developing countries. Five criteria appear in the sub-group relating to sustainability: long term self-financing, enabling public control over

project performance, capacity building of clinical experimentation in low income countries, adaptability to adverse grant and technology shocks through greater degree of freedom in scheme's controls, incorporation of the full R&D cycle.

Table 5 - Matrix of incentives for NDs

Criteria	AMC	PPPs-	ODD	PVOD	GPF	PEEND
	1	2	3	4	5	6
		Efficiency:				
rewards to efficiency	Possible	No	no	possible	possible	no
Distortions	Low	Low	low	medium	low	very high
Competition	Low	High	low	medium	possible	medium
cost driven	No	Medium	no	no	medium	no
information disclosure	Low	Medium	low	low	high	low
		Feasibility:				
binding international agreements	Yes	Optional	optional	optional	yes	yes
direct public/charity funding	several bn US$	100 m US$	10 m US$	no	10 m US$	no
public contributions from low-income countries	Income based	No	no	no	possible	no
complexities to administer	Medium	Medium	low	low	high	low
		Fairness:				
tackling international free-rider problem	Yes	No	no	no	possible	no
stockholders from affected countries as decision makers	possible, but donor driven	possible, but donor driven	no	no	possible	no
restraining product prices in developing countries	Yes	Somewhat	no	no	yes	no
		Sustainability				
Long term self-financing	depends on donors	depends on donors	demand driven	yes	depends on donors	Yes
enabling public controls over project performance	Medium	Medium	low	low	High	No
capacity building of clinical experimentation in developing countries	No	Medium	low	low	High priority is possible	No
Adaptability to adverse grant and technology shocks	low	Low	medium	medium	low	medium
Incorporation of the full R&D cycle	Yes	Somewhat	yes	yes	yes	yes

Notes:
* AMC: advanced market (purchase) commitment; PPPs: public-private partnerships; ODD: orphan drug designation; PVOD: the priority voucher and orphan designation; GPF: the global public funding; PEEND: patent extensions in exchange for NDs drugs.
** the first four schemes are already implemented in practice.

Taking account of all aspects of the drug discovery process, we draw out seven characteristics which should feature in an optimal R&D scheme:

1. *Long term R&D financing* to attract and keep human capital in the research. A regular program is needed to address drug resistant viruses and to create robust incentives. Maurer (2007:105) points out that repeat business enhances trust and reliability of incentives with inventors. Direct contributions from charities, international development organizations such as the World Bank and OECD governments and affected countries could fill the gap. The involvement of the World Bank would alleviate the problem of international free-rider whereby countries expect others to take the risks and of the incentives inconsistency pointed to by the authors of the AMC proposal. World Bank loans would allow access to cheap capital for drug development. This would give affected countries a voice, enhance cooperation and monitoring of the progress of related research projects, and ensure that R&D outcomes are tailored to developing countries' needs. Hotez, Molyneux et al. (2006) emphasize that disease controls countries should themselves set appropriate policies and priorities and call for greater integration of international disease controls and specific disease programs. While direct contributions by affected countries will be small, G-20 countries could commit as much as 1% of their actual public pharmaceutical R&D to NDs research, especially on target selection and validation with the goal to facilitate the proof of concept studies. This 1% can generate at least a $200 million annual push incentive for upstream discovery of new drug candidates. With an average proof of concept studies costing $5-10 million, this could generate 20-40 drug candidates for clinical trials.

2. *Public subsidies of clinical experimentation*. Commercial companies spend more than 70% of their drug development budgets on failed compounds (Finkelstein 2008: 66). Clinical trial subsidies could improve firms' expected returns and, hence, the attractiveness of ND-related R&D. Jayadev and Stiglitz (2009) propose public funding of clinical trials and health value-added pricing in the pharmaceutical industry to increase genuine innovations and reduce R&D costs for new drugs. They emphasize the public nature of information coming from clinical trials, greater confidence in the quality of testing, avoidance of duplicative trials, and reducing entry barriers for small firms. This public funding complemented with open transparent and low cost tenders could partly solve the problem as clinical trials are a less innovative and less sophisticated stage of drug development than discovery of a drug candidate. Subsidies of clinical experimentation in developing countries can be productive as shown by FDA data on investigational new drugs (INDs): the shares of non-commercial INDs (mainly filed in submissions by practicing physicians) in total INDs ranged from 72.9% to 85.6% for the period 1982-2003 (PAREXEL: 185).

3. *The payoff to innovators* should be based on the global cost-effectiveness of a new drug determined through clinical trials in several affected countries as suggested by Kremer and Glennerster (2004), Hollis (2006), and Pogge (2006). PriceWaterhouseCoopers (2007) foresees a cost-effectiveness analysis of new drugs becoming a requirement for all drug approval by 2020. Although cost-effectiveness analysis of medicines suffers from methodological difficulties (Drummond and Sculpher, 2005), Drummond (2007) notes that ten countries were already using cost-benefit analysis for national drug reimbursement policies and such decision process is workable.

Setting prices for drug innovators and consumers in developing countries must be separated so as to provide both proper incentives for drug R&D and affordability of prices (Finkelstein, 2008). A detailed discussion of pricing for developing countries by Lanjouw and Jack (2003) concludes that generic manufacturers should be allowed to start production as soon as possible to supply affected countries with newly designed drugs for NDs.

A clear compensation plan for companies would encourage R&D incentives, preferably using some simple formula with detailed calculation methodology to allow less discretion. For example, if age-adjusted global DALYs saved by a medication can be considered as an approximation to the marginal utility of a drug, a utility maximizing social planner should set ratio of drug prices to the ratio of their DALYs saved. Hence, a price offered to an innovator of a new drug through an APC scheme (APC PRICE) could be estimated as a fixed proportion of a current comparable drug price (CPRICE) for low income countries multiplied by the ratio of DALYs saved by the newly developed drug (DALYn) to DALYs saved by the current drug (DALYc):

APC PRICE = K*DALYn/DALYc*CPRICE

where K is some proportional coefficient set in advance through consultations with donors and pharmaceutical companies.

Attaran and Granville (2004: 180-182) discuss methodological problems of traditional cost-effectiveness analysis such as DALY and years of life saved (YLS), including the variability of the value of a life saved and the underestimation of costs of a particular disease at the macroeconomic level in the long run. The reward would be justified if there is a robust procedure to estimate cost-benefit effects for a new drug in

field conditions. Sponsors could then pay for the net benefit of a drug based on clinical trials with existing drugs rather than with placebos.

4. I*nsurance* to pharmaceutical companies that some partial compensation will be made in case of research project failures provided that the project outcomes are promptly analyzed and published. Failures must also be properly analyzed as they are a source of important knowledge for other projects and, thus, are not socially wasteful.

5. *Transparency and accountability*. In exchange for public subsidies, participating PPPs should promptly publish research project selection criteria, budgeting, research outcomes, and governance. Finkelstein (2008: 120) notes that pharmaceutical companies have a "financial incentive to hide unfavourable study results form investors and the public". A good scheme must encourage the public provision of all scientific information and related materials.

6. *Network based research*. PPPs network allows a high level of competition. Pharmaceutical companies increasingly follow more open innovation by outsourcing R&D, creating joint ventures, licensing research and working within large research networks. In 1999, a quarter of R&D spending was contracted via outsourcing contracts to clinical research organizations (CROs) (Gassmann et al, 2008). Outsourcing is widely used in the production of pharmaceuticals and is also increasingly utilized in drug development: more than 40% of all pharmaceutical R&D activities were outsourced in 2004 (Kalorama Information cited by Schwitzer (2006: 68)). For example the virtual drug development company Protodigm established by Roche managed the development of several drugs with 10 employees by choosing the most qualified subcontractor for each R&D stage, including pre-clinical and clinical trials, production, drug registration and

marketing (Gassmann et al, 2008). Global virtual networks could be extended by including "sharing drug-discovery tools, matching potential collaborators, databases, and with a common platform for management of intellectual property and administration" (Callan and Gillespie, 2007: 165). Virtual brokered drug-discovery networks might attract a wide range of contributors and provide access to industrial laboratories (Hopkins, Witty et al. 2007).

Proper incentives for each R&D stage of the project management cycle can be designed. Target identification is essentially an academic problem where university and public research institutions specialists can be involved. At this stage, open calls for potential drug targets, and relatively small research grants for the academic community might have the highest impact. Identification of drug candidates and their synthesis for the specified targets can be outsourced through procurement tenders. Preclinical tests of drug candidates for tropical infectious diseases can serve as a good proxy for success in clinical trials, preclinical trials costs are around $20 million for a drug candidate (Hopkins, Witty et al. 2007). Clinical trials can be conducted with the help of specialist business CROs in partnership with hospitals in developing countries. There should be both training programs and tenders for clinical trials in affected countries. This could reduce the costs, create additional capacities for clinical studies and optimize drug usage.

7. *Innovators coordination*. Drug R&D research has economies of scale and scope in maintaining a diverse compound portfolio and in capturing knowledge spillovers between projects (Henderson and Cockburn, 1996) suggesting that coordination and portfolio management of PPPs will be beneficial. Moran, Ropars et al. (2005) propose the creation of an Industry Research Facilitation Fund (IRFF) providing R&D grants for NDs

to the industry and academia through PPPs to a total amount of about US$250 million per year. This Fund could draw up and execute long term plans of drug development, accredit PPPs, manage global drug portfolios, provide management support, conduct negotiations with the industry and governments, give technical advice, provide legal support, act as an information hub for all stakeholders, and provide other shared services to PPPs to avoid redundancy across the partnerships. Such a coordination platform could be helpful as many services are common across all PPP projects and represent fixed costs. Performing such services through one hub could reduce fixed costs per project and, thus, contribute to lower R&D costs. Coordinated portfolio management could reduce the risks of failure through the pooling of drug candidates and also enable the purchase a cheaper collective insurance for possible product liabilities. The Fund could support a technology trust to pool patents related to NDs as advocated by So (2008). The platform could also negotiate access to medical expertise and drug discovery tools, including chemical libraries at big pharmaceutical companies, and provide advice on national academic grants for biomedical research.

5. Conclusion

In this paper, schemes for R&D on NDs have been summarized; a matrix evaluates these schemes according to seventeen criteria grouped into four categories: efficiency, feasibility, fairness, and sustainability with the conclusion that the best existing scheme for NDs is likely to be the proposal of Moran, Ropars et al. (2005) with subsidies and grants channelled through a centralized PPP platform. The public intervention should

target barriers in the way of a successful innovation process with a view to reducing its risks and costs, enhancing competition, and promoting the communication of ideas and all results. The nature of the drug discovery process requires (i) long term R&D financing, with G20 countries allocating to NDs a 1% share of their current spending on public pharmaceutical R&D, (ii) public subsidies for clinical experimentation, (iii) basing the payoff to innovators on the global cost-effectiveness of a new drug, (iv) R&D project insurance, (v) transparency and accountability in exchange for public funds, (vi) network based research to allow greater competition among many parallel experiments, (vii) coordination for innovators through a common service platform.

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References

Ahmed, K., F. Cudjoe, et al. (2007). Increasing access to medicines. Fighting the diseases of poverty. P. Stevens. London, International Policy Press: 141-184.

Attaran, A. and B. Granville (2004). Who needs to do what? Delivering essential medicines. A. Attaran and. B.Granville. London, Chatham House: 175-189.

Bartfai, T. and G. Lees (2006). Drug discovery: From bedside to Wall Street. London, Elsevier Academic Press.

Berndt, E., R. Glennerster, et al. (2007). "Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness." Health Economics **16**: 491-511.

Berndt, E., A. Gottschalk, et al. (2005). "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates." National Review Drug Discovery **4**(7): 545-554.

Berndt, E. and J. Hurvitz (2005). "Vaccine Advance-Purchase Agreements For Low-Income Countries: Practical Issues." Health Affairs **24**(3): 653-664.

Brogan, D. and E. Mossialos (2006). "Applying the Concepts of Financial Options To Stimulate Vaccine Development." Nature Reviews Drug Discovery **5**: 641-647.

Callan, B. and I. Gillespie (2007). "The Path To New Medicines." Nature: Neglected Diseases Outlook **449**(September): 164-165.

Carpenter, R. and B. Petersen (2002). "Capital Market Imperfections, High-Tech Investment, and New Equity Financing." The Economic Journal **112**(477): F54-F72.

Chirac, P. and E. Torreele (2006). The LANCET **367**(May 13): 1560-1561.

Cohen, J. and P. Dupas (2010). "Free Distribution Or Cost-sharing? Evidence From a Randomized Malaria Prevention Experiment " The Quarterly Journal of Economics **CXXV**(1): 1-46.

Cote, T. (2008). The Food and Drug Administration's Orphan Drug Program. Breakthrough Business Models. Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. T. Wizeman, S. Robinson and R. Giffin. Washington, D.C., The National Academies Press.

Danzon, P. (2007). "At What Price?" Nature Outlook Neglected Diseases **449**(13 September): 176-179.

Drummond, M. and M. Sculpher (2005). "Common Methodological Flaws in Economic Analysis." Medical care **43**(7): 5-14.

Drummond, M. (2007). Using Economic Evaluation in Reimbursement Decisions for Health Technologies. Pharmaceutical Innovation. F. Sloan and C.-R. Hsieh. NY, Cambridge University Press**:** 215-225.

Easterly, W. and T. Pfutze (2008). Where Does the Money Go? Best and Worst Practices in Foreign Aid. The Brookings World Economy and Development Working Paper. Washington D.C. **21:** p.22.

Farlow A., D.Light, R.Mahoney, and R.Widdus (2005). Concerns regarding the Making Markets for Vaccines', Submission to the Comission on Intelectual property Rights, Innovation and Public health, available at www.who.int/intellectualproperty/en, accessed April 20, 2009.

Farlow A. (2005). An Analysis of the Problems of R&D Finance For Vaccines And an Appraisal of Advance Purchase Commitments, available at http://www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf, , accessed March 10, 2009.

Finkelstein, S. (2008). Reasonable Rx: how to lower drug prices. London, Pearson Education LTD.

Finkelstein, A. (2004). "Static and Dynamic Effects of Health Policy: Evidence From the Vaccine Industry." Quarterly Journal of Economics **119**(May): 527-564.

Ford, N. (2006). The Enduring Crisis In Neglected Diseases. The Power of Pills: Social, Ethical And Legal Issues in Drug Development, Marketing and Pricing. J. Cohen, P. Illingworth and U. Schuklenk. London, Pluto Press: 109-116.

Gassmann, O., G. Reepmeyer, et al. (2008). Leading Pharmaceutical Innovation. Berlin, Springer-Verlag.

Grabowski, H. and J. Vernon (2000). "The Determinants of Pharmaceutical Research and Development Expenditures." Journal of Evolutionary Economics **10**: 201-215.

Grace, C. (2006). Developing New Technologies to Adress Neglected Diseases: The Role of Product Development Partnerships And Advanced Market Commitments. DFID health Resource Centre. London.

Henderson, R. and I. Cockburn (1996). "Scale, Scope, and Spillovers: The Determinants of Research Productivity in Drug Discovery." The RAND Journal of Economics **27**(1): 32-59.

Hall, B. (2002). "The Financing of Research And Development." Oxford Review of Economic Policy **18**(1): 35-51.

Hollis, A. (2006). Neglected Disease Research: Health Needs And New Models For R&D. The Power of Pills: Social, Ethical and Legal Issues in Drug Development, Marketing and Pricing. J. Cohen, P. Illingworth and U. Schuklenk. London, Pluto Press: 125-133.

Hollis, A. (2007). Drugs for Neglected Diseases. Pharmaceutical Innovation. F. Sloan and C.-R. Hsieh. NY, Cambridge University Press**:** 75-90.

Hopkins, A., M. Witty, et al. (2007). "Mission Possible." Nature Outlook Neglected Diseases **449**(13): 166-169.

Hotez, P. (2008). "neglected Infections of Poverty In the United States of America." PLoS Neglected Tropical Diseases **2**(6): e256.

Hotez, P., D. Molyneux, et al. (2007). "Control of Neglected Tropical Diseases." The New England Journal of Medicine **357**: 1018-1027.

Hotez, P., D. Molyneux, et al. (2006). "Incorporating a Rapid-Impact Package for Neglected Tropical Diseases with Programs for HIV/AIDS, Tuberculosis, and Malaria." PLoS Medicine **3**(5): e102.

Hsu, J. and E. Schwartz (2008). "A Model of R&D Valuation and the Design of Research Incentives." Insurance: Mathematics and Economics 43(3): 350-367.

Jayadev, A. and J. Stiglitz (2009). "Two Ideas To Increase Innovation And Reduce Pharmaceutical Costs And Prices." Health Affairs **28**(1): w165–w168.

Kremer, M., O. Barder, et al. (2005). Making Markets for Vaccines. Advance Market Commitment Working Group. Washington, D.C., The Center for Global Development.

Kremer, M. and R. Glennerster (2004). Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases. NJ, Princeton University Press.

Kremer, M. (2002). "Pharmaceuticals And the Developing World." The Journal of Economic Perspectives **16**(4): 67-90.

Lanjouw, J. and I. Cockburn (2001). "New Pills for Poor People? Empirical Evidence After GATT." World Development **29**: 265-89.

Lanjouw, J. and W. Jack (2003). Financing Pharmaceutical Innovation: How Much Should Poor Countries Contribute?". CGD Working Paper no. 28. Washington, D.C., The Center for Global Development.

Lewis, M. (2006). Governance and Corruption in Public Health Care Systems Working Paper. Washington, D.C., The center for Global Development.

Light, D. (2005). "Making Practical Markets for Vaccines." PLoS Medicine **2**(10): 934-938.

Light, D. (2009). Advanced Market Commitments: Current realities and alternate approaches. Health Action International Paper 03-2009/01. Amsterdam, Health Action International Europe: 1-38.

Lopez, A. D. and Disease Control Priorities Project (2006). Global burden of disease and risk factors, Alan D. Lopez et al eds. New York, NY, Washington, DC, Oxford University Press, World Bank.

Lorentzen, P., J. McMillan, et al. (2008). "Death and Development." Journal of Economic Growth **13**: 81-124.

Love J. (2003). Evidence Regarding Research and Development Investments in Innovative and Non-Innovative Medicines. Consumer Project on Technology Pages Relating to Pharmaceutical Research and Development, available at http://www.cptech.org/ip/health/rnd/evidenceregardingrnd.pdf

Mahoney, R., A. Krattiger, et al. (2007). Vaccine **25**: 4003-4011.

Maurer, S., A. Rai, et al. (2004). "Finding Cures for tropical Diseases: Is Open Source an Answer?" PLoS Medicine **3**(e56): 1-7.

Maurer, S. (2006). "Choosing the Right Incentive Strategy for Research And Development in Neglected Diseases." Bulletin of the World Health Organization 84(5): 376-381.

Maurer, S. (2007). When Patents Fail. Pharmaceutical Innovation. F. Sloan and C.-R. Hsieh. NY Cambridge University Press**:** 91-106.

McCarty, N. and A. Meirowitz (2007). Political Game Theory: An Introduction. Cambridge, Cambridge University Press.

Mfula, C. (2010). Global Fund freezes Zambia aid, citing corruption. International Business Times, June 18.

Milstein, J., A. Batson, et al. (2005). Vaccines and Drugs: Characteristics of Their Use to Meet Public Health Goals. The World Bank, Health, Nutrition, and Population Division. Washington, D.C.

Moran, M., A.-L. Ropars, et al. (2005). The New Landscape of Neglected Disease Drug Development. Pharmacetical R&D Policy Project. London, London School of Economics and Wellcome Trust.

Moran, M., J. Guzman, et al. (2008). Neglected Disease Research & Development: How Much Are We Really Spending? G-FINDER 2008. London, The George Institute for International Health.Mrazek, M. and E. Mossialos (2003). "Stimulating Pharmaceutical Research And Development for Neglected Diseases." Health Policy **64**: 75-88.

Munos, B. (2006). "Can Open-source R&D Reinvigorate Drug Research?" Nature Reviews Drug Discovery **5**(September): 723-729.

Muraskin, W. (1996). "Origins of the Children's Vaccine Initiative: The Political Foundations." Social Science and Medicine **42**(12): 1721-1734.

PAREXEL (2004). PAREXEL's pharmaceutical R&D statistical sourcebook 2004/2005. Waltham, MA, PAREXEL International Corporation.

Pisano, G. (2006). Science business: the promise, the reality, and teh future of biotech. Boston, Harvard Business School Press.

Philipson, T. and C. Dai (2003). "Between- vs. Within-Patent Competition." Regulation **26**(3): 42-48.

Pogge, T. (2006). Harnessing the Power of Pharmaceutical Innovation. The Power of Pills: Social, Ethical and Legal Issues in Drug Development, Marketing and Pricing. J. Cohen, P. Illingworth and U. Schuklenk. London, Pluto Press: 142-149.

Prescrire International (2007). "A Look Back at Pharmaceuticals in 2006: Aggressive Advertising Cannot Hide the Absence of Therapeutic Advances." Prescrire International (La Revue Prescrire) **16**(88): 80-86.

Preston, S. H. (1975). "The Changing Relation between Mortality and Level of Economic Development". Population Studies **29**: 231-248.

PriceWaterhouseCoopers (2007). Pharma 2020: The Vision - Which Path Will You Take? UK.

Pritchett, L. and L.H.Summers (1996). "Wealthier is Healthier". The Journal of Human Resources **31**: 841-868.

Report of the Commission on Macroeconomics and Health. Macroeconomics and Health: Investing in health for economic development. Geneva: World Health Organization; 2001, p.31.

Ridley, D., H. Grabowski, et al. (2006). "Developing Drugs For Developing Countries" Health Affairs **25**(2): 313-324.

Sarewitz, D., G. Foladori, et al. (2004). "Science Policy In Its Social Context." Philosophy Today Supplement **5**: 67-83.

Schwitzer, S. (2006). Pharmaceutical Economics and Policy. NY, Oxford University Press Inc, USA.

So, A. (2008). Strategies for Navigating Intellectual Property. Breakthrough Business Models. Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. T. Wizeman, S. Robinson and R. Giffin. Washington, D.C., The National Academies Press.

The World Bank (1995). Bureaucrats in Business. The Economics and Politics of Government Ownership. A World Bank Policy Research Report. Washington, D.C., The World Bank.

The World Bank (2005). World Development Report 2006 : Equity and Development. World Development Report Washington, D.C., The World Bank: 289-291.

Trouiller, P., P. Olliaro, et al. (2002). "Drug Development for Neglected Diseases: A Deficient Market and a Public-health Policy Failure." The LANCET **359**(June 22): 2188-2194.

Villa, S., A. Compagni, et al. (2009). "Orphan Drug Legislation: Lessons For Neglected Tropical Diseases." International Journal of Health Planning And Management **24**: 27-42.

The World Health Organization (2008). The global burden of disease: 2004 update. Geneva, Department of Measurement and Health Information, The World Health Organization Press.

The World Health Organization (2009). Neglected Topical Diseases, Hidden Successes, Emerging Opportunities. WHO/HTM/NTD. Geneva, The World Health Organization Press.