Working Paper

Institutions for New Product Development for Global Health: From Malaria to Mental Health and Beyond

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Abstract:

The development of new products to combat disease, whether drugs, diagnostics, vaccines or other health tools, has long been an important part of public health efforts. This paper traces the evolution over the past century of institutional arrangements for new product development (NPD), using the case of anti-malaria tools such as drugs, vaccines, bednets, and insecticides, as an illustration. We find that there have been major shifts in conceptions about who should *benefit* from, and who should *pay* for NPD, with gradual movement away from a primarily national to an increasingly global approach. This shift has had important implications and broadened our shared understandings about both the kinds of tools that get developed and who gets access to them. Innovative institutional arrangements, such as the 'public-private product development partnerships (PDP),' now take into account the need to develop tools that are adapted for use in developing countries, and to incorporate considerations of affordability into the early stages of development.

However, thus far such efforts have been limited to a sub-set of infectious diseases. The PDPs, as currently organized, are not likely to be the right model for providing NPD to counter the rapidly rising burden in developing countries of chronic non-infectious conditions such as heart disease and mental health. The debate over access to HIV/AIDS drugs has contributed to global norms that frame health tools as global public goods; political mobilization to demand access to new tools with significant therapeutic benefit is likely to rise. A new wave of institutional innovation will be necessary to meet these needs, based on two key principles: 1) that tools should be adapted and accessible to a global population of end-users (as with the PDPs), and 2) that contributions to NPD, whether of human, scientific or financial capital, should be a globally-shared burden.

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Introduction

Around the 4th century A.D. the Chinese physician Ge Hong recorded these instructions for curing intermittent fevers in his guidebook, *Emergency Prescriptions Kept Up One's Sleeves*: "Q*inghao:* one bunch, take two *sheng* of water for soaking it, wring it out, take the juice, ingest it in its entirety." (Ge c.340 AD, as cited in Hsu 2006). Sixteen centuries later during the Vietnam war, this simple text led Chinese government-sponsored researchers to identify artemisinin as a potent drug to treat malaria, which had become resistant to existing medicines in Southeast Asia. Today, artemisinin-based combination therapies have become the gold-standard treatment and strongest line of defense against the malaria parasite's uncanny ability to develop resistance to new drugs. Ge Hong's knowledge – translated, transferred, and developed – has now become a global public good.

The development of new products to combat disease, whether drugs, diagnostics, vaccines or other health technologies, has long been an important part of public health efforts. Though technology is far from the only element necessary to improve public health, it can sometimes play a pivotal role between sickness and health. This paper traces the evolution over the past century of institutional arrangements for new product development (NPD), using the case of anti-malaria tools such as drugs, vaccines, bednets, and insecticides, as an illustration. For the sake of brevity, I refer to these products generally as "health tools" for the remainder of this paper. Furthermore, when using the term 'institutions,' I refer not only to organizations, but more broadly to 'persistent and connected sets of rules (formal or informal), that prescribe behavioral roles, constrain activity, and shape expectations' (Keohane, 1988, p383).

There have been major shifts in conceptions about who should benefit from and who should pay for the development of new tools, with gradual movement away from a primarily narrow national approach that focused primarily on the industrialized countries, to an increasingly inclusive global approach that includes the needs of developing countries. This shift has had important implications and broadened our shared understandings about both the kinds of tools that get developed and who gets access to them.

The process of research and development (R&D) for new products can stretch across a long chain, especially in the case of medicines, from basic research to screening of potentially useful tools, to proof of concept, to clinical testing for safety and efficacy, to field application and dissemination. For the sake of analytical tractability, this paper focuses on the latter part of this chain, which I label "new product development" or NPD, and excludes from consideration the stage of basic research. (See paper by Keusch & Kilama for a discussion of institutions for basic research).

This paper offers a framework and narrative account of the conceptual evolution that has occurred concerning NPD for the needs of developing countries. It then ties this evolution to ongoing debates regarding the way NPD is currently organized. Finally, I conclude with two propositions for principles that ought to guide future institutional arrangements for NPD so that new health tools will be developed, affordable, and well-adapted for a global population of end-users.

Framework

The development of health tools to combat disease has a long and storied history that reaches back thousands of years from the development of traditional medicines, and continues forward through the germ theory of disease, the emergence of a modern pharmaceutical industry, up through today's myriad products of advanced science and technology. Within the era of modern medicines and health technologies, four separate

phases are discernible, which I label: National, International, Global/Neglected Diseases, and Global Health (summarized in Table 1 below). The following sections discuss and illustrate each of these in turn.

Table 1: Evolution of Institutional Arrangements for New Product Development

Time	System		Targeted End-Users	Funding	Innovators/ Product Developers	Disease Type
Late 19th-mid-20th century	National (e.g. US military)		National, High-income countries	Public, Private via national patent systems	Public research organizations, academia, private sector	Diseases affecting high-income countries
1960s-80s	International	Multinational pharmaceutical industry	High-income countries	Public, Private via national patent systems	Public research organizations, academia, private sector	Diseases affecting high-income countries
		TDR, Fogarty Center, Rockefeller Foundation	Developing countries	Public, Philanthropic	Public research organizations, academia	Diseases primarily affecting low/middle-income countries
1990s-present	Global/ Neglected Disease	Multinational pharmaceutical industry:	High- and middle-income countries	Private via globalized patent systems, public	Public research organizations, academia, private sector	Diseases affecting high- and middle-income populations
		PDPs for neglected diseases	Developing countries (Global)	Philanthropic, public, in-kind private	Public research organizations, academia, private sector	Diseases primarily affecting low/middle-income populations
Future?	Global Health		Global	Public, philanthropic, private	Public research organizations, academia, private sector	All

Phase I: National

From about the late 19th century through the 1950s, NPD efforts were organized along national lines and were situated predominantly in the more-industrialized countries. On the public side, governments would invest taxpayer money through institutions such as the United States National Institutes for Health (NIH) or military research organizations,

with the understanding that in the long run the national public would benefit from the discoveries that would result. On the private side, firms would invest in developing new products, with the expectation that profits made through government-granted, time-limited patent monopolies would provide a sufficient return to re-invest in the development of new products. While patients outside of national borders would also benefit from the development of new health tools, the institutions and policy frameworks that guided such investments were primarily national rather than international.

For example, in the field of malaria, many of the tools used today to prevent or treat the disease emerged from the efforts of national military research institutions. Militaries were often the lead investors in developing new anti-malarial tools because of the crippling effect the disease had on fighting capacity.[1] Of the main malaria medicines developed in the twentieth century, none emerged without significant military contribution to the R&D effort. Most often, the targeted end-user was a soldier from an industrialized country. For example, the medicine that was for many years the gold standard in malaria treatment, chloroquine, emerged from US military efforts to find viable synthetic alternatives to quinine during World War II (Burckhalter, 1950).[2] The US military research program also developed amodiaquine, primaquine, halofantrine, and mefloquine (Ockenhouse et al., 2005), while the British military developed proguanil and pyrimethamine (Russell, 1963, p.8). The development of artemisinin emerged from the Chinese government's efforts to develop a better drug for its soldiers and allies in Vietnam in the 1970s (Honigsbaum 2001: 241-243).

The initial development of insecticide-treated bednets (ITN) was also pioneered by military efforts. While evidence of using netting to protect humans from insect bites dates as far back as the 6th century in the Middle East (Curtis et al. 1991), the innovative step of treating bednets with insecticides emerged from military efforts. During World War II, US, German and Russian troops used insect repellant-treated uniforms and bednets to protect soldiers from vector-borne illnesses (Binka & Akweongo 2006). (The further development of insecticide-treated bednets is discussed below.)

The military also played a key role in applying DDT as an anti-malarial measure. The Swiss scientist Paul Muller first developed DDT as an insecticide in 1939, and was later awarded the Nobel Prize in Medicine for his discovery. However, it was only after the British and US militaries carried out field trials in southern Italy in WWII that DDT's potency against malarial mosquitoes was realized (Bruce-Chwatt 1985: 297, Ockenhouse et al., 2005). As a result of this demonstrated success, DDT became a mainstay of the global malaria eradication campaigns in the 1950s. Only later would DDT be heavily used in agriculture, leading to the discovery of its long-term environmental impacts and its ban in many markets in the 1970s. Other pesticides have since replaced DDT in the US and Europe, but there is not yet a chemical that matches DDT for its low-cost, effectiveness, and long-lasting properties for malaria control. Thus, with some controversy, DDT is now slowly being re-introduced in some endemic countries for indoor residual spraying. The DDT example illustrates how the early nationally-driven NPD system generated tools that were useful for the industrialized countries and could then be applied in developing countries.

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[1] Among 160,000 French and British troops fighting in Greece in 1918, there were 80,000 hospital admissions due to falciparum malaria (Honigsbaum, 2001, p.224); more recently, it was the leading cause of medical disability for US troops in the Vietnam war (Ockenhouse et al., 2005, p.14).

[2] Though the compound itself was first synthesized in Germany in 1934, it was the US military research effort that discovered its ideal safety and efficacy profile.

Under the "national" framework, innovation has followed a distinct trickle-down pattern: products were invented in the public and/or private sectors, national research organizations (e.g. militaries) then played a critical role in applying or discovering their utility against malaria; later, other organizations such as developing country governments, WHO, donors, or public health researchers, picked up these innovations and adapted or applied them for use in developing countries.

However, for the purposes of addressing malaria in endemic developing countries, there were important drawbacks to this nation-based NPD system. Namely, tools developed for the purposes of Northern militaries were often ill-suited for the needs of civilians in the South. Since the tools that emerged from this system were not specifically designed for use in developing countries, they were not always well-adapted or affordable.

For example, when drugs were developed for military use, the target end-user was an adult, and there was almost no need to test the drugs in children or to produce pediatric formulations; however, the majority of deaths from malaria today occur in children under 5 in sub-Saharan Africa, and lack of sufficient research into pediatric drugs is problematic. Similarly, clinical trials have tested the safety and efficacy of using chemoprophylaxis for a duration of 3 months, which would serve the needs of many military operations and the travelers' market. However, such studies do little to help prevent malaria in populations living in endemic regions (Hughes et al. 2003).[3] Furthermore, while ITNs were important preventive tools, they retained their potency for a maximum of 6 months, but then had to be re-treated – this problem created logistical nightmares for population-wide use in endemic countries (Lengeler et al. 1996). In addition, while Northern militaries (and farmers) now have alternatives to DDT, NPD institutions have failed to produce a viable replacement for the environmentally-harmful chemical for malaria control. In the area of vaccines, military research efforts have focused on identifying a vaccine that would provide 12 months of immunity to an adult with no prior exposure to malaria (no natural immunity), an extremely useful tool for military deployments but of limited utility in endemic areas where adults usually have some immunity and much longer-term protection would be required. As the US Military Infectious Diseases Research Program (MIDRP) points out, "Preventing death in children and keeping soldiers healthy and effective are distinct goals requiring different research strategies (MIDRP 2005)." Finally, though the world has benefited immensely from affordable and effective drugs like chloroquine and sulfadoxine-pyrimethamine, when resistance to these medicines was spreading quickly in the 1980s and 1990s, there was no system in place to make newer medicines available or affordable in most endemic countries. At that time, the relatively more profitable market for anti-malarials remained Northern militaries and travelers. Thus, in 1999, a drug pricing study found that the average retail price of mefloquine in Tanzania was 80% higher than the maximum allowable retail price for the travelers' market in Norway, where medicines prices are about average for the European Union (Myhr 1999). The high prices of newer malaria drugs reflected the problem that new health tools were not being specifically developed or priced for the developing world. Some of these problems began to be addressed during the second phase of the NPD system.

Phase II: International

In the 1960s and '70s, public health entered a phase of internationalization, in parallel with similar developments in other fields, as actors came to see the world as increasingly interdependent (Keohane & Nye 1973). For example, in the US, the 1960s saw

[3] However, the widespread long-term use of chemoprophylaxis in endemic settings is not likely.

increased attention to the health problems of the developing world with the establishment of the Fogarty International Center at NIH in 1968, and the joint USAID-Department of Defense launch of a multi-million dollar malaria vaccine research initiative (Desowitz 1991, GAO 1989). Of particular importance during this period was the establishment in 1975 of the Special Programme for Research and Training in Tropical Diseases (TDR), a joint initiative of the United Nations Children's Fund (UNICEF), UN Development Programme (UNDP), the World Bank and WHO, and alongside it the Rockefeller Foundation's Great Neglected Diseases of Mankind international research network in 1977. These initiatives marshaled donor resources to build research capacity in, and fund research on, diseases disproportionately affecting the developing countries.

TDR-supported research contributed to the development of a number of important new products, including demonstrating the effectiveness in humans of Merck's veterinary drug ivermectin for the treatment of onchocerciasis (river blindness) (WHO/TDR 2007). WHO and TDR also played the role of cultural broker when news of a Chinese-developed anti-malarial wonder drug, artemisinin, first emerged in the West during the Cold War in 1979 (British Broadcasting Company 2005).

The development of insecticide-treated bednets (ITNs) also owes a debt to the support of TDR. In the 1960s-70s, soldiers wearing insecticide-treated uniforms often failed to properly use these tools because the chemicals available at the time caused skin rashes and other side-effects; furthermore, the insect repellants usually wore off after one or two washings. In 1977, the US Departments of Defense and Agriculture began studying ways to treat textiles with permethrin, a synthetic version of the plant-based insecticide pyrethrum; permethrin offered important advances over previously used chemicals, because it was biodegradable, non-irritating, long-lasting, and had low mammalian toxicity (Gupta et al., 2003: 511). By 1983, researchers had developed technologies for treating textiles so that permethrin would retain its potency after multiple washings and users could go several months without re-treating their clothes and bednets. The same year, WHO convened an expert meeting to study the potential of ITNs for malaria control. TDR-supported researchers performed the important function throughout the 1980s of developing ways to apply permethrin to mosquito-nets used in sub-Saharan Africa (separate efforts were also underway in China) and documented their efficacy in reducing child morbidity and mortality from malaria (Alonso and Lindsay 1991; Lengeler and Snow 1996; Binka and Akweongo 2006). As a result of this work, ITNs came to be understood as an important additional tool in the fight against malaria.

Finally, some of TDR's practices established a model that the PDPs would later emulate; for example, TDR set up an international network of academic centers to screen compounds from pharmaceutical companies for usefulness against its target tropical diseases (WHO/TDR 2007).

Compared to the earlier "national" period, the type of innovation that occurred during this "international" period was broader in scope, combining knowledge from both high- and lower-income countries to develop new products for developing country health needs. However, by the late 1980s the Great Neglected Diseases initiative was winding down and TDR was seriously under-funded for its broad mandate. While TDR was charged to work on seven tropical diseases, among other activities, its annual budget was only about $30 million (WHO 1991); at the same time, a 1991 study found that the average cost of developing a new medicine was $114 million (1987 dollars) out-of-pocket and $231 million capitalized (diMasi et al., 1991). Though these new institutional arrangements for NPD had yielded important advances, overall they could not sufficiently meet the vast health needs of

the developing world. At the close of the 1980s, drug-resistant malaria was spreading across the globe, the AIDS epidemic had begun to gain momentum, and there were no new tools to detect or treat tuberculosis: NPD institutions had not kept up with global health needs.

Phase III: Global/Neglected Disease

The 1990s launched the third phase of NPD institutional arrangements, which I label "global/neglected disease" because the new system took into account the health needs of populations around the globe, but mainly for the so-called "neglected diseases" that predominantly affected poor populations.

The question of how to channel health research for developing country needs was revived during these years, particularly due to an increased understanding of health research as global. In distinguishing between the older term, "international health" and the now widely used "global health" Brown et al. (2006) argue that the former emphasizes "a focus on the control of epidemics across the boundaries between nations" whereas the latter "implies consideration of the health needs of the people of the whole planet above the concerns of particular nations" and underscores "the growing importance of actors beyond governmental or intergovernmental organizations." This definition describes well NPD institutions in the "global/neglected disease" era, in which governments partnered widely with corporations and non-governmental organizations to develop new tools for health needs specific to the developing world. This period witnessed a growing appreciation for the importance of health research for development, coupled with increasing dissatisfaction with the existing institutions for NPD, highlighted most dramatically by the AIDS drug crisis.

A resurgence of interest in the role of research was reflected at the start of the decade in the Commission on Health Research for Development's 1990 report *Health Research-Essential Link to Equity in Development*. This report argued that research had long been "under-recognized and neglected" as a tool for addressing growing global inequities in the health of populations, and urged greater investment in health research at national level in developing countries, to be supported internationally with increased funding, technical support, and partnerships (CHRD 1990: xvii-xix). Not long after, the 1993 World Bank report, *Investing in Health*, put health squarely back on the international development agenda, making the case that good health was critical to economic development as well as a worthy goal in and of itself. Closely following on its heels was the 1996 report, *Investing in Health Research and Development*, which focused more specifically on the questions of R&D and NPD. Finally, the 1999 publication of the Global Forum for Health Research, *10/90 Report on Health Research* added an overtly normative dimension to the debates by arguing that spending only 10% of the world's R&D dollars on health conditions primarily affecting 90% of the population was an unethical imbalance that needed to be corrected. It rested on the principle that the fruits of R&D ought to produce global benefits – in other words, the products of R&D were no longer framed as private goods but as potential public goods. (For a more detailed discussion of this evolution see Szlezak, 2006).

The demand for change in the NPD system had come from many quarters, but was most vividly highlighted by the AIDS crisis. By the late 1990s, antiretroviral therapy was reducing morbidity and extending life in the industrialized countries, translating a lethal diagnosis into a chronic one. However, at over $10,000 per patient/year, the therapy was beyond the reach of most people living with HIV, about 95% of whom were in the developing world. At the same time, developing countries were just beginning to implement the 1994 World Trade Organization's Agreement on Trade-Related Aspects of Intellectual

Property Rights (TRIPS), a treaty that mandated a minimum level of patent protection and dismantled longstanding national exceptions in patent law for medicines and food. As a result, developing countries were granting patent monopolies on AIDS drugs that made it illegal to import generic medicines, even when they cost 98% less than the patented price. In response to vocal and politically savvy AIDS activists around the globe, a public outcry emerged over a system that developed new medicines but denied access to them for the majority of patients in need.

The debate over access to AIDS drugs was highly contentious. While the major patent-owning pharmaceutical companies initially responded to public pressure by offering voluntary price discounts and donations, these were insufficient to meet the vast scale of the needs. Advocates pushed for the widespread use of lower-cost generic medicines, which would require overcoming patent barriers at country level. WTO rules allowed countries to override patents for the public interest using a measure called "compulsory licensing," but due to heavy political pressure from the industrialized countries, no developing country used this flexibility until after 2001. That year, the drug industry suffered a major public-relations debacle when it sued the South African government for attempting to access lower-cost medicines; by April 2001 the industry had dropped its lawsuit "exhausted by the vitriol that has been heaped upon it," according to the Financial Times (Pilling and degli Innocenti, 2001). Later that year, in the wake of the anthrax scare, US health secretary Tommy Thompson was facing the possibility of shortages and high prices for the only effective drug, ciprofloxacin. Thompson publicly threatened the patent holder, Bayer, with a compulsory license on the medicine, as did Canada. While he never issued the compulsory license, the episode changed the tenor of the debates around AIDS drugs. Two months later, at the WTO conference of trade ministers in Doha, Qatar, the WTO issued a unanimous declaration confirming the right of all member countries to use compulsory licensing and to decide the grounds upon which to use them (WTO 2001). The Doha Declaration provided the political support for developing countries to access generic versions of patented medicines either through compulsory licensing or other legal means.

By 2008, generic competition had dropped the best international price for a year's worth of AIDS drugs to less than $100, or about 1% of its price in 2000 (Médecins Sans Frontières, 2008; Clinton Foundation, 2008). Major donors such as the Global Fund to Fight AIDS, TB and Malaria and the US President's Emergency Plan for AIDS Relief (PEPFAR) both currently purchase large quantities of generic drugs to supply national treatment programs. Arguably, there is an emerging global norm that, in some circumstances, governments are allowed to put public health concerns before patent protection.

The AIDS drug debate has resulted in three outcomes that are important for ongoing discussions on NPD for developing country needs. First, it has contributed to re-framing medicines from being understood as private goods to global public goods. Second (and relatedly), it has legitimized the idea that public health concerns may trump intellectual property protection. Third, it has set the precedent of civil society mobilization for access to new health tools. I discuss the implications of these developments for future NPD institutions in the next section.

Thus, the public-private product development partnerships (PDPs) emerged in the late 1990s against a complex backdrop of scientific, medical, ideational, political and economic factors, including: increasing attention paid to health and the critical role played by research, the growing commercial potential of emerging markets in the developing world, the criticism of the negative impacts of the globalization of patents, the idea that NPD

investment was not globally equitable ("10/90 gap") and that patents would not remedy this imbalance, and the tattered image of the pharmaceutical industry due to its reaction to the AIDS crisis (see Moran et al., 2005 for an analysis of why major drug firms participate in PDPs). The new PDPs were designed to respond to the key shortcomings of the existing NPD system (Widdus & White, 2003; Buse & Harmer, 2007; Moran et al., 2005). One major problem was that in a market-driven system there would be insufficient investment into diseases primarily affecting poor populations; of 1393 new medicines developed from 1975-1999, only 16 – or about 1% -- were for tropical diseases and tuberculosis (Trouiller et al., 2002). The other key problem was that a monopoly-based innovation model relied on high prices to recoup the costs of research – this often resulted in unaffordable prices.

Four key principles of the PDPs that differentiated them from older institutional models were that: 1) tools should be affordable, 2) tools should be adapted for use in resource-poor settings (e.g. easy to use, relatively low-technology, pediatric formulations when necessary), 3) research should be driven by human health needs, not only market considerations, and 4) complementary public- and private-sector expertise should be mobilized.

Important PDPs include: the International AIDS Vaccine Initiative (IAVI, founded 1996), Medicines for Malaria Venture (MMV, 1999), Malaria Vaccine Initiative (MVI, 1999), Global Alliance for TB Drug Development (2000), Institute for OneWorld Health (IOWH, 2001), the Drugs for Neglected Diseases Initiative (DNDi, 2001), the Foundation for Innovative Diagnostics (FIND, 2003), and the long-lasting insecticide-treated (LLIN) bednets partnership between WHO and three firms (detailed below).

The Malaria Vaccine Initiative provides one example of the new thinking. The PDP describes its ideal malaria vaccine as: "easy to manufacture, easy to administer, and when administered in infancy, confer life-long immunity." Furthermore, MVI commits to ensuring "that successful, appropriate vaccines will be sold at affordable prices in the public sector (MVI 2008)." These criteria differ significantly from those of the US Department of Defense, which is trying to develop a vaccine primarily intended for adults that would confer short-term immunity (1 year minimum, 2 years desired), with no explicit mention of cost constraints (Graves and Levine, 2006). Finally, within the scope of MVI's seven ongoing projects are 51 "partners," of whom 35% are private firms and 65% public or publicly-oriented organizations (e.g. government research institutes, universities, foundations) (MVI 2008). This globally-networked partnership structure contrasts with the more centralized DoD program, which is largely carried out in-house (though DoD cooperates with MVI).

The rapid evolution of institutional arrangements in recent years is well illustrated by the example of the development of artemisinin-combination therapy for malaria. Coartem (artemether and lumefantrine) is a fixed-dose combination of two malaria drugs that was developed by the pharmaceutical company Novartis in partnership with a Chinese firm. When Novartis first launched Coartem in 1998 it was targeted at the European market. The drug was neither widely available nor affordable in developing countries until 2001, when Novartis and WHO announced an agreement to market the drug at a reduced price in low-income countries. At the time, Novartis only produced adult formulation tablets, which could be used but were not ideal for the treatment of small children. In 2003 the company announced jointly with MMV that it was beginning to develop a pediatric formulation which is expected to be approved in 2008 (IFPMA 2003; MMV 2007).

The trajectory of Coartem reflects institutional arrangements in flux: it was a product that was initially developed in the 1990s primarily for the Northern travelers' market. In response to changing norms, an access program was introduced in 2001 to sell the drugs "at

cost" or around 2.60 USD per adult treatment. By 2003 a changed institutional context made it feasible and politically desirable to begin developing a pediatric formulation that would primarily serve the developing world, and to drop the adult treatment price to around 1 USD.

Notably, the Coartem story repeated itself but within a compressed timeline when DNDi and Sanofi-Aventis released their combination malaria drug (artesunate and amodiaquine, "ASAQ") in 2007. ASAQ, like Coartem, was co-formulated into one tablet for ease of use and to facilitate patient adherence; however, it also allowed for a simplified once-a-day dosing schedule (compared to twice-a-day for Coartem). The combination was immediately marketed at a "no profit – no loss" price of about 1 USD/day, with a pediatric formulation available at about half the price, and an explicit no-patent policy to encourage generic competition in production of the drug (DNDi, 2007). That ASAQ was launched with affordability and children-under-five in endemic countries in mind reflects an ideational evolution in the purpose and intended beneficiaries of NPD efforts.

This evolution is also evident in other technologies for malaria. For example, the logistical problem posed by ITNs whose potency only lasted 6-months was significantly mitigated when Sumitomo Chemicals developed a long-lasting insecticide-treated bednet (LLIN) that retained its potency for up to five years. Sumitomo engineers had first developed the key technology in 1992 for other purposes, and in 1999 produced a first batch of LLINs targeted at travelers and the Southeast Asian market (Ito and Okuno 2006). In 2002, WHO approached Sumitomo and asked the firm to increase production volumes and also to consider transferring technology to an African firm to spur local production. By 2006, A to Z Textile Mills in Tanzania, along with two production plants in China and one in Vietnam were producing LLINs through a non-exclusive, royalty-free license (Ito and Okuno 2006). Significantly, affordability was an important criteria for the partnership; one objective of the technology transfer was to achieve production efficiencies at A to Z, which reduced the price of an LLIN from about 10 to 5 USD. While this price is higher than for a regular ITN, its per-year cost is about half that of ITNs (Yukich et al. 2007).

Both the development of new, affordable, fixed-dose combination malaria drugs and the LLINs reflect institutional changes that put an unprecedented level of attention on NPD for the developing world.

By targeting the needs of the world's poorest, the PDPs represented an important change in the orientation of NPD efforts. However, the funding model has not changed dramatically since the 1970s when donor governments and philanthropists footed the bill for TDR. The scale of funding has undeniably grown, particularly due to the growing involvement of the Bill & Melinda Gates Foundation, which has invested 6 billion USD in global health programs (many of them research oriented) from 1995-2006 (Gates Foundation 2008). One analysis of funding sources for four major PDPs (MMV, DNDi, IOWH, and TB Alliance) found that over the lifetime of these PDPs (through 2005), philanthropic sources comprised 78% (212 million USD) of funds, of which the Gates Foundation accounted for 75% (159 million USD); Northern donor governments had contributed about 16% (44 million USD) of the total (Moran et al., 2005). The rapid infusion of funds has kick-started multiple new research efforts in a short span of time, and quickly established these new institutional forms as important players in the NPD system. Nevertheless, the funding model underlying the PDPs is as donor-dependent as the initiatives in the previous 'international' phase. New ideas for financing NPD in ways that do not rely solely on donors are a characteristic of the next phase.

Phase IV: Global Health

As of the writing of this paper in 2008, we find ourselves at the beginning of a fourth phase whose contours remain undefined. There have been dramatic shifts in the organization of NPD for some infectious diseases over the past decade, leading to a broad array of new research efforts and an unprecedented level of political attention and funding; these developments bode well for the prospects for new, effective, adapted and affordable tools becoming available to promote global health. However, an important limitation is that these innovations have been limited to the so-called neglected diseases: malaria, TB, and a range of tropical diseases such as schistosomiasis, Chagas disease, leishmaniasis and dengue fever. The "neglected diseases" framework has a critical shortcoming, which is that it focuses only on diseases that by definition *only* affect the poor. One side-effect is that attention may be shifted away from the question of how accessible and appropriate are medical interventions for diseases that affect both rich and poor countries, such as chronic non-communicable diseases (NCD) (henceforth "Type 1" diseases, following the WHO terminology).[4]

Effective institutions for NPD for the Type 1 diseases are critical for several reasons. First, the number of deaths and burden of disease from chronic non-communicable disease is projected to increase, while those due to infectious diseases (with the important exception of HIV/AIDS) will fall by 2030 (Mathers & Loncar, 2006). In low- and middle-income countries it has already increased from 35% in 1990 to 45% of the burden of disease in 2003, and is projected to exceed 50% by 2030 (Mathers and Loncar, 2006).

Second, the precedent set by AIDS has encouraged patient advocates to organize to demand access to new health tools in other disease areas. A recent example of such mobilization concerns the cancer drug Glivec (imatinib mesylate), patented by the Swiss drug firm Novartis. Glivec is one of the most effective new cancer drugs to emerge in many years, and is used for the treatment of chronic myeloid leukemia and gastric stromal intestinal tumors. However, Glivec's high price, combined with its significant therapeutic advantages, have made it the target of cancer patient advocacy in many countries. In 2002, a patients' association in South Korea pressured both the firm and the government to reduce the price of the drug, which cost up to 50,000 USD per year; they also filed a request for a compulsory license, though this petition was denied (Nam & Park, 2002). More recently, in 2007 the patent on Glivec in India was overturned by a legal challenge from a patients' organization and a generic company producing the drug at lower cost (Sukumar, 2007). Finally, in January 2008, the government of Thailand issued a compulsory license for Glivec, but reversed its decision after Novartis offered to donate the drug free of charge to the national health system (New, 2008a). These developments occurred despite the global donation program Novartis had launched for the drug, which was accused of moving too slowly and mixing humanitarian gestures with commercial motives (Strom and Fleischer-Blac, 2003). The Glivec story reflects a broader problem in the NPD system: when new health tools are developed for diseases with global incidence, there is no institutional arrangement to ensure that they are affordable or available to people who need them. However, AIDS has established the idea that access should be broadly-shared, thus, the

[4] The WHO Commission on Macroeconomics and Health divided diseases into three categories based on the populations affected. Type I refers to diseases that affect both rich and poor countries, with large populations affected in each (e.g. cardiovascular disease, diabetes). Type II are diseases prevalent in both rich and poor countries, but with a large proportion of cases in poor countries (e.g. HIV/AIDS). Type III diseases are those that almost exclusively affect the poor countries (e.g. most of the 'neglected diseases').

kinds of political conflict that took place over Glivec are likely to re-occur with other effective new health tools and may further tarnish the reputation of global drug firms unless access issues can be resolved.

Third, emerging global norms about the human right to health, health tools as global public goods, and the proper balance between patent-protection and access, are likely to favor the concerns of developing countries. There is increasing understanding that we need new global governance arrangements to manage the provision of public goods such as NPD (Ruggie, 2004). If we are to avoid constant political battles over each important new health tool, a new set of institutional arrangements will be necessary that encourages and rewards innovation but does not sacrifice access.

Are the PDPs the right answer? The emergence of PDPs in the past decade has led to a bifurcated NPD system. On the one hand, the private sector develops new products for diseases that affect the industrialized world, funded by a combination of public support for basic research and monopoly profits from sales. On the other hand, PDPs address the neglected diseases for which market mechanisms had failed to generate sufficient investment, and are financed by philanthropists and donor governments. However, reliance on this old funding model has raised questions regarding its sustainability. In addition, concerns have been raised about the governance of PDPs – how priorities are set, decisions made, and funding allocated (Buse & Walt, 2000; Buse, 2004; Birn 2005; Buse & Harmer, 2007; McNeil 2008).

Furthermore, the PDPs, as they are currently organized, are likely to be ill-suited to the Type 1 diseases. First, the PDPs rely on cooperation and contributions from major pharmaceutical companies, who are willing to do so, in part, because the end products are not highly profitable; in other words, because there is virtually no market for a leishmaniasis drug, companies can share information and compounds with little fear of losing competitive advantage. Second, the PDPs can attract public and charitable funds to subsidize their costs precisely because they will not attract sufficient private sector money to function. Third, PDPs are designed to spur research in areas where it is lacking. These conditions do not generally hold for Type 1 diseases, and PDPs are likely not the appropriate response. This is not to imply that cooperation between the public, private, and non-profit sectors is unimportant– on the contrary, it is likely to play a key role in future institutional arrangements. However, the model of cooperation currently embodied in the PDPs will not be viable when sizable profits are at stake and when major research efforts are already underway.

(The one exception may be IAVI, since an AIDS vaccine shares important traits with health tools for Type 1 diseases: it would be of tremendous value in both developing and industrialized countries, there have long been ongoing research efforts, and management of intellectual property has been a thorny problem. However, there are other key differences between an AIDS vaccine and tools for NCD, including the high uncertainty around a vaccine, the unprecedented amount of global attention paid to AIDS, the high ratio of cases in the developing world, and the discrepancy between the financial attractiveness of a drug versus a vaccine. Notably, there is no PDP for AIDS drugs while there is one for an AIDS vaccine. Nevertheless, of the PDPs, IAVI may provide the most interesting example from which to draw lessons for institutions for Type 1 disease NPD. However, this is beyond the scope of this paper.)

If not the PDPs, then what about the patent system? If we take a global perspective of the needs, it is clear that the current NPD system for Type 1 diseases generates innovative tools that are relatively well-suited for the industrialized countries. For example, the new

human papilloma virus vaccine represents a significant therapeutic advance. But for many parts of the developing world, these innovations may not be affordable or well-adapted for use in resource-poor settings.[5] In some ways, the current situation for Type 1 diseases parallels the earlier nation-based NPD system, in that innovative products are developed in the industrialized world and will possibly later 'trickle-down' to the developing world, but the new tools that emerge will not necessarily be well-adapted or affordable. This was indeed the situation with antiretroviral drugs for AIDS before global political mobilization changed the way in which access to these medicines was governed.

Will another wave of institutional innovation emerge in time to address the coming crisis in Type 1 diseases?

At this point it is difficult to predict how future institutions will evolve. Therefore, the following section will present the author's perspective on the principles that ought to guide institutional design for NPD, based on conclusions drawn from this historical review.

Current Debates & Perspectives

Who should benefit from NPD?

One idea that has grown in strength over the past two decades, and that I argue ought to continue to inform efforts at institutional reform, is the principle that NPD should be targeted at a global population of beneficiary end-users. This principle is important on human rights grounds, as well as for reasons of political expediency. Health tools, as knowledge-intensive products, have the potential to become global public goods – consumption by one person does not necessarily reduce consumption by another (Kaul et al 2003). Civil society organizations are likely to continue mobilizing to demand widespread access to new health tools.

Who should pay for NPD?:

While ideas about who should benefit from NPD have steadily expanded over time, there has been remarkably less evolution on the question of who should pay, as noted in the above discussions about PDP financing. I propose that a second key principle that ought to guide future institutional arrangements for Type 1 NPD is that financing should be a globally-shared burden. Given the chronic need for new health tools, sustainable financing of NPD efforts will be critical; we cannot expect philanthropy to underwrite NPD indefinitely. In order to be *politically* sustainable, such financing must be globally shared. One reason is that some developing countries, such as the BRICS (Brazil, Russia, India, China, South Africa) are rapidly increasing both their scientific and financing capacity, and will be expected to pay. Another reason is that calls for global access will only be tenable in the long-term if they are matched by calls for global contributions to public goods provision.

Global burden-sharing is not a new idea. Rather, the globalization of patents on medicines was premised, in part, on the same logic. Beginning in the 1970s, the research-based pharmaceutical industry began systematically lobbying the US government to push for an expansion in the number of countries granting patent protection on medicines, and a ratcheting-up of protection levels in countries where it already existed (Drahos and Braithwaite, 2002). Such a system would, presumably, increase profits to the patent-holders,

[5] Notably, even in the United States and even for the insured population, the rising cost of new medicines is becoming a heavy financial burden (Kolata 2008; New York Times Editorial Board 2008).

but the industry also portrayed it as a way of spreading the cost of financing research across the globe. These efforts were sustained throughout the Uruguay Round of world trade negotiations in the 1980s, and came to fruition in 1994 when TRIPS was signed. TRIPS set in motion the globalization of a uniform set of intellectual property (IP) standards that would, in theory, allow a more broad-based system of extracting rents for future NPD investment.

However, globalizing patents on health tools was extremely controversial. Historically, many countries had adopted national IP policies to meet domestic needs, with less industrialized countries usually offering lower levels of IP protection (Jaffe & Lerner 2004). Many countries, even relatively wealthy ones, also excluded food and medicine from patentability because of the negative effects of monopoly pricing of these products on social welfare; for example, Spain, Norway and Greece did not grant product patents on medicines until 1992 (Lanjouw, 2004). However, TRIPS required all WTO Members to provide a uniform level of IP protection (e.g. 20-year patent terms) and disallowed the exclusion of food or medicines from patentability.

Many scholars and civil society groups were highly critical of TRIPS, characterizing it as a wholesale rent transfer from poor to rich countries that would retard rather than induce industrialization and economic development. Of particular concern was the expected increase in the price of new medicines in developing countries (Chaudhuri et al. 2003); patents could also increase the prices of other critical innovative health products, including insecticides, vaccines and diagnostics. Thus, throughout the 1980s and '90s there was a push to globalize the financing of health NPD through a uniform system of patent protection. However, strong social reaction coupled with growing concern about the AIDS epidemic undermined support in many parts of the world for this NPD financing model.

Today, there is a need for new institutional arrangements for funding NPD on a sustainable and globally equitable basis that would provide alternative ways to stimulate and reward innovation. While treating health products as global public goods can provide widespread benefits, it will also be necessary to address the classic economic problem with public goods: underinvestment and free-riding.

While the idea of globally-shared financing for NPD has not yet been realized, there are indications that the idea of global burden-sharing has gained momentum. For example, the UNITAID partnership co-founded by France, Brazil, Chile, Norway and the United Kingdom in 2006, has implemented an airline tax to finance the purchase of health products in low-income countries. The driving rationale was that predictable, long-term funding would be necessary to sustain global health efforts, particularly for long-term chronic conditions such as AIDS. The progressive tax is currently implemented in 9 countries, and is in process in 15 others.[6] Notably, 13 of these participants are UN-designated Least-Developed Countries, reflecting the idea that all countries – even the poorest – should contribute in some way. While UNITAID began as an "international drug purchasing facility," it has since expanded its focus to other types of activities and has been discussing

[6] Implemented: France, Chile, Côte d'Ivoire, Democratic Republic of Congo, Republic of Korea, Madagascar, Mauritius, Niger, Norway (Norway also dedicates part of its CO2 tax to UNITAID). In process of implementation: Benin, Brazil, Burkina Faso, Cameroon, Cyprus, Gabon, Guinea, Liberia, Mali, Morocco, Namibia, Central African Republic, Senegal, Sao Tome & Principe, Togo. Source: http://www.unitaid.eu/en/The-air-ticket-levy.html, accessed 15 April 2008.

the possibility of dedicating a portion of the tax proceeds to the development of new products such as fixed-dose combinations (J. Bermudez, personal communication, 2 May 2008). Funding for 2007 was $320 million and is projected to reach $500 million by 2009; by taking advantage of international bulk purchasing, the initiative also tries to stretch these dollars further. The institutional design of UNITAID reflects the importance of several ideas: the need to globally share the burden of financing health tools, the freedom to adapt the tax to individual country contexts, the acceptability of progressive taxation even in the poorest countries, and the utility of long-term dependable financing.

Another important arena in which there has been increasing discussion of global burden-sharing is among Member States involved in the WHO Intergovernmental Working Group on Public Health, Innovation, and Intellectual Property (IGWG). The IGWG process is an attempt to build a sustainable system for funding the development of global public goods for health with the support of all WHO Member States. As such, it can also be interpreted as an attempt to build a more stable financing model and a more broad-based governance system for NPD than the one currently existing. The IGWG process was launched by a World Health Assembly (WHA) resolution in 2006, sponsored by Kenya and Brazil, and charged with identifying a "global strategy and plan of action" aimed at "securing an enhanced and sustainable basis for needs-driven, essential health research and development relevant to diseases that disproportionately affect developing countries [and] proposing clear objectives and priorities for research and development (WHA 59.24 2006)." The creation of IGWG emerges out of two earlier initiatives: the publication in 2002 of the UK Government Commission on Intellectual Property Rights, which was followed in 2006 by the report of the WHO Commission on Intellectual Property, Innovation and Public Health. Both of these reports, drafted by a diverse and well-respected group of expert commissioners, concluded that a patent-based system would be insufficient to finance and set global health priorities for NPD (CIPR 2002, CIPIH 2006). In the past several years a broad range of new ideas for institutional arrangements have been put on the table, including: a global R&D treaty, a global R&D fund (India), international agreements for access to compound libraries, global free access to publications based on publicly-funded research, special licensing arrangements for publicly-funded research (Keusch, 2004), patent pools, advanced market commitments (Berndt et al., 2006), funding for clinical trials as global public goods, and a series of prize funds for specific new products (Stiglitz, 2006; Love, 2006; Mision Permanente de la Republica de Bolivia-Ginebra, 2008). Many of these measures would involve contributions from developing countries, and move away from an overly donor-dependent model of NPD.

After intense eleventh-hour negotiations, particularly over the thorny IP issues, IGWG concluded at the 2008 World Health Assembly (New, 2008b). One important idea that all Member States agreed upon was that it would be necessary to finance and stimulate NPD for *all* diseases that affect the developing countries– not only the neglected diseases. Furthermore, eight PDPs issued a position statement at the meeting, emphasizing the need for new incentive mechanisms and new funding for NPD (IAVI, Pediatric Dengue Vaccine Initiative, DNDi, Innovative Vector Control Consortium, MMV, Aeras Global TB Vaccine Foundation, TB Alliance, MVI, 2008). In other words, many of the PDPs do not see themselves as a sufficient response to global health NPD needs. While the IGWG discussions have yet to translate into action, the agreements reached so far indicate the beginnings of a normative shift toward a new "global health" phase of NPD, based on the principles of global access and global burden-sharing.

Summary & Conclusions:

This paper has outlined the progression of the NPD system through four main phases. We began at the start of the twentieth century with the 'national' system in which financing, intended beneficiaries and policy frameworks were confined to the national level mostly in the industrialized countries. We then progressed in the 1960s-70s to an 'international' system in which donors put increasing emphasis on NPD for the health needs of the developing world. By the 1990s we had shifted to a 'global/neglected disease' phase, characterized by PDPs that channeled an unprecedented amount of attention and resources to addressing the 'neglected diseases' that almost exclusively affected developing countries. And finally, we are perhaps at the beginning of a fourth phase of 'global health,' in which the scope of diseases is expanded to include *all* diseases that affect developing and industrialized countries.

The outlines of the current phase remain blurred. However, I suggest two principles that ought to shape future institutional responses. First, knowledge and innovation for all diseases should be treated as a global public good, which can benefit a global population of end-users. Second, the financing of NPD should not rely on philanthropic initiatives, but rather, should be supported through a politically sustainable and globally-equitable sharing of the burden of long-term funding. There are a number of proposals on the table for new incentive mechanisms, and some experimentation is likely to be necessary to achieve concrete outcomes. However, as the history of the evolution of NPD systems demonstrates, there is momentum and political demand for a system that will be ever more inclusive.

Such a system would be of benefit, not only to the world's poorest countries, but also to the most powerful. In 2003, when 290 US Marines briefly went ashore to support international peacekeepers in Liberia, over one in four returned with malaria (Malaria Outbreak Among Members of JTF Liberia: Consensus Conference Report, 2003). Though artemisinin-based combination therapy is not yet registered in the US, this example demonstrates the potential advantages of developing new health tools as global public goods.

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