Fatal Imbalance

The Crisis in Research and Development for Drugs for Neglected Diseases

DND drugs for neglected diseases working group

CAMPAIGN FOR ACCESS TO ESSENTIAL MEDICINES

MEDECINS SANS FRONTIERES

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Médecins Sans Frontières Access to Essential Medicines Campaign

Médecins Sans Frontières (MSF) is an independent medical humanitarian organization committed to providing medical assistance to people in need regardless of race, religion, politics or gender, and to raising awareness of the plight of the people it helps. Too often, MSF volunteers, who work in over 80 countries worldwide, are left without adequate treatment options when the only available drugs are archaic, ineffective or toxic. To address this chronic emergency, MSF launched the Access to Essential Medicines Campaign in 1999.

Successes of the Campaign include raising awareness internationally of the access crisis, contributing to the dramatic fall in prices of antiretroviral drugs for the treatment of HIV/AIDS, securing a supply of discounted second-line drugs for multi-drug resistant tuberculosis, and ensuring the long-term production of four drugs for sleeping sickness. The Campaign has also helped put the problem of access to essential medicines on the international agenda.

The Drugs for Neglected Diseases Working Group

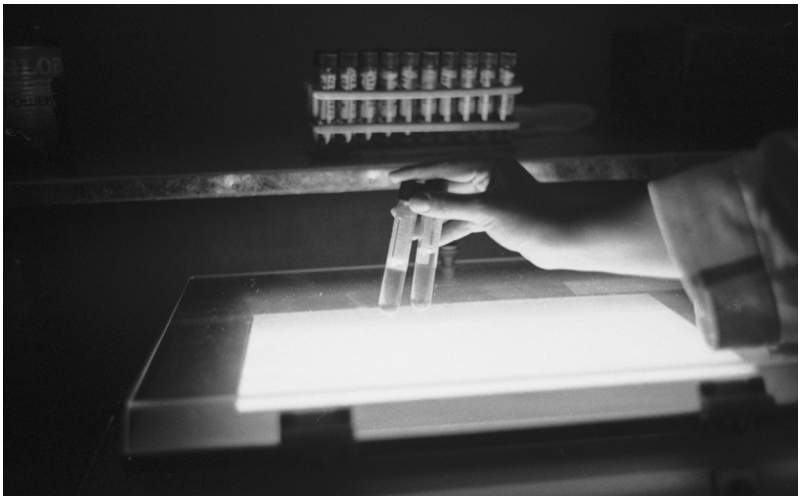
In October 1999, a group of concerned scientists, health professionals, and representatives from non-governmental organizations, the pharmaceutical industry, developing country governments and international organizations met in Paris to discuss stimulating the development and securing the availability of drugs for neglected diseases. Médecins Sans Frontières, the World Health Organization and the Rockefeller Foundation convened the meeting.

Following the meeting, the Drugs for Neglected Diseases (DND) Working Group was formed to continue the work begun at the conference by developing new ideas to restart research and development (R&D) of drugs for neglected diseases. The DND Working Group is a multi-disciplinary and independent group that includes researchers, drug development experts, and regulatory affairs professionals from the public and private sectors of developed and developing countries.

According to the DND Working Group mission statement, "it is the responsibility of society to address this public health failure, and seek new and creative strategies to solve this problem…. Solutions and recommendations need to be sustainable, affordable, need-driven and involve input and active engagement of developing countries."

The DND Working Group has studied the causes and proposed solutions for the R&D crisis. The group has also advocated for the active engagement and financial support of governments, private enterprises, foundations and international organizations to compensate for the failure of the market to provide drugs for neglected diseases. The work of the group focuses on the most neglected diseases, such as sleeping sickness and leishmaniasis, in addition to neglected diseases that are already receiving some renewed attention, such as tuberculosis and malaria. Close links have been established with other institutions such as the Special Programme for Research and Training in Tropical Diseases (TDR), which is based at the World Health Organization, and the Global Alliance for Tuberculosis Drug Development.

Part of the DND Working Group strategy is to fund and manage pilot drug development projects. The DND and TDR are working together to undertake several drug development projects that have not been completed due to lack of funds and human resources. Funding for these pilot projects is being provided partially by MSF and will be managed by drug development experts.



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An MSF volunteer visits a young boy with Chagas disease near the town of Yoro, in central Honduras. Only children are treated for the disease, because no drugs exist that are effective for adults.

Executive summary

The health revolution of the last 30 years, which has produced substantial gains in life expectancy and unparalleled medical advances, has left most of the world's population behind in important ways.

People in developing countries, who make up about 80% of the population, only represent about 20% of worldwide medicine sales. For these people, the imbalance between their needs and the availability of medicines is fatal. This report seeks to explore one element of this stark reality: the lack of research and development (R&D) into drugs to treat the diseases of the poor.

In 30 years of work, MSF has witnessed first-hand the human impact of the lack of drugs for infectious diseases. Until very recently, patients suffering from sleeping sickness had to undergo painful treatment with an arsenic-based medicine because more effective treatment was unavailable. Yet the disease afflicts up to 500,000 people and threatens another 60 million in Africa. For Chagas disease, which threatens a quarter of the population of Latin America, only children can be treated because no effective drugs exist for adults. The human suffering caused by infectious diseases could be reduced; with billions of dollars dedicated to health R&D it should be possible to develop effective treatments for these diseases. However, the lack of R&D for diseases common in developing countries means that very few new drugs have been brought to market for them.

In 1999, MSF convened an international body of health experts to study the current state of drug R&D for diseases that affect people in the developing world. This independent body, the Drugs for Neglected Diseases (DND) Working Group, has since undertaken an analysis and proposed some recommendations for moving forward.

When treatment options don't exist or are inadequate, a disease can be considered "neglected," or even "most neglected" in some cases. The neglect is a result of market failure and public policy failure. Strategies must be developed to address neglected and most neglected diseases specifically.

In spring 2001, the 20 top-grossing pharmaceutical companies in the world were surveyed about recent drug development activity. While the survey demonstrated some activity in neglected diseases, it indicated that private sector investment in this field was minimal. None of the responding companies has brought a drug to market in the last five years for any of the most neglected diseases included in the survey.

The DND Working Group has also explored the failure of the public sector to take a needs-based approach to managing drug development. Basic research leading to discovery of compounds – and thus potential drugs – has almost always been publicly funded. However, because politicians naturally respond to the needs of their constituencies, and because wealth is concentrated in industrialized countries, research money goes to the diseases primarily affecting these wealthier constituencies. While some government money has been devoted to diseases affecting developing countries, it is a pittance compared with overall spending on drug development. Private philanthropy has in recent years sought to fill in a bit of this gap, but it is not sufficient and cannot and should not take the place of public support.

Recent initiatives and policies seeking to redress the R&D imbalance are also outlined here. Public-private partnerships have been successful in mobilizing public and private sector expertise around certain diseases. Yet, to date, none of these provides an adequate strategy for developing drugs for the most neglected diseases.

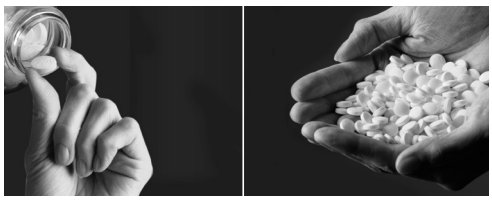
Finally, recommendations for moving forward are presented, among them: that a well-defined and needs-driven research agenda be established at a global level; that governments fulfill their responsibility to become directly and proactively involved in searching for solutions; that funding be increased for research into neglected and most neglected diseases; and that a new not-for-profit initiative be explored as one way to address the shortage of R&D for the most neglected diseases.

A young patient receives treatment at an MSF sleeping sickness clinic in Omugo, Uganda. This painful disease infects up to 500,000 people and threatens 60 million more, predominantly in sub-Saharan Africa. The drugs available to treat sleeping sickness are archaic, toxic or difficult to administer.

Whose health revolution?

| The past 30 years have witnessed unprecedented transformations in global health, with, for example, life expectancy around the world rising by an average of four months every year.[1] However, such impressive statistics should not obscure the fact that the benefits of the "global health revolution" have not been distributed evenly. Millions continue to die each year of preventable and treatable diseases. Communicable diseases killed 14 million people worldwide in 1999, mostly in developing countries.[2] One cause of this is the vacuum in research and development (R&D) for medicines to treat the diseases of the poor.

| There is a strong link between poverty and health. People from low- and middle-income countries carry a disproportionate burden of disease, particularly with regard to communicable diseases. Those living in absolute poverty (on less than one dollar per day) are five times more likely to die before reaching the age of five, and two and a half times more likely to die between the ages of 15 and 59.[3] Infectious and parasitic diseases account for 25% of the disease burden in low- and middle-income countries, compared to only 3% in high-income countries.[4] According to the World Bank, eliminating communicable diseases would almost completely level the mortality gap between the richest 20% of the world population and the poorest 20%.[5]



There is a vast difference between the number of new drugs developed between 1975 and 1999 for tropical diseases and tuberculosis, and those developed for cardiovascular disease, despite the fact that the disease burden for the two groups is nearly the same.

Figure 1A

The vacuum in drug R&D for the diseases of the poor

| Eliminating the mortality gap will likely remain an elusive goal, because R&D efforts are not addressing many of the communicable diseases that plague developing countries. An analysis of drug development outcomes over the past 25 years shows that only 15 new drugs were indicated for tropical diseases (11+2) and tuberculosis (2).[6] These diseases primarily affect poor populations and account for 12% of the global disease burden. In comparison, 179 new drugs were developed for cardiovascular diseases, which represent 11% of the global disease burden (Figure 1A).

| Too little money is going into health research that addresses the needs of the world's poorest people. While it might be expected that health research would concentrate on the areas where the needs are greatest, the reality is quite different. Only 10% of global health research is devoted to conditions that account for 90% of the global disease burden – an imbalance that has been referred to as the 10/90 disequilibrium.[7]

| Heavy reliance on an increasingly consolidated and highly competitive multinational drug industry to generate new medicines has left the development of lifesaving drugs subject to the forces of a market economy. Currently, it is largely purchasing power that is defining research agendas and priorities, which means that poor people's health needs are not being met.

| This failure does not rest exclusively on the shoulders of the private sector. Governments hold the ultimate responsibility for ensuring that peoples' basic health needs are met. They have the responsibility to take appropriate action when market forces fail to address these needs. In the past few decades, despite clear evidence of waning

1) World Health Organization, *Health: A precious asset, Accelerating follow-up to the World Summit for Social Development,* proposal by the World Health Organization, WHO/HSD/HID/00.1 (Geneva: World Health Organization, May 2000).
2) World Health Organization, *The World Health Report 2000,* estimates for 1999, Mortality by sex, cause and WHO Regions. (Geneva: World Health Organization, 2000).
3) World Health Organization, *Health: A precious asset, Accelerating follow-up to the World Summit for Social Development.*
4) World Health Organization, *The World Health Report 1999,* estimates for 1998, Burden of disease by cause, sex and mortality stratum in WHO Regions. (Geneva: World Health Organization, 2000). Disease burdens are expressed in DALYs, or Disability-Adjusted Life Years.
5) Davidson R. Gwatkin and Michel Guillot, "The Burden of Disease among the Global Poor: Current Situation, Future Trends and Implications for Strategy" (Washington, D.C.: World Bank, 2000).
6) Patrice Trouiller et al., "Neglected diseases and pharmaceuticals: between deficient market and public health failure," forthcoming publication, 2001. Note: Disease burden is expressed in DALYs, or Disability-Adjusted Life Years. Tropical diseases include parasitic diseases (malaria, African trypanosomiasis, Chagas disease, schistosomiasis, leishmaniasis, lymphatic filariasis, onchocerciasis), dengue, diarrhoeal diseases, intestinal nematode infections, leprosy and trachoma. For these diseases, the following 11 new chemical entities were developed between 1975 and 1999: *halofantrine, mefloquine, artemether, atovaquone* (malaria); *benznidazole, nifurtimox* (Chagas disease); *albendazole* (helminth infections); *eflornithine* (African trypanosomiasis); *ivermectine* (onchocerciasis); *oxamniquine, praziquantel* (schistosomiasis). In addition, two reformulations of already existing drugs came onto the market: *pentamidine isetionate* (African trypanosomiasis) and *liposomal amphotericin B* (leishmaniasis). The two new drugs for tuberculosis are *pyrazinamide and rifapentine.*
7) Global Forum for Health Research, *The 10/90 Report on Health Research.* [Online]. (2000). Available: **http://www.globalforumhealth.org**.

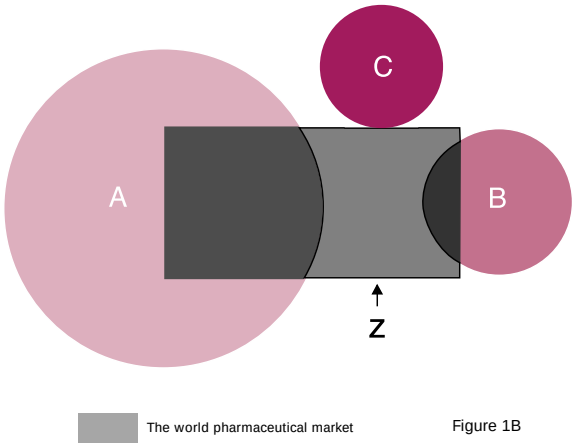


Figure 1B

What kinds of needs does the pharmaceutical market cover?

A represents Global Diseases,
such as cancer, cardiovascular diseases, mental illness and neurological disorders, which constitute the major focus of the R&D-based pharmaceutical industry. Although affecting developed and developing countries, most people in developing countries who have needs for drugs to treat these diseases cannot afford them, and are thus not covered by the pharmaceutical market.

B represents Neglected Diseases,
such as malaria and tuberculosis (TB), for which the R&D-based pharmaceutical industry has only marginal interest. Although also affecting people in wealthy countries, for example TB patients or people who get malaria while travelling, these illnesses primarily affect people in developing countries.

C represents the Most Neglected Diseases,
such as sleeping sickness, Chagas disease and leishmaniasis, which exclusively affect people in developing countries. Because most of these patients are too poor to pay for any kind of treatment, they represent virtually no market and for the most part fall outside the scope of the drug industry's R&D efforts, and thus outside the pharmaceutical market.

Z represents the part of the pharmaceutical market for products addressing conditions other than those which are purely medical (such as cellulite, baldness, wrinkles, dieting, stress and jet-lag), which nonetheless represent a highly profitable market segment in wealthy countries.

private sector interest in the diseases of the poor, government action has been inadequate.

While it is urgent for decision-makers to address this issue, efforts are hampered by a lack of comprehensive information and understanding on the dynamics of R&D into diseases that primarily affect poor people. This lack of information makes it more difficult for policymakers to understand the extent of the problem and make informed decisions to address the crisis.

What are neglected diseases?

A seriously disabling or life-threatening disease can be considered neglected when treatment options are inadequate or don't exist, and when their drug-market potential is insufficient to readily attract a private sector response. Government response is also inadequate. In short, for neglected diseases, there has been a failure of the market and a failure of public policy. Neglected diseases mainly affect people in developing countries. Public research institutes in the industrialized world do not view these diseases as either a priority or a major threat to their populations, and research-based drug companies do not pursue promising compounds for drugs to treat these illnesses because of an inadequate return on investment.

A look at the dynamics of this market failure shows that a distinction between "neglected" and "most neglected" diseases can also be made. For the "most neglected" diseases, patients are so poor that they have virtually no purchasing power, and no amount of tinkering with market forces is likely to stimulate interest among drug companies. If the market is failing poor people suffering from neglected diseases, it has failed people suffering from the most neglected diseases even more (Figure 1B). Some examples of neglected diseases are malaria, tuberculosis, human African trypanosomiasis (sleeping sickness), South American trypanosomiasis (Chagas disease), Buruli ulcer, dengue fever, leishmaniasis, leprosy, lymphatic filariasis and schistosomiasis. All but the first two can be considered most neglected diseases.

Tropical diseases are good examples of neglected diseases. Of the 1,393 total new drugs approved between 1975 and 1999, only 1% (13 drugs) were specifically indicated for a tropical disease.[8]

An empty pipeline

An examination of current research efforts in the pharmaceutical industry reveals that the pipeline of drugs for neglected diseases is virtually empty (see Figure 1C). In spring 2001, the DND Working Group and the Harvard School of Public Health sent written questionnaires to the world's top 20 pharmaceutical companies to assess the level of R&D activity in several neglected diseases (sleeping sickness, leishmaniasis, Chagas disease, malaria and tuberculosis).[9] Thirteen companies responded, eleven of which completed the questionnaire. Of the two others, one indicated no reportable research activities in infectious disease and the other said time constraints prevented completion of the survey. The eleven companies who responded fully include at least six of the top ten. Together the respondents represent nearly US$117 billion of the global pharmaceutical market, which is estimated at $406 billion for 2002.[10]

8) Patrice Trouiller et al., "Neglected diseases and pharmaceuticals: between deficient market and public health failure," forthcoming publication, 2001.
9) Dyann F. Wirth, survey for the Drugs for Neglected Diseases Working Group, Switzerland, May 2001. [Online]. Original survey and letter available: **www.accessmed-msf.org.**
Andra Brichacek, Top 50 Phamaceutical Companies of 2000, Pharmaceutical Executive, April 2001.
Available: **http://www.pharmaportal.com/articles/pe/pe0401_062-82.pdf** [2001, August 6].
10) Six respondents were among the top ten companies worldwide, by sales; two other respondents chose to remain anonymous.

Number of companies (out of 11 respondents) with research and development activities targeting drugs for neglected diseases

Disease	**R&D Spending**	Screening	Pre-clinical or Clinical Development	Product to market in last five years
sleeping sickness	0	0	0	0
Chagas disease	1	0	1	0
leishmaniasis	1	0	1	0
malaria	2	1	2	2
tuberculosis	5	4	3	1
Other infectious diseases (includes viral, bacterial and fungal diseases)	9	N/A	8	6

Figure 1C

Methodology: The survey was sent to the CEOs and/or Directors of Research of 20 pharmaceutical companies in Europe, Japan, and the US. The questionnaire inquired about overall resources devoted to infectious diseases, and specific resources devoted to particular neglected diseases. The survey stated that individual company names would not be disclosed when reporting the results. Results relied on self-reporting and reports were not independently validated.

Overall R&D budgets for the responding companies ranged from $500 million to greater than $1 billion per year. Of these amounts, 25% or less was devoted to R&D for infectious diseases. Eight out of the eleven companies spent nothing at all over the last fiscal year on R&D for the most neglected diseases included in the survey (sleeping sickness, leishmaniaisis and Chagas disease); one company did not answer this question. Only two companies reported spending on malaria. Five companies reported spending on tuberculosis, one of which devoted over 15% of its infectious disease R&D budget to tuberculosis and malaria. However, seven companies reported spending less than 1% on any of the five diseases included in the survey or failed to respond to that question. All other infectious disease spending fell under the category "other," which includes viral, bacterial and fungal diseases.

Company involvement in various stages of the R&D process was also very limited (see Figure 1C). None of the companies screened chemical compounds for usefulness against sleeping sickness, Chagas disease or leishmaniasis, one screened for malaria, and four screened for tuberculosis. Similarly, no company had any compounds in clinical development for sleeping sickness, while one company reported having at least one compound in pre-clinical or clinical development for Chagas disease and one company reported the same for leishmaniasis. There seemed to be slightly more activity for malaria and tuberculosis: a few companies have products in pre-clinical or clinical development or have brought a product to market within the last five years.

Yet, despite low in-house investment into neglected diseases, participation in public-private partnerships was considerable. Six of the eleven companies reported participation in these kinds of partnerships, with individual financial commitments ranging from $500,000 to $4 million.

While the survey demonstrated some activity in neglected diseases – above all in tuberculosis – by and large, it indicated that private sector investment into this field was minimal.

An equally bleak picture emerges from recent surveys on new medicines in development conducted by the US drug industry lobby group, the Pharmaceutical Research and Manufacturers of America (PhRMA).[11] Of the 137 medicines for infectious diseases in the pipeline during 2000, only one mentioned sleeping sickness as an indication, and only one mentioned malaria. There were no new medicines in the pipeline for tuberculosis or leishmaniasis. PhRMA's current "New Medicines in Development" list shows eight drugs in development for impotence and erectile dysfunction, seven for obesity, and four for sleep disorders.[12]

11) Pharmaceutical Research and Manufacturers of America. *New Medicines in Development for Infectious Diseases: A 2000 Survey*. [Online]. Available: **http://www.phrma.org/searchcures/newmeds** [2001, August 22].
12) Pharmaceutical Research and Manufacturers of America. *New Medicines in Development*. [Online]. Available: **http://www.phrma.org** [2001, August 22].

Teno

Teno Worku is in Kahsay Abera hospital in Humera, Ethiopia. He doesn't get any visitors. His only family, his mother, lives 300 km further south in Gondar. "I'm a commercial traveller and I pass through this region a lot. Five months ago I took ill. I had a headache and a fever, so I went back to Gondar to see a doctor. He treated me for malaria. But a month later I still hadn't recovered." Frail and emaciated, the 28-year-old looks at least ten years older than his age.

Eventually, Teno went to the Ethiopian capital of Addis Ababa for tests. Four months later, not a single doctor had been able to explain his symptoms. Bitterly disappointed and by now critically ill, he returned to his mother in Gondar, where, at long last, a doctor in a private clinic suspected kala azar and advised him to go to Humera.

"The doctor said that this hospital is specialized in kala azar. Tests showed that I did have the disease, and the injections were begun right away. I was very late starting the treatment but I'm getting a bit better every day," he says, sounding as if he is trying to convince himself more than anyone else.

Teno is about to receive his twentieth injection. He grits his teeth and braces himself for a painful experience. The needle has to penetrate deep into the upper buttock in order to inject the fluid into the muscle tissue.

Bianga

Bianga had been ill for ten months. She had become too weak to work in the fields near her home in Omugo, Uganda, fetch water, or care for her six-year-old son, Lino.

At first, Bianga found herself sleeping all day long but lying wide awake at night. Her behavior changed: she would run out into the street, shouting loudly at the sky. At this point, her husband left her. Bianga and her son went to live with Bianga's elderly mother in her small hut. With no one in the family earning money and unable to produce their own food, they were penniless. Lino became malnourished.

Finally, in despair, Bianga's mother took her to the hospital to see if something could be done. The doctor discovered that she was suffering from sleeping sickness and had already reached the stage at which the parasite invades the brain. She was admitted directly to the treatment center where she was given a course of melarsoprol. Although the treatment was painful, she began to feel better. After the 20-day course, she was able to return home and pick up her life again.

After a month, Bianga began behaving strangely again, and Lino brought her to the hospital. It was discovered that she had gone into relapse. Her ankle had to be tied to the bed to prevent her from running away and getting lost. Bianga received another course of melarsoprol, but this time her condition did not show much improvement. With no other treatment available and little hope for recovery, she was sent home. For Bianga, some of the treatments that are only now becoming available arrived too late.

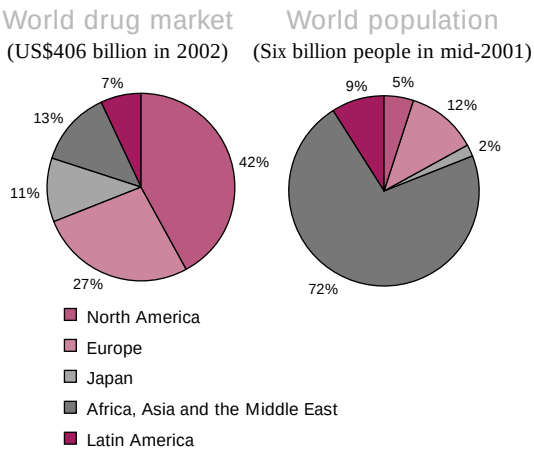
A patient suffering from visceral leishmaniasis, also called kala azar, is checked by his doctor at a hospital in Humera, Ethiopia. Leishmaniasis threatens 350 million people worldwide, mostly in developing countries. The disease is still treated as it was in the 1940s.

Dropped from the private research agenda

Over the last few decades, major progress in molecular biology and biotechnology has enabled the development of increasingly sophisticated medicines to cure a wide variety of diseases. Moreover, global expenditure on health R&D has increased dramatically and is still on the rise. For 2001, an estimated record US$70 billion will be invested globally in health R&D, with the U.S. private sector alone accounting for just under half of the spending at US$30.5 billion.[1] While the public sector has traditionally been the major funder of health research, the private sector has recently taken the lead. Global health research priorities are changing accordingly.

In the "social contract" that has over the years emerged around drug development, industrialized countries rely on the pharmaceutical industry to develop and produce medicines, and governments attempt to ensure that the industry meets public needs through a variety of incentives. These incentives include the patent system, tax credits, and R&D grants, as well as subsidies provided by national health care or insurance systems to help pay for health commodities.

This balance between public and private capacity, investments, and interests has worked well to develop drugs for diseases such as heart disease and cancer, and has helped the pharmaceutical industry to prosper, with companies often having sales of hundreds of millions or even billions of dollars a year on a single drug. This profit-driven system has also mobilized R&D funds for "lifestyle" conditions such as impotence, baldness and obesity. By investing in these conditions or in "me-too" drugs (medicines that are only slightly different from existing compounds and are not considered to be true innovations or clinical advances), drug companies can also expect phenomenal sales figures.



Sources: IMS Health/Population Reference Bureau (see note 3, below)

Figure 2A

According to the 2000 Fortune 500 ranking, pharmaceutical companies top the US industry performance list for return on investment, with a 39% return for shareholders.[2] Furthermore, corporate mergers and consolidations have led to fierce competition between a shrinking number of players. To maintain expected profit levels, the R&D-based pharmaceutical industry focuses on the profit potential of wealthy markets. Figure 2A projections show that North America, Europe and Japan will account for 80% of the world pharmaceutical market in 2002 (with a total projected world value of $406 billion), while Africa, Asia, Latin America and the Middle East, representing 80% of the world's population, will account for only 20% of the pharmaceutical market.[3]

1) The latest figures available are US$56 billion (from 1992), but experts estimate current annual health research funding at around $70 billion (including $40 billion on the part of the private sector). Global Forum for Health Research, *The 10/90 Report on Health Research*. [Online]. (2000). Available: **http://www.globalforumhealth.org**. Pharmaceutical Research and Manufacturers of America, *2001 Industry Profile*. (Washington, D.C.: PhRMA, 2001).
2) Fortune 500 Top Performing Industries, (2000, April 16). Fortune. [Online], F-26, F-28. Available: **http://www.fortune500.com** [2001, July].
3) IMS Health Market Report: Five Year Forecast of the Global Pharmaceutical Markets. [Online]. (2000). Available: **http://www.ims-global.com/insight/report/global/report.htm** [2001, August].
Population Reference Bureau, 2001 World Population Data Sheet, estimates for mid-2001. [Online]. (2001). Available: **http://www.worldpop.org/prbdata.htm** [2001 August 20].

Lida

Lida weighs 35 kilograms. She says she feels "destroyed inside." In her room in the department of "chronics" at the tuberculosis hospital in Guliripchi, Abkhazia, she waits for the results of an analysis of her sputum. She hopes for the impossible: the destruction of all the bacteria eating away at her lungs in spite of four successive treatments.

The tuberculosis from which Lida suffers is multi-drug resistant, no doubt contracted as a result of two previous treatments that were incomplete.

The first treatment, prescribed by the doctor at the iron and steel plant where Lida worked, included only two of the anti-tuberculosis drugs recommended by the World Health Organization protocol. As for the second, following crisis and war in her country, she didn't have enough money to pay for the medication.

The two treatments that followed in the hospital were appropriate but arrived too late. A chronic patient, she would now need second-line medication, but that's not available in Guliripchi. The complete treatment costs $15,000 and cures only up to 60-70% of the patients. There are terrible side effects, and hospitalization and treatment last up to 24 months.

During the year and a half that Lida has been in the hospital, she has put on a little bit of weight. She moves slowly from her bed to the window to breathe.

MYTH:

The typical new drug, brought successfully to market, costs approximately US$500 million for research and development.

This often quoted figure is based on a paper written by J.A. DiMasi and published in 1991.[4] The DiMasi paper put the cost of developing a new drug at US$231 million. Subsequent studies used a higher opportunity cost of capital and changed other parameters, and the figure became $312 – $359 million.[5] Adjusted to 2000 dollars the amount turns into $473 million. And this figure is quite simply rounded up to arrive at $500 million.

Yet the original study has several limitations, and the subsequent estimates based on the study inherit these flaws.

The initial calculation was based on several assumptions that can be disputed. Assumptions were made for the cost of pre-clinical studies. Assumptions were also made about the length of the R&D process, the opportunity cost of capital (in other words, potential revenue if the capital were invested elsewhere) and success rates.[6] Additionally, the study puts the opportunity cost of capital (not actual spending) at half of total R&D costs, but it doesn't take into account tax deductions or government grants awarded to a company for R&D expenses.

Aside from relying on assumptions, the initial study wasn't representative of the 'average' drug, nor was it designed to be. The original study focused on drugs that were researched and developed exclusively by multinational pharmaceutical companies. Yet development of many drugs depends on major public involvement in both basic research and clinical trials.[7] Calculating an average cost for R&D has limited usefulness, in any case, because costs may differ greatly between drugs for chronic diseases and drugs for acute infections, or between innovative drugs and me-too drugs.

Recent independent estimates on drug development costs vary. The group Public Citizen (using DiMasi's original study as a base) computes the cash outlay for new drugs at $110 million, excluding opportunity cost but taking into account inflation and tax deduction;[8] the Global Alliance for TB Drug Development (GATB) puts the cost of a new tuberculosis drug at around $40 million (excluding the cost of failure) using a chemical entity already identified. When the cost of failure is included, GATB estimates the cost at $76 – $115 million.[9]

One final drawback to the original DiMasi study, and a limitation for these subsequent efforts to put a price tag on drug development, is the data: it came from confidential industry sources in the 1980s and has not been available to other researchers. To gain a better sense of what it would cost to develop a drug, access to actual data is essential.

4) J.A. DiMasi, R.W. Hansen, H.G. Grabowski, and L. Lasagna, "Cost of innovation in the pharmaceutical industry," *Journal of Health Economics* l 10 (February 1991): 107-142.
5) Dr. Hannah Kettler, *Updating the cost of a new chemical entity*, (London: Office of Health Economics, 1999).
U.S. Congress, *Pharmaceutical R&D: costs, risks and rewards,* (Washington, D.C.: Office of Technology Assessment, 1993).
6) William S. Comanor, "The pharmaceutical research and development process, and its costs" (paper produced for the MSF/WHO Workshop on Drugs for Communicable Diseases, stimulating development and securing availability, Paris, October 14-15, 1999).
7) National Institutes of Health, "NIH contributions to pharmaceutical development," administrative document, (2000).
Stéphane Jacobzone, *Pharmaceutical policies in OECD countries: reconciling social and industrial goals*, Labour market and social policy occasional papers, no. 40 (Paris: OECD, 2000).
8) "Rx R&D Myths: the Case Against the Drug Industry's R&D 'Scare Card," Public Citizen Congress Watch, (July 2001): 2-3.
9) Initial Estimates from "Pharmacoeconomics of TB Drug Development," Global Alliance for TB Drug Development. (New York, September 2001).

Gaps in the drug development process

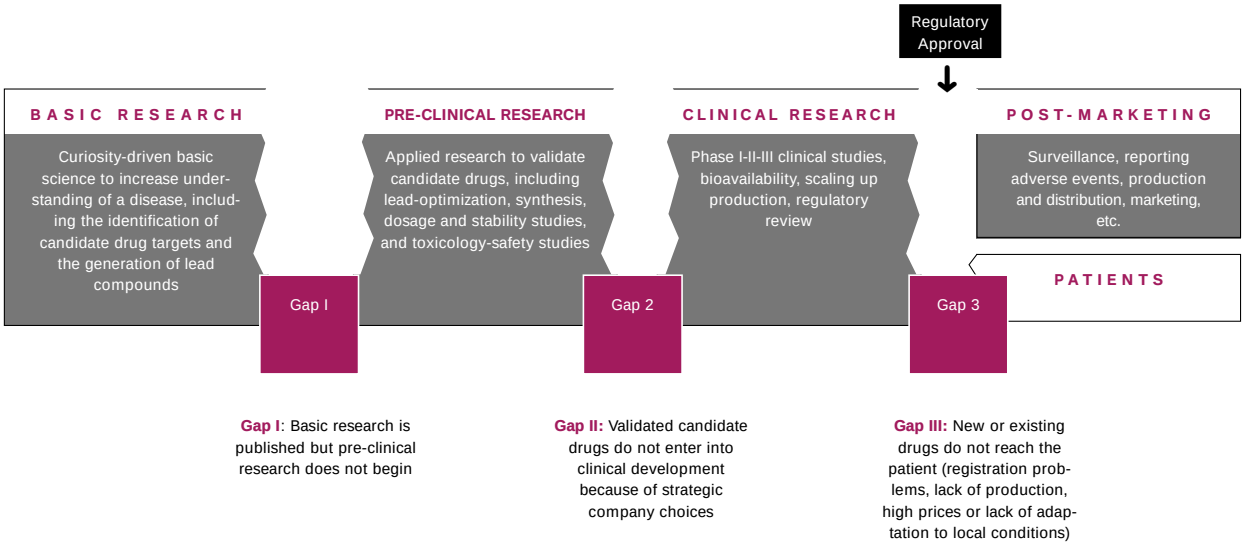


Figure 2B

It is a matter of simple economics: potential return on investment, not global health needs, determines how companies decide to allocate R&D funds. According to the drug industry, the low purchasing power of developing countries – coupled with the high cost of R&D and drug registration – rationalizes their focus on wealthy country markets.[10] Fierce market competition means that for diseases that primarily affect developing countries, neither promising drug leads nor research on new applications of existing drugs will be pursued.

> "...the United States has become the must-win market for every pharmaceutical company. In addition, there are just 6 or 7 other critical markets, including Japan and key countries in Europe....This does not mean ignoring other markets. But it does mean strategically concentrating resources and top management attention on success in the key market. Again, this is very different from our industry's approach in the past, which focused on therapeutic areas across geographical regions."
> *Fred Hassan, CEO of Pharmacia, in a speech on "Being a modern pharmaceutical company..."*[11]

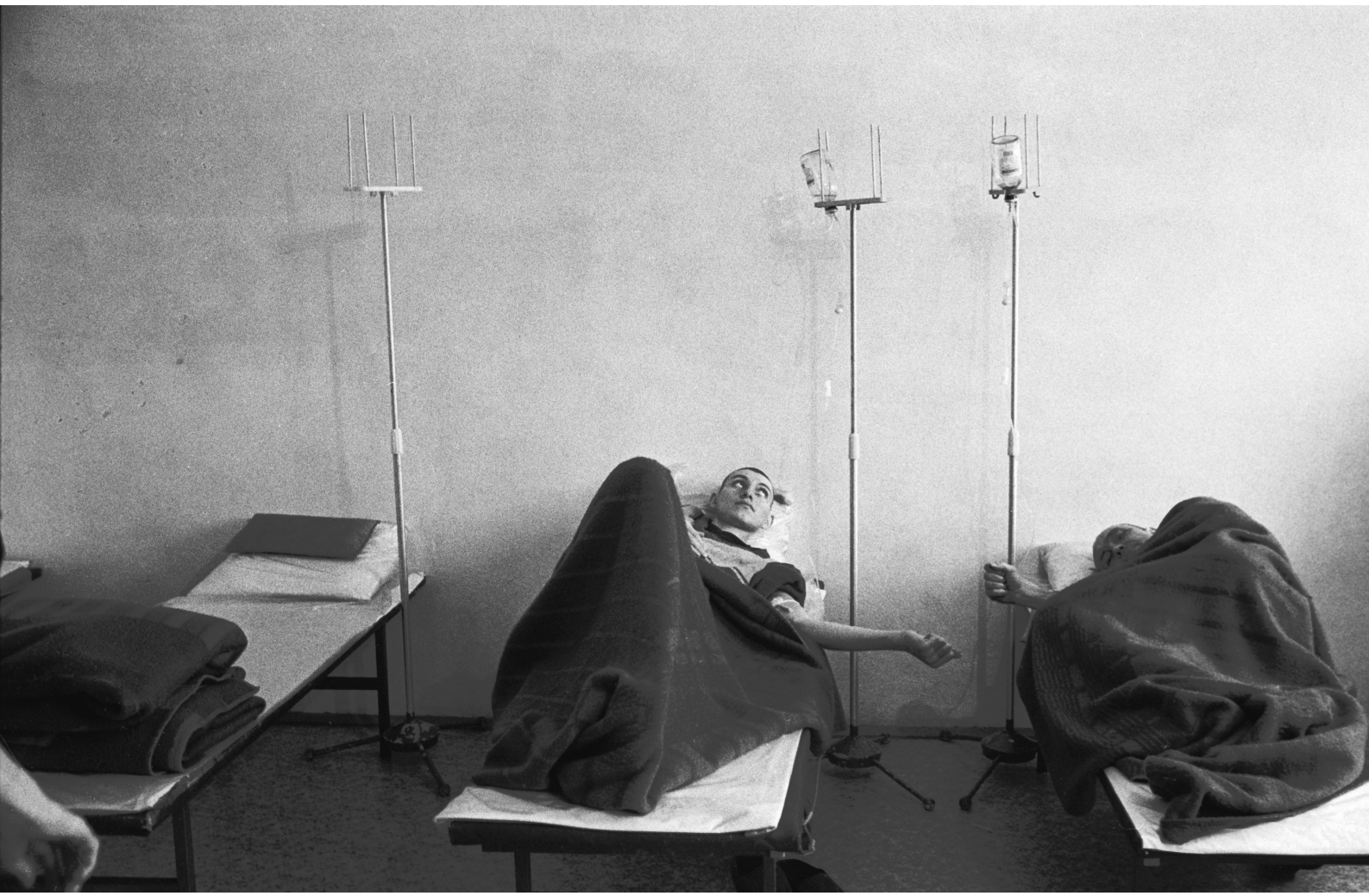
Gaps in the drug development process

A closer examination of the drug development process shows exactly where the system breaks down. Developing a new drug from basic research can be a complex, capital-intensive and time-consuming activity. In order to produce one successful drug, thousands of candidate-compounds and successive selections based on biochemical properties, safety, clinical performance, and market considerations may be needed. Figure 2B outlines this process and identifies the gaps that occur when market prospects are low.

The public research community, namely universities and institutes, is primarily involved in the early phases of basic research and drug discovery. The expertise, infrastructure and management capacity for moving these discoveries through the drug development process is concentrated in the private sector. Thus, final drug development is largely conducted by private industry, according to its own priorities.

It is clear that the multinational pharmaceutical industry cannot be relied on to develop the medicines required to treat the diseases that affect the world's poor. Governments are ultimately responsible for ensuring that people's health needs are met. They must take action when the private sector or the market fails. The current crisis in R&D for neglected diseases is a result not only of the failure of the market, but also of the failure of public policy.

10) Barton Gellman, (2000, December 27) "An Unequal Calculus of Life and Death," The Washington Post, [Online]. Available: **http://www.washingtonpost.com** [2001, August 13].
11) Fred Hassan, "Being a modern pharmaceutical company: New paradigms for the pharmaceutical industry" (plenary lecture given by Chief Executive Officer of the Pharmacia Corporation at the World Conference on Clinical Pharmacology and Therapeutics, Florence, Italy, July 17, 2000), quoted in *Clinical Pharmacology and Therapeutics* 69 (May 2001): 281-285.



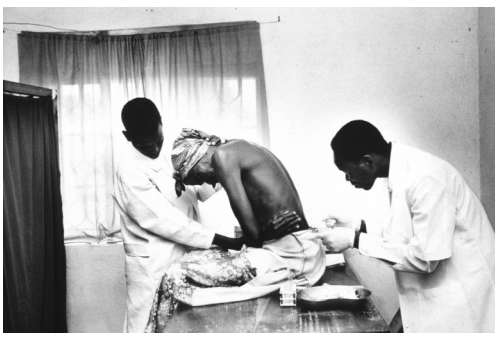
Patients with multi-drug resistant tuberculosis lie in an isolated ward in Prison Colony #16 in Novokuznetsk, Siberia. There are eight million cases of tuberculosis around the world each year, and nearly two million deaths. About 95% of cases occur in developing countries. Patients are still treated with the same drugs that were discovered 40 years ago.

A Matter of public responsibility

Inadequate public policy has compounded the failure of the market to generate R&D for drugs for neglected diseases. Governments have the power to influence drug development, both through direct research funding and policies to influence the activities of the private sector. Not only can governments make a difference, they have a responsibility to do so. They should increase both their funding of and direct involvement in drug development for neglected diseases. But for the past 20 years, despite clear evidence of the decline in private sector interest in neglected diseases, government leaders have often stood by silently.

Government inaction compounds crisis

A needs-based approach and consolidated public funding of R&D for neglected disease drugs could have compensated for the market failure. Instead, public sector research has increasingly focused on diseases that affect wealthy countries. There is increasing pressure for publicly funded research to have commercial applications, further reinforcing the focus on lucrative diseases.[1] Governments fund public research according to the health needs of their own constituencies. The end of colonial presence and declining military involvement in tropical countries has led to a further waning of interest in tropical diseases in the latter half of the 20th century.



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Sleeping sickness test in Omugo, Uganda

Leaders in disease-endemic countries have also done little to improve the R&D situation for neglected diseases. In 1990, the Commission on Health Research for Development proposed that all governments allocate 2% of health expenditure to research. According to the Global Forum for Health Research and its partners, none of the low- and middle-income countries studied were making this level of contribution in 1998.[2]

Basic research that leads to the discovery of potential "drug leads" has almost always been publicly funded at universities, in-house government facilities, or research institutes in Europe, North America, and Japan. Since the beginning of the 20th century, publicly funded research has led to major drug lead discoveries in, for example, tuberculosis (streptomycin and rifampicin), other infectious diseases (various antibiotics), and cancer (various types of chemotherapy). More recently, publicly funded research has led to the discovery of antiretrovirals for the treatment of HIV/AIDS. Publicly funded genome research has also produced many drug leads.

Meanwhile, public sector policies increasingly view public research as an investment that needs to create economic value. Scientists are requested to not only publish their research and advance science, but also promote and actively pursue the possible commercialization of research findings (through active patenting and licensing strategies, research collaborations with industry, creation of spin-off companies, etc.). This so-called valorization of research has become an important policy objective of public research, especially in the biotechnology and health sector where financial returns are very attractive. Thus, the same market failure that deters the pharmaceutical industry from investing in neglected diseases also discourages the public research community.

While supporting basic and drug-lead discovery research, the public sector has rarely developed its own drug development expertise and capacity. It is the pharmaceutical industry that leads product development, from pre-clinical research through regulatory approval. However, the most innovative part of the process is the initial identification of lead compounds, which often happens in the public or academic research sectors. In these settings, publishing innovative research in high-ranking journals often makes a career and ensures continued funding. Not surprisingly, the most important gap in the drug R&D process for neglected diseases is between basic research and pre-clinical research (see Figure 2B, page 18).[3]

1) Els Torreele, "From Louis Pasteur to J. Craig Venter: When Biomedical Scientists Became Bioentrepreneurs," working paper of the Drugs for Neglected Diseases Working Group, Switzerland, November 2000.
2) Commission on Health Research for Development, *Health Research: Essential link to equity in development.* (New York, N.Y.: Oxford University Press, 1990). Global Forum for Health Research, "Monitoring Financial Flows for Health Research," forthcoming publication, 2001.
3) Els Torreele, "Public disease research," Biotechnology and Development Monitor, No. 46, p. 24. (2001). Available: **http://www.biotech-monitor.nl/4611.htm**.

Estimates of public, nonprofit, and foundation spending

Because there is a lack of basic, up-to-date information concerning spending on neglected disease drug R&D, the DND Working Group asked leading international experts on several neglected diseases to estimate the current level of investment in R&D:

Leishmaniasis

Dr. Farrokh Modabber, Director of the Infectious Disease Research Institute, Seattle, USA, estimates current research spending for leishmaniasis at US$20 million. Of the total, 15-20% is directly spent on drug development.[9]

Malaria

Dr. Catherine Davies of Wellcome Trust estimates that funds committed by major funders to malaria research in 1999 were over US$150 million (excluding US Department of Defence and French sources, for which detailed figures were not available). The equivalent figure for 2000 is over $200 million.[10]

Dr. Rob Ridley of the Medicines for Malaria Venture (MMV) says that, depending on how it is defined, drug discovery and development might constitute between 10-20% of the overall malaria research spending figure for 2000.[11]

Sleeping sickness

Mr. Felix Kuzoe, an expert in African trypanosomiasis (sleeping sickness) at the Special Programme for Research and Training in Tropical Diseases (TDR) estimates total research spending at as little as US$20 million in 2000. Of this total approximately $4 million (20% of the total) is devoted to drug development thanks mainly to a donation from the Gates Foundation. In 2001, the total research spending will increase to $21 million due to a recent donation from Aventis Pharma. This will increase the proportion for drug development to 24% (about $5 million) in 2001.[12]

Tuberculosis

Dr. Paul Nunn at TDR estimates research spending on tuberculosis by governments and private foundations during 2000 at US$143 million. Of this figure, only $37 million (27%) is devoted to drug development.[13]

Recent spending patterns

The drug development outcomes for a particular disease clearly reflect the money invested in R&D. To gain an indication of the amounts currently being spent specifically on drug R&D for neglected diseases, the DND Working Group spoke with recognized experts on tuberculosis, malaria, sleeping sickness, and leishmaniasis. Based on their estimations (see above), government, nonprofit, and foundation funding for drug R&D appears to be little more than US$100 million per year for these four diseases combined. Putting this figure into perspective, total public spending on health research worldwide is estimated at $30 billion,[4] of which $3.1 billion is devoted to cancer research in the US alone.[5]

TDR

Another symptom of government indifference to the R&D crisis is the plight of the Special Programme for Research and Training in Tropical Diseases (TDR), the main international public body charged with research into tropical diseases. Established in 1975 as a joint program of the United Nations Development Program, the World Bank and the World Health Organization, TDR was intended to be a public sector response to pleas from countries where neglected diseases were endemic.

TDR has two objectives. The first is to conduct research into new medicines to help control a defined group of tropical diseases.[6] The second is to train scientists and strengthen institutions from disease-endemic countries and encourage them to play a larger role in the research process. TDR has achieved some considerable successes.[7] Six of the thirteen drugs developed for tropical diseases between 1975 and 1999 were developed with TDR support, and the program has also raised awareness of tropical diseases and helped set the agenda for research.[8] However, it has remained chronically under-funded. For many years the program has struggled by on about $30 million per year to fulfill a mandate for both research and training activities in the ten diseases it covers. Furthermore, TDR works within the UN system, abiding by international civil service norms, and the program is pulled by the differing priorities of its multiple sponsoring agencies. This is not an ideal management structure in a field where decisions on research and allocation of resources must be made quickly.

4) Global Forum for Health Research, *The 10/90 Report on Health Research*, estimate for 1999. [Online]. (2000). Available: **http://www.globalforumhealth.org**.
5) National Cancer Institute, National Institute of Health, Cancer Facts. [Online]. Available: **http://www.graylab.ac.uk/cancernet/600011.html**.
6) Diseases currently in the TDR portfolio are leishmaniasis, onchocerciasis, schistosomiasis, lymphatic filariasis, Chagas disease, malaria, leprosy, African trypanosomiasis, tuberculosis and dengue.
7) C.M. Morel, "Reaching Maturity: 25 Years of TDR," Parasitology Today 16 (December 2000): 522-528.
8) Patrice Trouiller et al., "Neglected diseases and pharmaceuticals: between deficient market and public health failure," forthcoming publication, 2001.
9) Dr. Farrokh Modabber. Electronic communication. (2001, June 25 and 2001, August 10). Leishmaniasis. Email to Diana Smith.
10) Dr. Catherine Davies. Electronic communication. (1999, December and 2001, August 10). Malaria. Email to Diana Smith.
11) Dr. Rob Ridley. Electronic communication. (2001, August 22 and 23). Malaria. Email to Diana Smith.
12) Mr. Felix Kuzoe. Electronic communication. (2001, March 13 and 2001, August 10). African trypanosomiasis. Email to Diana Smith.
13) Dr. Paul Nunn. Electronic communication. (1999, December and 2001, August 13). Tuberculosis. Email to Diana Smith.

The third sector: philanthropy

It is notable that the single biggest change in funding for neglected diseases over the past few years has come not from private industry or the public sector, but from the increased commitment of foundations.

The Bill and Melinda Gates Foundation, in addition to providing substantial funding for vaccines, has become a major force in neglected disease drug development. In the last few years, the Gates Foundation has given $25 million (over five years) to the Medicines for Malaria Venture, $25 million (over five years) to the Global Alliance for TB Drug Development (GATB), and another $15 million to vaccine research for leishmaniasis.[14] Previously, leishmaniasis vaccine trials had relied on small TDR resources plus in-kind donations from affected countries. The Gates donation has "completely changed the picture," according to Dr. Farrokh Modabber, Director of the Infectious Disease Research Institute in Seattle (see page 21).

The foundation also gave $15 million (over five years) for sleeping sickness and leishmaniasis drug development. Prior to this donation, the main funding for sleeping sickness drug R&D was less than $500,000 a year through TDR. The award of $15 million "has no precedence in the history of African trypanosomiasis," according to Felix Kuzoe, an expert on sleeping sickness at TDR (see page 21).[15] The Gates Foundation has also funded various research-related activities around several other neglected diseases.

The Rockefeller Foundation has also played a crucial role in raising awareness of global health issues and, in 2000, awarded $15 million to the public-private R&D initiative, the Global Alliance for Tuberculosis Drug Development (GATB).[16] The Wellcome Trust has been a traditional funder of tropical disease research for many years, although they invest little in drug development activities.[17]

However, while additional support from foundations is welcome, foundations cannot and should not take the place of public sector responsibility. Because private philanthropy lacks the accountability and transparency demanded of governments, it can be neither a substitute nor an alibi for government inaction. More comprehensive public sector solutions are needed to address the R&D crisis on a sustainable basis.

MYTH:

There is little investment in tropical diseases because there is weak patent protection in the countries most affected by these illnesses. After 2006, when all countries will have implemented TRIPS (international trade rules that mandate minimum 20-year patents), drug development will increase in developing countries.[18]

Drug development for neglected diseases will not automatically increase, no matter how strong the level of intellectual property protection, because private R&D is driven primarily by market potential. People who suffer from diseases like malaria, sleeping sickness and leishmaniasis, with or without strong patent protection in their countries, will not have the necessary purchasing power to constitute a market attractive to drug developers.

Intellectual property rights, including patents, are part of a complex legal and economic system that can motivate investment in R&D under certain circumstances. Protection of intellectual property in a country has historically followed industrial development. It is doubtful that the reverse will also occur – that industrial development will follow strong intellectual property protection. In fact, patents may actually hamper medical research activities in developing countries. Patents are often owned by private companies or research institutions, and, during the period of protection, put limits on research knowledge. Molecules that could be promising for the treatment of neglected diseases are consequently not easily accessible for research.[19]

In addition, most developing countries are unlikely to significantly improve their R&D capacity solely on the basis of an expanded and stronger intellectual property rights regime. Even in industrialized countries, innovation is assisted by other incentives, including substantial government spending. Without significant government research spending, stronger patent protection may lead to higher prices without stimulating research.[20]

Since the 1970s, some industries in developing countries have been developing new production processes through reverse engineering for medicines still under patent elsewhere in the world. This generic production has contributed to both industrial development and greater access to medicines through lower prices. With stronger patent protection, these countries will not be able to continue this practice.[21]

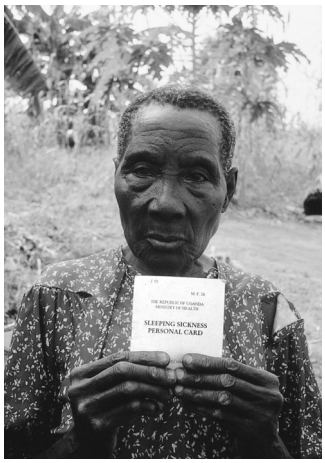
14) Bill and Melinda Gates Foundation, Recent Global Health Grants. [Online]. Available: **http://www.gatesfoundation.org/globalhealth/grantlist.asp** [2001, August 9].
15) Felix A. S. Kuzoe, "A Position Paper on African Trypanosomiasis," position paper, World Health Organization, Geneva, May 2001.
16) Grant Peck, "Public-private sector alliance vows new TB drug by end of decade," Associated Press (October 10, 2000).
17) The Wellcome Trust. [Online]. Available: **http://www.wellcome.ac.uk** [2001, August 13].
18) World Trade Organization. Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Geneva, 1994.
19) United Nations Development Programme, Human Development Report [Online]. (2001), 98. Available: **http://www.undp.org** [2001, August 13].
Carlos M. Correa. Intellectual property rights, the WTO and Developing countries: The TRIPS Agreement and Policy Options (London and New York: Zed Books Ltd., 2000), 38.
20) UNCTAD. The TRIPS Agreement and Developing Countries. Geneva, 1996.
21) Carmen Perez-Casas, Pierre Chirac, Daniel Berman, and Nathan Ford, "Access to Fluconazole in less-developed Countries," Lancet, vol. 356, no. 9247 (December 2000).

A young girl is treated for malaria in Anlong Veng, Cambodia. Worldwide, there are an estimated 300 – 500 million malaria cases a year, and up to 2.7 million deaths, of which 75% are children. In many areas, strains of the disease are becoming resistant to existing drugs.

What has been done so far to address the R&D crisis?

Over the last few years, there has been increasing awareness of the lack of effective treatments for some diseases. Some recent initiatives have sought to find novel approaches for stimulating research into neglected diseases. The following brief review describes some current approaches, policy tools, and initiatives.

Some examples of recent government response to the R&D crisis in neglected diseases include the European Commission's "Programme for Action: Accelerated Action on HIV/AIDS, Malaria and Tuberculosis in the Context of Poverty Reduction" and the report "Tackling the Diseases of Poverty," produced by the Prime Minister's office in the United Kingdom.[1]



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Kiri, Sudan

Both institutions conducted a multi-sectoral analysis of the problem and their reports map out potential solutions. Although these efforts demonstrate some positive government engagement, recommendations focus primarily on market-oriented strategies. This is demonstrated by the European Commission's statement that it plans to offer "appropriate incentives to encourage private investment into Research and Development." The UK report also stresses incentives to private industry.

Moreover, both analyses focus exclusively on drugs for HIV/AIDS, tuberculosis (TB), and malaria, the UK plan going as far as recommending restricting "activities related to new products" to those for these three diseases, with this restriction up for periodic review. Strategies designed to focus on these three diseases are unlikely to stimulate the search for drugs to treat the most neglected diseases. The failure of both analyses to address the diseases that are most neglected – such as leishmaniasis and sleeping sickness – means that their proposed solutions will leave the people with these illnesses on the sidelines (see Figure 1B, page 11).

Traditionally, governments have played a positive role in developing drugs for communicable diseases. For example, with very few exceptions, today's malaria drugs were initially discovered outside the private sector in universities or government labs – institutions known for their competence in identifying promising prospective drugs. The Walter Reed Army Institute of Research, for instance, with a small budget from the US Department of Defense, invented four important anti-malarial drugs, which were then developed in collaboration with multinational drug companies.[2]

Despite the efforts of individual actors in the public sector, R&D into neglected diseases remains woefully inadequate. While the public sector is not powerless, it currently depends largely on the skills and expertise of the private sector to conduct final drug development. If the private sector is unwilling to take a drug through this final stage of development, it never leaves the laboratory. Recent proposals have sought to increase public sector involvement while increasing incentives for the private sector to move compounds beyond the laboratory and ultimately deliver them as drugs to patients.

"Push" and "Pull"

In order to attract private sector R&D capacity back into needed areas, what are called "push" and "pull" mechanisms have begun to emerge as possible answers. "Push" mechanisms reduce costs and risks of R&D and can include tax credits, R&D grants, and support for clinical trials.

"Pull" measures help create a market for drugs or increase their profitability. Two examples are the creation of purchase funds and "patent exchange," whereby a company would invest in developing a drug for a neglected disease and

1) European Commission, *Programme for Action: Accelerated Action on HIV/AIDS, Malaria and Tuberculosis in the Context of Poverty Reduction*, COM(2001)96, (Brussels: European Commission, 2001).
Performance and Innovation Unit, *Tackling Diseases of Poverty: Meeting the Okinawa Millenium targets for HIV/AIDS, tuberculosis and malaria.* (London: Cabinet Office, 8 May 2001).
2) Amir Attaran, "Malaria Drug Treatment: Prescription for Curing Policy," working paper of the Drugs for Neglected Diseases Group, Geneva, October 23-24, 2000.

The International Conference on Harmonization: Is the bar being raised too high?

Getting a drug to market requires a complex series of evaluations and regulatory reviews to ensure that it meets quality, safety and efficacy standards. Approval of new drugs is done by national governments, which set standards. The United States, Japan, and the European Union have attempted to harmonize their standards through the creation of the International Conference on Harmonization (ICH), an initiative of drug regulatory authorities and research-based pharmaceutical industries. The goal of harmonization is to reduce drug development and regulatory review times.

The ICH is tightening requirements beyond those stipulated by the World Health Organization (WHO). The quality, efficacy and safety requirements that constitute the ICH guidelines deal specifically with drug development in a wealthy market, where cost is not a major issue and where safety is defined as near-zero risk. For neglected diseases, cost is a major issue, and the risk-to-benefit ratio in terms of quality, efficacy and safety should be put into the perspective of the gross public health failure of having no treatment at all.

These more stringent ICH guidelines raise costs and present barriers to drug development, particularly for small or medium-sized companies in developing countries. The risk is that the bar will be raised so high that only drugs developed in the industrialized world will be able to be marketed internationally. This will seriously hamper the development of R&D capacity in developing countries, which has been identified as a necessary component in the long-term solution to the R&D crisis. This potentially negative public health implication needs to be carefully weighed against the possible benefits of raising R&D requirements, which some have argued would be marginal and of little value to patients.[7]

Many questions remain unanswered on the implications of the ICH guidelines. An independent and thorough technical review of ICH guidelines should be undertaken by WHO. If ICH is to become a global standard, it must be reexamined to ensure that it meets the needs of both developing and developed countries.

then, once the drug was approved, would have the right to extend the patent on one of its other, more profitable drugs. Both "push" and "pull" mechanisms are market-based measures that aim to increase the investment return for a drug to a level that will attract the private sector.

Orphan drug laws

Orphan drugs laws are an example of a "push" mechanism. Orphan drug laws use tax credits and grants to promote research into drugs for diseases that affect a relatively small number of people (in the US this is set at 200,000 or fewer people).[3] These rare diseases would otherwise represent a market return inadequate to motivate drug investment.

The Orphan Drug Act in the US (similar laws exist in Europe, Japan, Singapore and Australia) has successfully provided incentives for research into diseases such as cystic fibrosis.[4] Some policymakers are recommending amending these kinds of laws to include neglected diseases in developing countries. However, it is critical to note that orphan drug legislation has succeeded because, in addition to tax incentives and government grants, companies can recoup costs by charging high prices for the drugs. One extreme example is the drug Ceredase, used to treat Gaucher's disease, which was priced at hundreds of thousands of dollars per year of treatment.[5] Since purchasing power is limited or non-existent among people with neglected diseases, the orphan drug mechanism alone is not likely to work. However, the concept may be useful if paired with other mechanisms, or modified to fit neglected diseases more specifically.

The history of this type of legislation also shows that it could be particularly effective in motivating small and medium-sized enterprises; in the US, over 50% of companies applying for orphan drug status are small and medium-sized.[6] However, many of these companies depend on outside financing to support their R&D programs, and also need to maximize profits for their shareholders.

3) U.S. Orphan Drug Act of 1983 [Online]. Available: **http://www.fda.gov/orphan/regs.htm**.
4) James Love, "Paying for health care R&D: Carrots and Sticks," working paper of the Drugs for Neglected Diseases Working Group, Geneva, October 18, 2000.
5) James Love, affidavit at the High Court of South Africa in the matter between Pharmaceutical Manufacturers' Association of South Africa and Others and The President of South Africa and Others, and Treatment Action Campaign (Amicus Curaie), Case: 4183/98, 9 April 2001 (South Africa, 2001).
6) Institute for Global Health, "Creating Global Markets for Neglected Drugs and Vaccines: A Challenge for Public-Private Partnership," (consensus statement of Creating Global Markets for Neglected Drugs Vaccines: A Challenge for Public-Private Partnership conference, Carmel Valley, California, February 18-21, 2000).
7) Patrice Trouiller, Peter Folb, and Kris Weersuriya, "Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use," working paper of the Drugs for Neglected Diseases Working Group, Geneva, October 23-34, 2000.

What about a "Pot of Gold"?

One commonly suggested "pull" strategy is the creation in advance of purchase funds for drugs for neglected diseases. The idea is to secure purchase funds through donors – the "pot of gold" waiting at the end of the drug development rainbow – in order to supplement an existing market, and thus "pull" companies into drug development. However, to prompt a major pharmaceutical company to invest, the existing market plus the "pot of gold" would need to compete with the average return on commercial sales, put at about US$265 million annually in 1998.[8] This would be a great expense, and in a sense is "buying into" the existing drug development system by subsidizing shareholders' needs for profits and other costs associated with private industry drug development.

This strategy could potentially work for some neglected diseases that affect large numbers of people, such as TB or malaria, because an existing market in wealthy countries would supplement the pot of gold (eg, TB in Europe or the malaria traveller market). For the most neglected diseases, a purchase fund by itself would likely be too costly for governments and other funders. Drugs for the most neglected diseases – again, those for whom a potential market does not exist – are still likely to be overlooked. Still, the concept may be useful if paired with other mechanisms or modified to fit the most neglected diseases specifically.

Building capacity in developing countries

Building capacity in developing countries is another important strategy for stimulating R&D. Public health institutes in some developing countries are playing an increasingly important role in drug development. For example, the Thai government's support for malaria research has led to the development of an effective modern pharmaceutical version of artemisinin, a traditional Chinese medicine. In clinical trials, drugs using Thai artemisinin cured 90% of malaria cases,[9] and elsewhere cut infection among children by 90% in camps for displaced people on the Thai/Burmese border.[10] However, while this new formulation is saving lives in Thailand, it is not recognized as a legitimate treatment by international regulatory agencies because the research reporting methods used in Thailand do not match international agencies' reporting requirements. In this case, "harmonization" regulations on drug R&D, which

MYTH:

If we introduce new medicines into poor countries, we will accelerate the development of resistance. We don't necessarily need new drugs but we need to better use the ones we have.

Drug resistance is often perceived as a problem restricted to a few diseases in poor countries. It is, however, an inescapable phenomenon in both the industrialized and developing world, due to the normal genetic survival mechanism of most parasites, bacteria, and viruses. Resistance to drugs will inevitably develop, and can do so despite good drug management and high compliance to treatment.

For example, in the Moyo district of Uganda, sleeping sickness patients have been treated with the 50-year old drug melarsoprol for more than ten years. In spite of strict drug management and good compliance, recent studies have shown resistance in excess of 30%. In this case, although introducing combinations of drugs may forestall resistance, new drugs will also be needed.

In general, two things are required in the fight against drug resistance. Existing therapies must be used rationally in order to delay the onset of resistance, and new drugs must continuously be developed to create future therapeutic choices to face the inevitability of drug resistance. As with sleeping sickness, the neglect of tuberculosis and malaria drug research in the last thirty years has made treatment increasingly difficult and led to a situation where, in some instances, treatment is becoming less effective.

Finally, fear of inducing resistance has never been a sufficient reason to withhold necessary treatment in the industrialized world. It should not be considered justifiable in the developing world.

8) This $265 million refers to the 1998 average revenue of new launched drugs as calculated by Dr. Steve Arlington. Dr. Steve Arlington, "Pharma 2005: The Challenges" (paper presented at the American Society for Clinical Pharmacology and Therapeutics meeting, Orlando, Florida, March 7, 2001).

9) Dr. Krisana Kraisintu and Dr. Chada Phisalaphong, et al, "Domestic Production of Dihydroartemisinin in Thailand," paper, Research and Development Institute, Government Pharmaceutical Organization, Thailand (June 2001).

10) "One Perfect Combination: Malaria Therapies Double up to Beat Resistance," Wellcome News. Wellcome Trust. [Online]. Available: **www.wellcome.ac.uk/en/1/biosfginttrpinfcom.html** [2001, September 4].

Pau

Pau no longer has a fever. Just one week ago, shakes, hot flushes, headaches and nausea began to overwhelm the frail body of this 14-year-old. Malaria. The third attack in three years. The small amount of chloroquine that she managed to find did not cure her: In Cambodia, malaria is now resistant to this medicine. The combination drug recommended by the health authorities is only available in health centers. The products sold on the private market are either fake or too expensive.

So Pau gathered the last bit of strength she had and walked for several hours to reach the health centre of Anlong Veng, the modest capital of this region in the northern Cambodia.

Like many settlers attracted by the lure of virgin land, Pau's family lives in a poor hut on the side of the road that cuts through the forest.

Pau spends her day collecting bark off trees, which she sells to Thais. It seems that they make a kind of incense from it, intended to keep the mosquitoes away. At nightfall, when she has gone too far into the forest, she sleeps on the ground. It is at this hour that the mosquitoes attack.

Tomorrow Pau leaves the hospital. She will return to the forest – risking her life to earn a living.

were created to meet the needs of wealthy markets, are hampering access to new treatments created in developing countries (see box page 25).

Drug research, development and production is increasing in, among other countries, Brazil, India, South Korea, Thailand, Malaysia and Argentina, countries that had not been considered in the past to have innovative R&D capacity. Some initiatives to build capacity in developing countries involve stimulating collaboration between the public and private sectors in those countries. For example, the International AIDS Vaccine Initiative (IAVI) is working directly with university scientists, governments and companies in South Africa, Kenya, Uganda, India and China. The IAVI has in particular identified India as an ideal location for "fast-tracking" vaccine development, given the country's thriving pharmaceutical industry, experience in clinical trials and government commitment to research.[11]

Regional ventures also attempt to maximize developing country capacity through inter-country collaboration. The International Vaccine Institute in South Korea is a non-profit organization that was created to develop vaccines for diseases prevalent in developing countries. The Institute has pooled the skills and knowledge of scientists in various developing countries, and has been identified as a possible model for drug development and production.[12]

Public-private partnerships

Another type of policy initiative that is often discussed as a potential solution to the R&D crisis is the public-private partnership (PPP). PPPs attempt to foster R&D for neglected diseases by mobilizing expertise, capacity, and funding from both the public and private sectors. Typically, the PPP plays a coordinating and management role around a disease-specific R&D agenda, tries to take advantage of appropriate push and pull mechanisms, and seeks a combination of public funding, philanthropic donations and in-kind donations from industry. Major examples of this kind of approach are the Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development (GATB), and International AIDS Vaccine Initiative (IAVI). So far, no public-private partnerships have been designed specifically for developing drugs for the most neglected diseases.

Current government initiatives, "push" and "pull" mechanisms, building capacity for R&D in developing countries, and public-private partnerships are all only partial solutions to the continuing R&D crisis for neglected diseases. Many are new initiatives whose effectiveness will need to be evaluated over time. And all depend to a greater or lesser extent on market forces. None of them provides an adequate strategy for developing drugs for the most neglected diseases.

11) International AIDS Vaccine Initiative. [Online]. Available: **http://www.iavi.org** [2001, August 13].
12) International Vaccine Institute. [Online]. Available: **http://www.ivi.org** [2001, August 13].

Recommendations for moving forward

Since its formation in 1999, the DND Working Group has been studying the extent and causes of the R&D crisis in neglected diseases and analyzing potential solutions. This research has led to the following insights and recommendations:

1. Because drug development is done almost exclusively within the context of the proprietary pharmaceutical industry, investment in R&D is guided by market considerations. Therefore R&D for diseases that mainly affect the poor is stifled.

2. Public policy has failed to correct this failure, with the result that some diseases are being neglected.

3. The dynamics of the neglect are different depending on the number of people affected and their purchasing power. Therefore it is impossible to develop a single strategy to stimulate R&D. It is crucial to acknowledge the different dynamics of neglected and most neglected diseases: each category will need distinct strategies.

4. A well-defined and needs-driven R&D agenda is required to assist policy makers, funding agencies and the research community in setting priorities for developing safe, effective and affordable medicines. The World Health Organization (WHO), as the only legally mandated international governmental agency responsible for global health, should work toward establishing an essential R&D agenda.
WHO should lead this process. The DND Working Group, with input from WHO, has begun by drafting agendas that prioritize R&D needs for leishmaniasis, sleeping sickness, and malaria. These documents analyze the disease burden, current research strategies, and existing and potential treatments for each of these diseases. A critical next step is for governments and international organizations to examine carefully how they can contribute to dislodging the bottlenecks that currently restrict development of new treatments.

5. Governments in both developed and developing countries need to take comprehensive action to compensate for the market failure in drug development for neglected and most neglected diseases.
Governments must lead in restarting R&D on diseases that are currently being ignored. They need to create and support new structures designed to develop essential medicines for diseases that are being sidelined by the private sector. The current model of profit-driven R&D should not be an exclusive model. Developing drugs as public goods should also be pursued.

6. Increased and reliable long-term funding for R&D into neglected diseases is urgently needed.
The DND Working Group is exploring sustainable options to support R&D for neglected diseases through legal obligations. Governments can and do mandate industry spending in a wide range of areas. One example of a potential mandate would be an “essential research obligation” that would require companies to reinvest a percentage of pharmaceutical sales into R&D for neglected diseases, either directly or through public R&D programs.

A global treaty on R&D for neglected diseases could provide a framework for such mandates. Such a treaty should correct the imbalance that exists between private sector rights and obligations under present international treaties and agreements (eg, the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property), and provide new legal options to make drugs for neglected diseases global public goods.

7. A complete cost analysis of the true costs of drug R&D should be carried out.
Existing estimates on the costs of drug R&D vary widely and remain highly controversial. In order to address the R&D imbalance effectively and make informed funding decisions, policymakers need objective, accurate figures on the true costs of developing drugs. Calculating drug development costs within a commercial context, which will include items such as opportunity costs, will be dramatically different from calculating the funding needed to develop a drug in a non-commercial setting.

8. Public funds for R&D into neglected diseases should be tied to guarantees of equitable access and affordability of the end product.

Equitable access to medicines in developing countries should be a basic principle that guides policy initiatives from the start. If public funds are to be invested in correcting market failures in drug development, there must be guarantees that the new medicines developed are affordable to those who need them.

9. Focused capacity-building and technology transfer projects in developing countries should be encouraged as a direct way to increase R&D expertise and infrastructure.

Long-term solutions to the current crisis in drug development for neglected diseases ultimately rest within developing countries. Therefore, the DND Working Group is cataloguing and examining means of increasing existing drug development capacity in developing countries, and is also working to promote technology transfer that will support sustainable drug development and production facilities.

10. An independent and thorough evaluation is needed of the current and future impact of the ongoing regulatory harmonization efforts (ICH process) on the ability of developing countries to increase their drug development efforts.

11. A new type of body is needed to contribute to drug development for the most neglected diseases. The DND Working Group is exploring the feasibility of a Not-for-Profit Initiative (DND NfPI) that would focus on drug development projects for neglected diseases.

The DND Working Group's analysis has concluded that current approaches to address the lack of R&D for neglected diseases do not sufficiently address the most neglected diseases. To ensure a sustainable solution, a new approach is needed that would systemically harness funding, new science and technology, and foster public-private cooperation for these diseases.

Encompassing the recommendations listed above, and based on the research of the DND Working Group, the vision of the proposed DND NfPI includes the following:

- Ensuring equitable access to effective, field-relevant and easy-to-use drugs for neglected diseases.
- Prioritizing the most neglected diseases, such as sleeping sickness, Chagas disease, and leishmaniasis.
- Using sound science and management techniques to pursue a vision of developing new drugs for neglected diseases.
- Collaborating closely with TDR, industry, and research institutes in developing and developed countries.
- Securing support of public and private resources over the long term, with the majority of funding coming from the public sector.
- Working with drug development experts in developing countries to build national capacity for future drug development.

It is hoped that the public sector will take a strong leadership role in the NfPI to establish its legitimacy and accountability to the public and provide it with the necessary funds.

Conclusion

Despite impressive advances in science and medicine, society has failed to allocate sufficient resources to battle the diseases that particularly affect people in poor countries. The vacuum in R&D for neglected and most neglected diseases means that doctors and nurses in developing countries still do not have effective medicines for many of the diseases they see every day. However, encouraging initiatives have emerged to counter the market and public policy failures that have led to this crisis. Many of these initiatives are new, and their effectiveness will need to be evaluated. For the most neglected diseases, implementation of new solutions, such as a not-for-profit initiative for developing drugs for neglected diseases, will be essential.