Introduction

Research articles and funding applications for health care interventions typically begin with justifications for the research. The authors will describe the potential impact of the intervention, often by noting the personal suffering or economic cost of the illness or disability. The number of people with the illness often will be included to lend weight to the importance of funding this research or publishing its results. Underlying this approach is a common-sense assumption that the more people affected by an illness, and the more serious its impact, the greater the ethical justification for funding and conducting that research. However, a number of reports published since 1990 have found that many highly prevalent diseases in the world receive little or no attention from health researchers and their funders. Given the devastation caused by these diseases, some are saying that the current system of health research funding and reward leads to the violation of people’s human rights. The 10/90 gap—the discrepancy between disease burden and research investment—must be addressed. Research projects focused primarily on the health concerns of developed countries could be expanded to include developing world concerns. This article reviews the 10/90 gap and presents options for how the developed world can help the developing world through health research to narrow the gap.

Key words: 10/90 gap, developing countries, disease burden, health research

The 10/90 gap

The discrepancy between disease burden and research investment is called the 10/90 gap. The term was coined to convey the findings of a report published in 1990 by the Commission on Health Research for Development. This landmark report found that while 93% of the burden of premature mortality is borne by the developing world, only about 5% of the world’s investment in health research is directed toward the health problems of the developing world. That disparity has since been rounded off to give the 10/90 gap. The term has been expressed in a number of different ways. That only 10% of the world’s investment in health research is directed toward 90% of the world’s health problems. That less than 10% of global funding for health research is spent on diseases that afflict 90% of the world’s population.

The important thing with the phrase is not its numerical precision. Some calling for changes acknowledge that the number may be overstated. Yet the problem is real and of immense proportions. Eighteen million people die prematurely each year from medical conditions for which cures exist. This is roughly one-third of all human deaths. About 11 million of these deaths lead to the violation of people’s human rights. Thomas Pogge, professor of political science at Columbia University, is a vocal critic of the current system. He has stated, “The governments and citizens of the high-income countries could and should know that most of the current premature mortality and morbidity is avoidable through feasible and modest reforms.” The 10/90 gap is one example of global injustice.
are of infants and children. The numbers of people who suffer directly from having these diseases runs into the hundreds of millions, with hundreds of millions more impacted through the suffering and death of those within their families. Almost all of this avoidable mortality and morbidity occurs in poor developing countries. Table 1 lists some of the most common causes of death from illnesses for which cures exist.

People in the developing world are intensely burdened by disease. The interrelationship between health, poverty, and development is complicated. For these countries to develop, poverty and disease must be tackled. Health research can play an important role in any strategy attempting to ameliorate conditions in these countries.

The 10/90 gap seeks to draw attention to global inequities in investment in health research. For example, malaria, pneumonia, diarrhea, and tuberculosis are among the leading causes of avoidable death and together account for 21% of the global disease burden. Yet they receive 0.3% of all public and private funds invested in health research.

The gap in drug development

In 2002, an analysis of drug development during the previous 25 years was published. This report concluded that despite “an ever-increasing need for safe, effective, and affordable medicines” to treat the diseases of the developing world, “drug development [for these diseases] has virtually stopped.” The authors defined neglected diseases as infectious and parasitic diseases (excluding HIV/AIDS) that primarily affect poor people in the developing world. Some of the most common ones are listed in Table 2, along with 2005 estimates of how many people they infect.

Between 1975 and 2004, a total of 1,556 new chemical entities were marketed. Only 1% of these new drugs were directed at these neglected diseases, despite the fact that they constituted 11.4% of the total global disease burden. The 16 new drugs for neglected diseases developed before 1999 were later listed on the World Health Organization (WHO) Essential Drugs List, an indication of the significance of their development. Fewer than 2% of all the other new drugs developed during the same period became part of the WHO list. A further measure of the lack of impact of most new drugs is that the overall innovation index for 1975–1999 was 0.313. This means that 68.7% of the new drugs had little or no therapeutic gain compared to what was already on the market. The motivation for their development was more about profit than medical innovation.

The overall burden of a disease can be quantified in what is called disability adjusted life years (DALYs). This score is the number of years of life lost due to disability or premature death. Non-infectious respiratory diseases (like asthma) make up 4.5% of the global disease burden and generate $307 million per million DALY. Tropical diseases contribute 9.4% of the global disease burden and generate $3 million per million DALY. In 1999, the pharmaceutical industry invested about $3.5 billion into research on all infectious diseases; total investment by industry and the public sector into research on infections prevalent in the developing world (malaria, tuberculosis, leishmaniasis, and African trypanosomiasis) was $70 million.

Sleeping sickness exemplifies some of the problems in this area. The incidence of the infection is on the wane, though thousands still die from the infection every year in Africa. The disease itself is complex, with acute and chronic forms, and early and late stages. Different subspecies of the infecting organism lead to...
the different forms and are carried by different domestic and wild animals. A person in the early stage can be infected for years without showing symptoms. Current drug treatments often are unavailable, difficult to administer, and toxic. Melarsoprol was developed more than 50 years ago and causes death in up to 10% of those who take it. Resistance to this drug also is on the increase. Eflornithine is another drug, but it is only effective against the more virulent subspecies that causes the acute form of the disease. The drug is expensive to manufacture and its production was stopped in 1995 for commercial reasons. However, the drug became available again in 2000 after it was found to reduce unwanted facial hair in women. Production for the cosmetic market led to the drug being donated to treat sleeping sickness in Africa. The Tropical Disease Research program at the WHO is now sponsoring research into the development of new drugs and diagnostic tests for this infection.

One side of the 10/90 gap is exemplified by the lack of investment in diseases like the parasitic infections of developing countries. The other side is the burden of these diseases. The following summarizes the current situation well.

Parasitic diseases affect hundreds of millions of people worldwide and result in significant mortality and devastating social and economic consequences. Nevertheless, most of the drugs available to treat these diseases are decades old and are frequently limited in efficacy, plagued by severe side effects and poor patient compliance, or hamstrung by drug resistance. Few, if any, of the currently available drugs for parasitic diseases would pass through even a discovery-stage screening funnel today, let alone preclinical and clinical development.

The gap in vaccine development

Another area within the 10/90 gap is vaccine development. One review focused on 11 poverty-promoting infections that have, to date, been largely neglected in terms of vaccine development. The authors used the DALY scale to compare the impact of these diseases. For example, HIV/AIDS results in loss of 84.5 million DALY annually; malaria, 46.5 million DALY; and the neglected tropical diseases, 56.6 million DALY. Among these diseases, three have vaccines under development to the point of Phase 1 or 2 trials having commenced (as of 2006).
The infecting organisms themselves have not been neglected, but have received extensive scientific study because of their “exotic biology.” As a result, the complete genome already has been identified for the causative agents of seven of the 11 neglected diseases: amebiasis (Entamoeba histolytica), Chagas disease (Trypanosoma cruzi), leishmaniasis (Leishmania major), leprosy (Mycobacterium leprae), trachoma (Chlamydia trachomatis), leptospirosis (Leptospira interrogans), and treponematoses, a group of infections related to syphilis (Treponema pallidum).

The barriers to vaccine production are not scientific. “Instead, our technical ability to produce neglected disease vaccines has outpaced the social and political will needed to translate scientific discoveries into products.” The review concluded that “clinical development has not progressed for many of the antipoverty vaccines because of the absence of commercial markets and, therefore, industry interest.”

The broader gap

The 10/90 gap cannot be addressed by simply getting more pharmaceutical companies to invest more heavily in developing drugs and vaccines for neglected diseases. Global health inequalities are part of the larger problem of global poverty. Almost one-quarter of all human beings live below the international poverty line, of which 1.2 billion live on less than US$1 per day. About 1 billion people live without access to clean drinking water. Every year, about 18 million people living below the poverty line die prematurely from poverty-related causes. That is about 50,000 people per day or 2,000 per hour. Every 80 minutes, the same number of people who died in the Twin Towers on 9/11 die around the world because they happened to be born where they don’t have access to the food, water, or health care that those in the developed world take for granted. Just as global poverty won’t be eliminated by simplistic handouts, the 10/90 gap will not be closed by pharmaceutical research alone. It is part of a much bigger set of problems that have to do with global poverty and justice. The work of Jeffrey Sachs and the Earth Institute exemplifies some of this complexity and how research can contribute to potential solutions.

Health research and global development

Health research is an important way to combat poverty and promote development. The Copenhagen Consensus was issued in 2004 by a group of leading economists. It ranked various proposals on how to obtain the greatest social benefit from development investment. Four proposals achieved the highest priority, with benefits exceeding costs by a factor of 10 or more. Of these four, three involved health priorities: controlling the spread of HIV and AIDS, reducing malnutrition through provision of vitamins and other micronutrients, and controlling and treating malaria. The top priorities had changed little in 2006 when the next meeting included 24 United Nations ambassadors and senior diplomats. Health issues dominated the list of priorities as shown in Table 3.

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Each of these areas requires research on how best to attain the goal. Too often projects have been implemented and reforms initiated without sufficient understanding of the problems or how best to correct them. The 1990 Commission on Health Research for Development put it this way: “Research is an essential key to enable people in diverse circumstances to apply solutions that are already available, and to generate new knowledge to tackle problems for which solutions are not yet known.”

Health research relevant to the developing world often will need to be conducted in those countries. This will require investing in their health research infrastructure. The 1990 Commission recommended that every country, no matter how poor, invest at least 2% of its national health expenditure to support health
research. This would be used to identify essential health priorities and build up long-term health research capacity. Although research from developed countries often can transfer directly into developing countries, this may not always be the case. The diseases in each region may be different, the causes of similar diseases may vary or have complicating environmental factors, and treatments or vaccines may not work as well in the developing countries.

Although development of new treatments plays an important part in closing the 10/90 gap, other issues need other types of research. The Commission on Health Research for Development led to the formation in 1998 of the Global Forum for Health Research. This organization’s major aim is to reduce the 10/90 gap, and focuses most of its attention on improving health systems and infrastructure in developing countries. This requires much more than pharmaceutical development. The Prime Minister of Mozambique stated in 2001 that “Well-designed research—not only biomedical but also socioeconomic, behavioural, and political—can help us enormously.”

Part of the reason for this is that health and poverty are interwoven and one cannot be addressed without the other. While the poor live in conditions that make them more susceptible to some diseases and unable to afford some treatments, some diseases promote poverty. An official in Tanzania’s Ministry of Health noted that “a sickly population cannot participate in development.”

In the developing world, this is especially the case as much of the disease burden is carried by infants, children, and women. Childhood diseases can slow or stunt children’s physical and mental development, thus reducing their potential for productive lives. Many of the diseases are disabling or chronic, impacting people throughout their lives. Some of them cause disfigurement leading to social ostracism (such as leprosy, lymphatic filariasis, or river blindness). All these factors can reduce an individual worker’s productivity and reduce the available workforce in a region. For these reasons, vaccines under development against developing world diseases have been called “antipoverty vaccines.”

The fundamental reason the developed world should promote research on conditions affecting the developing world is moral. People with few resources need our help and we have the resources that could help.

Providing help for those with fewer resources is also supported by more pragmatic reasons. Recent outbreaks of SARS and avian flu demonstrate how quickly infectious diseases can spread around the world. Infectious diseases do not respect borders. Some neglected tropical diseases are already present in developed countries. For example, Chagas disease or American trypanosomiasis is an infection spread by the “kissing bug” insects that live in substandard Latin American housing. In that region, 16 to 18 million people are thought to have Chagas disease, 90 million are at risk of infection, and an estimated 50,000 die from it each year. As a result of emigration, an estimated half a million people in the United States are infected with Chagas disease. Yet it is one of the world’s most neglected infectious diseases for which there is no effective, affordable, or easy-to-use treatment. As in many cases, helping strangers may ultimately turn out to be a way to help ourselves and our neighbors.

**What can be done**

As noted throughout this article, global health organizations are making health research a priority goal. The Global Forum for Health Research is an independent international organization focused on narrowing the 10/90 gap. In January 2000, the WHO set up the Commission on Macroeconomics and Health. Its 2001 report documented the deep interconnection between chronic poverty and disease. It explored several ways in which investment in health could lead to economic growth in developing countries. Also in 2000, the United Nations adopted eight Millennium Development Goals aimed at reducing poverty through sustainable development. The sixth of these goals emphasizes reducing the incidence of infectious diseases, especially HIV/AIDS, malaria, and “other diseases,” including the neglected tropical diseases.

Encouragement of and investment in research to produce new vaccines and treatments for developing country diseases is one important strategy. But new drugs for neglected diseases are not enough to solve this problem. Access to affordable drugs is needed also. One-third of the world’s population lacks access to the
essential drugs that already exist, while in Africa and Asia more than half the populations have no access to these drugs.\textsuperscript{21} Eleven million children die annually in the developing world; two-thirds of these deaths could be prevented by available, effective, low-cost interventions such as vaccines, vitamins, and insecticide-treated bed-nets.\textsuperscript{6} Once drugs are available, systems must be established to ensure they can be acquired, stored, and distributed properly.\textsuperscript{22} Problems also occur with maintaining the quality of the supply. Counterfeit drugs are widely available in developing countries, causing widespread harm and loss of confidence in modern health care systems.\textsuperscript{23} Regulatory systems that effectively guard against such deceptive products need to be developed and maintained.\textsuperscript{24}

Combating disease requires broader approaches than just getting drugs to people. For example, eliminating Chagas disease requires struggling against the insects that spread the infection. These insects infest the thatched roofs of substandard housing.\textsuperscript{17} Dealing with the disease thus requires addressing housing issues. An infected insect can drop feces onto people's skin, usually when they are sleeping. If they inadvertently rub the feces into a bite, wound, eye, or mouth, the infection can spread. People also become infected if they eat uncooked food containing contaminated feces or through mother-to-infant transmission during pregnancy, delivery, or breast-feeding. All of these aspects of the disease require education for those living in infected areas. Infection also can be transmitted via blood transfusion or organ donation, which requires vigilance and testing in the health care system. All of these factors have to be addressed simultaneously for progress to be made against the disease. Research of different types is needed to determine which approach to each factor works best.

Knowledgeable health care professionals are required to deliver available interventions and information to prevent and treat disease. Health research in developing countries requires trained researchers doing research in those countries. People from developing countries can be taken to developed countries for training, but they will need support and resources to set up research and educational facilities when they return home. Research is needed to demonstrate which strategies are most effective in developing the desired infrastructure, yet that has rarely been conducted.\textsuperscript{25}

For example, some research reveals an anomalous situation in Cuba, which has a developing world economy but health outcomes comparable to many developed countries.\textsuperscript{5} Malaria was eradicated in Cuba in 1967 and dengue fever is almost eliminated. Social science research reveals a distinctive health care system that includes highly efficient immunization programs, a constitutional right to treatment, and a largely indigenous pharmaceutical industry focused on supplying essential drugs.\textsuperscript{26} While life in Cuba has many problems, including aspects of its health care system, it has made public health a top national priority. Kofi Annan, former Secretary General of the United Nations, stated that Cuba “demonstrates how much nations can do with the resources they have if they focus on the right priorities—health, education, and literacy.”\textsuperscript{27}

Collaborative research projects should be encouraged, with researchers in developing countries given significant roles in keeping with their experience and skills. Past collaborations have viewed developing countries as sources of interesting samples or participants for clinical trials.\textsuperscript{28} Early career researchers may need to be mentored, but the goal should be to help them develop local research infrastructure. Open access electronic journals have been helpful by allowing researchers in developing countries to access significant cutting-edge resources.

Even with health care interventions, what is needed may not necessarily be more bench or clinical research. Systematic reviews of health care interventions bring together all the studies that have already been conducted on an intervention and summarize the results. The Cochrane Collaboration is one organization carrying out such reviews. It developed after it was noticed that practice sometimes lagged far behind research because the results of studies were not made available in appropriately summarized formats for busy practitioners. Health care questions of relevance to developing world practitioners could be reviewed systematically to help ensure practice is guided by the best available evidence.

In the area of drug development, changes in licensing and patenting practices have been called for and, in some situations, already begun. Current international patent practice is regulated under the Trade-Related Aspects of Intellectual Property Rights (TRIPS)
agreement. The TRIPS agreement came into effect in 1995 along with the creation of the World Trade Organization (WTO). Prior to TRIPS, some countries ignored the patents established by developed countries and produced or imported generic versions of patented drugs. This made important drugs available at reduced cost, although concerns existed about their quality. For example, generic versions of certain antiretroviral drugs were available for $140 per year compared to $30,000 per year for patented products.

TRIPS caused intense controversy from the start, leading to revisions in 2001 called the Doha Declaration and subsequent clarifications. Under these arrangements, members of WTO were permitted to extract “compulsory licenses” from pharmaceutical companies to manufacture patented medicines or import generic versions. The regulations sometimes have led to negotiated compromises, with patent holders providing patented drugs at significantly reduced prices or choosing to ignore their rights as patent holders. In other situations the interactions have been more like tense stand-offs with developing countries attempting to override patent protections and companies withholding the release of new medications into those countries.

Thomas Pogge maintains that the problem with TRIPS lies with the way it attempts to address the very high costs of conducting pharmaceutical research. The underlying premise is that inventors of new drugs (pharmaceutical companies) are best reimbursed by giving them a 20-year monopoly on the production and sale of those drugs. This leads to high prices for the drugs so that the companies can recoup the costs of the years of research on the marketed drug and all the others that never made it to market. The other effect is that other companies are restricted from copying the drug.

Pogge has proposed a completely different system of patenting “essential drugs” for diseases that predominate in developing countries. The current system would remain in place for drugs for other conditions, with pharmaceutical companies choosing which system to use for each new drug they patent. The new system would allow pharmaceutical manufacturers to recoup their research costs in a way that avoids trying to extract money from sick poor people or countries with limited resources. However, it would remain to be seen whether the companies would continue to focus on drugs for developed countries or increase investment in research on diseases of the developing countries.

The reform proposal would permit inventors to patent their products, but under a very different basis to current arrangements. Pogge’s “public good strategy” would require inventors to provide open access to all information about their new drug free of charge. In exchange, the inventor company would obtain a multi-year patent that would pay the company from a special public fund in proportion to the impact of the new drug on the global disease burden. Generic products would increase this impact and therefore the return for the patent holder also.

Pogge admits that growing this public fund would be a major challenge. Convincing politicians and the public to use this approach would require a compelling argument. However, Pogge calculates that a sufficiently large fund could be created by redirecting existing subsidies given to pharmaceutical companies and raising an additional $70 billion. This corresponds to 0.27% of the aggregate gross national income of developed countries or $70 per resident.

Changing the patent system would be difficult, but Pogge presents a strong argument for the moral basis of his approach. Current practice drives up the costs of drugs for everyone and puts everyone’s interests in conflict. People in developing countries see the rich get healthier while they suffer and die. Those with essential drugs are in conflict with those who need them. The companies with research capacity are in conflict with patients, generic manufacturers, and governments concerned about their ill citizens. The thinking behind the new proposal is that it aligns the interests of inventor companies with those of patients and generic manufacturers. “The reform would also align the moral and prudential interests of the inventor firms who, under the present regime, are forced to choose between recouping their investments in the search for essential drugs and preventing avoidable suffering and deaths.”

Already, some limited versions of these approaches to essential drug development are being put into practice. Public-private partnerships (PPPs) have developed where governments and philanthropies provide
funding to scientists, usually in academia. In return, the scientists focus on developing world diseases and agree to not-for-profit distribution of any resulting intellectual property in the developing world. When target compounds are developed, the PPPs contract with industry to bring about further developments. Several dozen new potential products for developing country diseases have thus been developed. However, these projects are limited by the relatively small funding available from philanthropies.

Another approach has been to urge universities to agree to socially responsible technology transfer. Given that much academic research ultimately is funded by government agencies, universities have been called on to make drugs and medical products invented on campus available for the public good. For example, the AIDS drug d4T (stavudine) was invented at Yale University and licensed to Bristol-Myers Squibb. After student protests and external pressure, the university and company agreed to allow companies in developing countries to produce a generic version. Similar agreements have been reached with other universities. Underlying the approach is a change in motivating principles similar to that urged by Pogge. Instead of measuring the success of intellectual property agreements in purely financial terms, they are measured in terms of social impact and the public good.

Conclusion

The 10/90 gap has been clearly visible for a number of years. In 1999, an article in the Journal of the American Medical Association declared that the attempt to close the gap was “a lost battle.” The years since then have seen some progress, especially in innovative ways to develop partnerships between industry, academics, funders, and developing countries.

Most attention is directed to the impact of the 10/90 gap on drug development for diseases prevalent in developing countries. The lack of vaccines and effective, safe, low-cost drugs for many conditions is highly problematic. The burden of death, disability, and suffering on individuals and countries is immense. While this occurs, it is difficult to see how research investment in me-too drugs that extend patents and drugs for non-essential conditions can be justified. The only way to do so is by making profit the primary concern of drug development. This is the morally problematic stance that needs to be addressed. Part of the solution lies in introducing other incentives alongside profit-making into health research. Ultimately, these are based on the moral premise that the wealthy ought to help the poor.

Investment in research should be motivated by ethically, socially, and politically responsible goals. Drugs are not the same as washing machines or music. Additional concerns should influence decisions on which conditions get research investment. People will not die if washing machines are not made more efficient or if new music is not released. They will if new treatments are not developed and made available to those who need them, not just to those who can afford them.

At the same time, inequalities in global health care exist for numerous reasons. Control of infectious diseases requires more than new vaccines and drugs. Access to already existing interventions must be ensured. Housing, nutrition, water, sanitation, and other social and cultural practices must be made healthier. Health care systems and research infrastructure must be developed. Political and regulatory systems need to be examined and improved.

The 10/90 gap must be addressed on a large scale, but also on a small scale. Research projects focused primarily on the health concerns of developed countries could be expanded to include developing world concerns. Intellectual property agreements could be modified to ensure easier, inexpensive access for developing countries. Educational institutions could pursue collaborative arrangements with research institutions in developing countries to facilitate their development. Mentoring arrangements could be pursued on individual bases. The possibilities are endless. The question is whether the developed world will find the moral courage to help the developing world through health research or will allow the gap to widen further.

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