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Investing in Exposure

Abdul Moiz Khan

The problems of the overwhelming amount of medical literature have been thoughtfully highlighted in the *PLoS Medicine* editorial "Drowning or Thirsting: The Extremes of Availability of Medical Information" [1]. It is of vital importance to medical professionals that they improve on their skills of sifting through the huge amounts of literature that are made available to them every month. But this task becomes exponentially more difficult in the less-developed world, where basic knowledge of medical literature is limited [2].

There are no alternatives to the good analytical skills that come through continued exposure to medical literature. This exposure should begin at the medical student level. Exercises such as those requiring medical students to analytically criticize medical literature can go a long way in developing reading skills.

The second issue is that of disseminating the literature that has been published. Access to reliable health information has been described as "the single most cost-effective and achievable strategy for sustainable improvement in health care" [3].

A useful strategy could be making less-expensive paper versions of medical journals widely available in less-developed countries. Publishers should be willing to look into this approach. Regional copies of journals can be produced locally and inexpensively. This will boost the circulation of medical journals. Medical professionals will not mind a little compromise in the quality of paper in a journal, so long as they are able to afford it at a low price.

The business model of offshore call centers can serve as a useful one in the case of publishing low-cost copies of medical journals. Companies have shifted their call centers to less-developed countries where services are available at very low costs. The costs of publishing are likewise bound to be cheaper in the less-developed countries; therefore, journals can be produced at affordable prices. If this model can be followed by multinationals, why is it not possible for a cause as noble as publishing medical literature?

Another approach could be that journal volumes could be condensed, so that only research relevant to the local area is published in the local version of the journal.

The Internet's widely spreading use as a resource can be of vital value in substantially quenching the thirst of professionals. The wide availability of Internet access in Pakistan [4], for example, helps the cause of disseminating information. Internet access such as that given through the platform of HINARI or the Ptolemy project [5] is also a viable option. But these networks need to be expanded to include more countries and individuals [6].

One should hope that investing in improving exposure of health professionals to medical literature will help improve their practices and the quality of healthcare that they provide to impoverished populations in their local area. The need of the hour is to be innovative and be ready to embrace new and thoughtful ideas for the collective good of humanity. ■

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Hyperinfectivity in Cholera: A New Mechanism for an Old Epidemiological Model?

Mercedes Pascual, Katia Koelle, Andrew P. Dobson

Hartley et al. [1] have recently proposed an epidemiological model for the dynamics of cholera that explicitly incorporates a hyperinfectious stage of the pathogen *Vibrio cholerae*, following laboratory findings that passage of the bacterium through the gastrointestinal tract results in a short-lived more highly infectious state. The paper and its commentary [2] emphasize that this model provides a basis for the transmission pathway known as "human-to-human" and demonstrates its importance, relative to the "environment-to-human" pathway, in the "explosive" character of cholera epidemics. Nevertheless, several important points seem to be missing from the discussion.

First, epidemiological models that treat transmission as "human-to-human" do exist in both the older literature [3] and in more recent cholera studies [4,5]. The latter use time series models to explain the interannual dynamics of cholera outbreaks in endemic areas. Their application to the temporal patterns of cholera in both recent and historical records from Bangladesh show that the force of infection is clearly related to previous incidence levels, as expected for "human-to-human" transmission. This work has also shown that environmental variables (El Niño, rainfall) modulate this type of transmission [5], so that the focus on the environment is relevant even for the "human-to-human" pathway.

Second and more importantly, we can ask whether the model of Hartley et al. differs from the standard treatment of "human-to-human" transmission in epidemiological models. In particular, does the so-called "explosive" behavior differ from the well-known exponential growth of cases at the beginning of an epidemic, when there is little or

no immunity built into the population? Inspection of the temporal scales involved in the dynamics tells us that this is not the case: we can collapse their treatment of transmission via a hyperinfectious stage into a more standard direct-transmission formulation. This is because the dynamics of the hyperinfectious stage in the environment are much faster than that of the number of cases, with the average lifespan of a hyperinfectious bacterium (their variable BHI) being on the order of 5 h, whereas an infected individual (their variable I) continues to shed for approximately 5 d. Therefore, to a first approximation, BHI sees I as "constant" for a sufficient length of time to reach "equilibrium" for any given value of I. It follows that this "equilibrium" concentration of the hyperinfectious stage in the environment effectively tracks the size of the infected population; in other words, BHI is simply proportional to I. Simulations of the model with the parameter values of the Hartley et al. paper confirm this expectation for the whole course of an epidemic. We can then get rid of this variable and write the transmission rate as a function of the number of susceptibles and the number of infected individuals, as is traditionally done in epidemiological models. Thus, for purposes of modeling cholera epidemics, we do not need to explicitly represent the hyperinfectious stage, unless the questions and mechanisms we are examining are specifically about this stage (as was the case in Hartley et al.), and "explosive" behavior does not refer to a different type of dynamics than that of standard models for human-to-human transmission.

There is another way, however, in which the epidemics may have been called "explosive" by Hartley et al.: the growth rate of the epidemics in their model is much higher when "human-to-human" transmission becomes dominant relative to "environment-to-human" transmission. This brings us to the important epidemiological quantity known as R0, which measures the number of secondary cases produced by an infected individual in a pool of susceptibles, that is, at the beginning of an outbreak. Hartley et al. report a new formula for cholera's R0 (Equation 4 in their paper). There is an interesting discrepancy between Hartley et al.'s R0 estimate when "human-to-human" is dominant (R0, ~18) and the value we obtain for cholera data for Matlab, Bangladesh (R0, ~3) (unpublished result). Our estimate is close to the values Hartley et al. propose when "environment-to-human" transmission is dominant, even though our estimate is obtained from a model of "human-to-human" transmission. As far as we can tell from the information provided, the derived expression for R0 in Hartley et al. is an approximation. It appears to hold exactly when the dynamics of both the hyperinfectious and the environmental stage occur on fast temporal scales, quickly "equilibrating" and tracking the number of cases. While this assumption, as we have argued, applies to the hyperinfectious stage, it does not to the environmental one, as demonstrated by similar model simulations. Hartley et al.'s expression for R0 would then overestimate the reproductive number of the disease, making it more explosive than it is (see Figure 4 in the paper).

The discrepancy in our estimates has an important consequence: while an epidemic declines from a depletion of susceptibles in the Hartley et al. model, the seasonal outbreaks we observe in Bangladesh are curtailed prior to a significant depletion of susceptibles [5]. This implies that the transmission rate must effectively be decreasing as the epidemic peaks. Indeed, recent observations of vibriophage dynamics in Bangladesh have given rise to the hypothesis that seasonal outbreaks may be self-limiting due to amplification of *Vibrio*-specific phage [6,7]. The dynamics of phage predation are a likely mechanism for the observed reduction in cholera transmission rate at the end of seasonal outbreak.

Despite these differences, both our analyses and Hartley et al.'s model accentuate the need to consider some variant of "human-to-human" transmission to explain cholera dynamics. An important issue is therefore what we should call "human-to-human" transmission. Clearly, the categorization of the two routes of transmission ("human-to-human" and "environment-to-human") is a simplification, albeit useful for the purpose of modeling the disease, that considers only the two extremes of a continuous axis defined by the strength of the feedback between (previous) cases and transmission rate and by the different temporal scales of transmission. For the "environment-to-human" type, this feedback is weak (in the extreme, nonexistent) as the bacterium concentration in the environment becomes dominated by its survival, population growth, environmental drivers, and the stochastic nature of these processes. At the other extreme, the feedback is strong and the transmission rate is a function of cases. This definition is more general and more practical than the one that restricts "human-to-human" transmission to that mediated by the hyperinfectious state. For issues of control, the more general definition appears more relevant, unless we are considering control measures that would specifically target the concentration of the hyperinfectious stage.

Many open questions remain on the modeling of cholera in connection to transmission pathways. For example, early-warning systems and associated predictive models for endemic and epidemic regions remain to be developed and tested. In contrast, the importance of sanitary conditions, sewage treatment, and clean water for cholera prevention and eradication has been known for a very long time. Nevertheless, cholera is today in its seventh pandemic and, as a "disease of poverty" [8], continues to represent a significant public health burden around the world. Neither an exclusive focus on the environment nor an emphasis on socio-economic factors alone is sufficient to address the cholera problem today. Developing a better mechanistic understanding of the factors that initiate, amplify, and defuse regular seasonal outbreaks in endemic areas and irregular "epidemic" outbreaks in others should prove valuable to develop viable control strategies for this and other enteric diseases. ■

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Industry and Bioethics: What Price the Relationship?

Mark Boyd, Wendy Rogers

We read with interest the article by Mackie et al. entitled "Lessons on Ethical Decision Making from the Bioscience Industry" [1]. The authors recognise some study limitations, including the possibility of social desirability bias, but fail to address other limitations that in our view seriously weaken the paper.

Firstly, there is no discussion regarding an understanding of the use of the term "ethics" by the authors and bioscience companies. There appears to be an assumption that "ethics" is a straightforward term whose meaning would be agreed by all those engaged in the field. However, the requirements of business ethics, for example, may differ significantly from the requirements of healthcare ethics. When one considers issues such as priority-setting, environmental concerns, sales and marketing, and the like, it is not clear that the ethical imperatives of the bioscience and healthcare industries substantially overlap. This study engages with what might be defined as procedural issues, but ignores substantive philosophical issues. The latter may have been beyond the scope of the paper, but if this were the case, it should have been acknowledged.

Secondly, there is no comment upon the authors' industry links. These are disclosed in their listing of their competing interests and include receipt of industry funding, direct links with companies subject to study, and funding awarded by some of the involved companies after the study. However, there is no discussion of the potential for these links to interfere with study conduct and interpretation. The authors do acknowledge the debate regarding bioethics and links with industry, but such acknowledgements cannot realistically compensate for the conflict of interest faced in the conduct of this particular study. Despite the growing literature on these links, there is no comprehensive analysis of industry-associated bioethics research [2,3]. We cannot therefore confidently claim that there is an observable industry bias in such research. There is, however, overwhelming evidence that bias favourable toward funders occurs in medical research and healthcare prescribing [4–6]. It would therefore seem naive to believe that bioethicists are in some way immune from factors that demonstrably lead to bias in other disciplines.

In addition to these omissions, the accompanying Perspectives commentary [7] neglects to discuss the implications of the conflicts of interest for the design, conduct, conclusions, and interpretation of the study. There was an allusion to these conflicts, but in this context we would have expected a review to be far more explicit regarding the potentially crucial importance of such conflicts.

Ethicists are wooed by industry precisely because their views and opinions carry weight. This currency will soon become valueless unless researchers, authors, reviewers, and journal editors take a strong stand for intellectual honesty and self-critique in the presence of conflicts of interest. ■

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Authors' Reply

We thank Boyd and Rogers for their comments [1] about our article "Lessons on Ethical Decision Making from the Bioscience Industry" [2].

In response to their first point, we would like to refer them to our book, entitled *BioIndustry Ethics*, on which our article was based [3]. In the introduction of the book, we provide a discussion about the intersection of traditional medical ethics and business ethics as well as business strategy and

explain that it is this intersection that is the focus of our study. The decisions made by management in bioscience companies (about what drugs to develop, where and how to conduct clinical trials, etc.) are not merely procedural but a combination of procedural and substantive ethical decision-making. We would also like to point out that the purpose of our article was to highlight the *mechanisms* being used by bioscience companies. It is our belief that by instituting processes that encourage ethical discussions (through an ethics department, an ethics advisory boards, with ethics education and forums for ethics discussion), management in bioscience companies will begin to make tough ethical decisions openly and consciously. We would like to reiterate that our primary audience for this article are decision-makers in bioscience companies who, as a first step, can learn from such approaches.

With respect to Boyd and Rogers' second point, as we write in the funding section of the paper, the primary funding for this study came from public sources. Moreover, as we also emphasise in our book, members of our research team with ties to a particular company did not participate in the case study of that company. Beyond our disclosing funding sources—which is, of course, necessary and appropriate—it is not clear what Boyd and Rogers are really asking for. They seem to feel our article is incomplete because it is missing an exegesis on how this funding might influence our results. In fact, we think they are trying to imply that it is inappropriate for anyone with industry funding to study ethical practices in industry. This is of course not the standard in clinical research: the standard is disclosure. But there is something more fundamental here. Our study is the very first, to our knowledge, to systematically document practices in bioscience companies with respect to ethical challenges. In clinical ethics, it took several decades after the advent of ethics committees for analogous studies to be conducted. Science has a simple solution to Boyd and Rogers' complaint—it's called replication. Boyd and Rogers themselves, or others, should roll up their sleeves and study industry practices rather than, like some bioethicists, simply cast aspersions about "intellectual honesty and self-critique." But the logical extension of Boyd and Rogers' critique is that people within companies—or with real-world experience of companies' attempts to address ethical challenges—would be ineligible to conduct studies aimed at improving companies' practices in response to ethical challenges. This is the type of Alice in Wonderland world that is the end result of Boyd and Rogers' world view. ■

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To Fully Tackle the Gang of Four, Needs-Driven R & D Is Essential

Els Torreele, Catherine Royce, Robert Don, Ann-Marie Sevcsik, Simon Croft

We congratulate Hotez et al. [1] for a compelling and important paper that challenges the global health audience to address neglected tropical diseases affecting the poor and powerless in resource-poor settings. Full support should be given to the call for a global strategy to tackle the neglected "gang of four," which will add the most neglected tropical diseases to the well-known big three (HIV/AIDS, malaria, and TB).

For those neglected diseases for which adequate tools exist, a strategy of integrated chemotherapy linked to the big three could be the best way to reduce disease burden and disease-related deaths, as is convincingly argued by the authors in the case of helminth infections. However, this is a simplification of the situation we face for other neglected tropical diseases such as human African trypanosomiasis (HAT), Chagas disease, and Buruli ulcer. No adequate tools exist to diagnose and treat these fatal or severely debilitating conditions. The top priority therefore should be new and innovative research and development (R & D) to develop adequate treatments: simple and cheap diagnostics and safe, efficacious, easy-to-use, and affordable medicines.

In the case of HAT, current diagnosis is cumbersome and invasive, while the few existing drugs are old, toxic, difficult to use, and increasingly ineffective [2]. For visceral leishmaniasis, another fatal disease when left untreated, major treatment complications are invasive diagnostics, long durations of treatment (30 d), and drug resistance (up to 40% in India) [3]. No drugs even exist to treat patients with Buruli ulcer or chronic Chagas disease.

Several new initiatives are beginning to address these challenges. For instance, the Drugs for Neglected Diseases initiative (DNDi) (http://www.dndi.org) was launched in 2003 to develop new and field-adapted treatments for neglected diseases like HAT, leishmaniasis, and Chagas

disease. The Foundation for Innovative New Diagnostics recently initiated a new HAT diagnostics programme, and several groups in academia and pharma are increasing their R & D efforts in neglected tropical diseases. However, this is just a start. These efforts will only come to fruition if sustained support can be mobilized.

Needs-driven R & D for new tools is essential, as is government support for both R & D and implementation of effective interventions when available. In 2005, DNDi launched an international R & D appeal (http://www.researchappeal.org) that urges governments to set global public health priorities, to fund R & D for neglected diseases, and to provide new rules to stimulate essential health R & D. This effort builds on momentum gained over the past years to provide an international response to correct the fatal imbalance of adequate health tools for neglected diseases.

We hope all governments will sustain this momentum in May 2006 at the World Health Assembly, which will consider an essential health R & D resolution calling for a global framework to support needs-driven research and to set R & D priorities in the interest of public health, especially for the most neglected diseases [4]. The G8 summit in July provides an opportunity for those governments to financially commit to their 2005 pledge to support drug R & D for neglected diseases.

Hotez and colleagues have offered original proposals to increase the effectiveness of existing tools in the control of certain neglected tropical diseases outside of the big three. But to really tackle the gang of four, adequate and field-adapted health tools must be available, and governments must prioritize needs-driven R & D for those diseases where no such tools exist. ■

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Authors' Reply

We appreciate the comments by our colleagues from the Drugs for Neglected Diseases initiative (DNDi) highlighting the importance of research and development programs for a new generation of control tools (e.g., drugs, diagnostics, vaccines, surveillance instruments) to combat the neglected tropical diseases [1]. Indeed, we have great admiration for the outstanding track record of the DNDi along with its sister organizations, including the Institute for One World Health, TDR-WHO, and the Seattle Biomedical Research Institute, as well as a small but distinguished community of academic and government scientists.

In both our paper cited by Torreele et al. [2] and an earlier companion paper also published in *PLoS Medicine* [3], we went to some lengths to point out that the ultimate elimination of some of the most burdensome endemic neglected tropical diseases will likely require more than simply innovations in preventative chemotherapy, such as our proposed rapid-impact, pro-poor package. Such achievements, especially for diseases such as Buruli ulcer, hookworm, human African trypanosomiasis, and leishmaniasis, will almost certainly also require advances in biotechnology leading to the development and distribution of new drugs and vaccines. It is also for that reason that each of the biomedical scientists who co-authored the *PLoS Medicine* papers has devoted his or her lifetime to research on neglected tropical diseases and has contributed to the development of new control tools for hookworm, lymphatic filariasis, malaria, onchocerciasis, schistosomiasis, and other diseases of poverty. In addition, Jeffrey Sachs, the health economist on our project, previously led an international call to establish a US$1.5 billion Global Health Research Fund, to finance basic and applied research on the diseases of poverty [4]. In short, we completely agree with the plea by Torreele et al. to embrace research and development as an essential component for any global neglected tropical disease initiative.

The major points of our *PLoS Medicine* articles are these: (1) the disease burden of neglected tropical diseases has been underestimated and this group of diseases may be as important as HIV/AIDS, malaria, and tuberculosis; (2) there is a moral imperative to recognize the plight of the world's most impoverished who suffer from neglected tropical diseases; and (3) beginning today, we can make a rapid impact on the lives of these populations through an effective, sustainable, rapid, and highly cost-effective intervention package of donated drugs.

Ultimately, control and elimination of some of our most devastating neglected tropical diseases will likely require additional biotechnological solutions. Even then, this will require careful integration of the new with the old, along the lines of the vaccine-linked chemotherapy strategies recently proposed by Bergquist et al. [5]. Therefore, we need to do our very best to achieve sustainable morbidity reductions by using the donated drugs we have in hand today, with the understanding that success in this endeavor must not lead to complacency. We know all too well how the emergence of chloroquine and DDT resistance derailed global malaria eradication efforts during the 1960s [6] and that we must be ready to simultaneously champion research as well as implementation. We also believe that it would be unethical in the context of the timeframe of the Millennium Development Goals to ignore what we can do for poor people now at such

a low cost [7], as we know that research takes time to come to fruition in terms of products, policies, financing, and practice. Drugs of proven efficacy and quality are available now for some of the neglected tropical diseases, and they can be delivered despite the resource constraints in African health systems. It is gratifying to see a number of countries are now prioritizing the control or elimination of neglected tropical diseases as a national policy and are establishing budget lines to ensure sustainable implementation of the tools we have. There have been too many public health failures in the past—and so it is essential that we take the real opportunity to act on behalf of the world's poor. ■

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Competing Interests: PJH is partially supported by the Bill and Melinda Gates Foundation, Seattle, Washington, United States of America, through the Human Hookworm Vaccine Initiative of the Albert B. Sabin Vaccine Institute, Washington, District of Columbia, United States of America. He is an inventor on an international patent application (PCT/US02/33106; filed November 11, 2002) entitled "Hookworm Vaccine." The patent was filed in the United States, Brazil, India, China, and Mexico. If awarded, the patent would belong to The George Washington University, with an exclusive license to the Human Hookworm Vaccine Initiative of the Albert B. Sabin Vaccine Institute, a nonprofit (501(c)3) organization devoted to increasing the use of vaccines worldwide. Because hookworm is a neglected disease afflicting the poorest of the poor in developing countries, a hookworm vaccine has no anticipated commercial value or income-generating potential. The rationale for filing a patent is to ensure that the vaccine is developed for those who need it in developing countries and to encourage vaccine manufacturers in developing countries to work with the Albert B. Sabin Vaccine Institute for manufacture of the hookworm vaccine. The first-generation hookworm vaccine, the Na-ASP-2 Hookworm Vaccine, was developed entirely in the nonprofit sector through the Human Hookworm Vaccine Initiative of the Albert B. Sabin Vaccine Institute. PJH is also co-chair of the Scientific Advisory Council of the Albert B. Sabin Vaccine Institute (he receives no compensation for this activity). DHM is partially supported by the United Kingdom Department for International Development and by GlaxoSmithKline, London, United Kingdom, and participates in the Mectizan Expert Committee/Albendazole Coordination meetings, which are supported by Merck, Whitehouse Station, New Jersey, United States of America, and by GlaxoSmithKline, London, United Kingdom. AF is director of the Schistosomiasis Control Initiative, which is supported by the Bill and Melinda Gates Foundation, Seattle, Washington, United States of America. EO is supported through the Task Force for Child Survival and Development and the Carter Center, Atlanta, Georgia, United States of America; by the Bill and Melinda Gates Foundation, Seattle, Washington, United States of America; by GlaxoSmithKline, London, United Kingdom; and by the Global Alliance to Eliminate Lymphatic Filariasis, Liverpool, United Kingdom. SES declares that she has no competing interests. JDS is partially supported by the United Nations, New York, New York, United States of America.

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Response from Savioli and Colleagues from the Department of Neglected Tropical Diseases, World Health Organization

Lorenzo Savioli, Dirk Engels, Denis Daumerie, Jean Jannin, Jorge Alvar, Kingsley Asiedu, Marc Gastellu-Etchegorry, Pere Simarro, Silvio P. Mariotti

We have read the article by Hotez et al. [1] and the letter by Torreele et al. [2].

The priority today is immediate action to expand delivery of effective tools and to strengthen the capacity of health and innovative delivery systems in the poorest sections of endemic countries to tackle the control, elimination, and eradication of neglected tropical diseases (NTDs). To this end, it is extremely important that all these neglected diseases be placed on the global public health agenda.

Approximately 1 billion people—one person in every six—suffer from one or more NTDs, such as Buruli ulcer, cholera, cysticercosis, dengue and dengue hemorrhagic fever, dracunculiasis (Guinea-worm disease), food-borne trematode infections, hydatidosis, leishmaniasis, lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, trachoma, Chagas disease, and human African trypanosomiasis. Several of these diseases are vector borne. Some diseases affect individuals throughout their lives, causing a high degree of morbidity and physical disability and, in certain cases, gross disfigurement. Others are acute infections, with transient, severe, and sometimes fatal outcomes. Patients can face social stigmatization and abuse, which only adds to the already heavy disease burden. The common denominator of all the NTDs is that these diseases are invariably the diseases of the poorest in low-income countries.

For the majority of these diseases, inexpensive or donated drugs are available for their prevention and control or are part of strategies for control and elimination. These, when used on a large scale, are able to wipe out the burden caused by these ancient scourges of humanity. For leprosy, treatment with effective antibiotics, now kindly donated by Novartis, is leading to the elimination of this ancient disabling disease. In the case of blinding trachoma, the use of the recommended SAFE strategy (surgery, antibiotic therapy, facial cleanliness, and environmental improvement), including an effective antibiotic, donated by Pfizer through an ad hoc initiative (the International Trachoma Initiative), is enhancing the progress towards final elimination. Large-scale, regular treatment plays a central role in the control of many NTDs such as filariasis, onchocerciasis, schistosomiasis, and soil-transmitted nematode infections. For example, regular chemotherapy against intestinal worms reduces mortality and morbidity in preschool children, improves the nutritional status and academic performance of schoolchildren, and improves the health and well-being of pregnant women and their infants.

There is a second group of NTDs for which the only clinical option currently available is systematic case-finding and management at an early stage. These diseases include Buruli ulcer, Chagas disease, cholera and other diarrhoeal diseases, human African trypanosomiasis, and leishmaniasis. Simple diagnostic tools and safe and effective treatment regimens urgently need to be developed for these diseases. However, even for these infections, systematic and widespread use of the present "imperfect" tools at an early stage of disease can dramatically reduce mortality, morbidity, and disability. For others, vector-control tools are available and present the main method for successful transmission control, as in the case of Chagas disease.

There are examples of great successes in the fight against NTDs in both these groups, and these offer optimism for the future. Since 1985, 14.5 million patients have been cured of leprosy through multidrug therapy; today, fewer than 1 million people are newly affected by the disease. Before the start of the Guinea-worm Eradication Programme in the early 1980s, an estimated 3.5 million people were infected with the disease in 20 endemic countries. In 2005, only about 10,000 cases were reported in nine endemic countries, and the programme is moving towards eradication by 2009.

The control of onchocerciasis has freed more than 25 million hectares of previously onchocerciasis-infested land and made it available for resettlement and agricultural cultivation, thereby considerably improving rural development prospects in Africa and Latin America. During the last years, thanks to public–private partnerships with sanofi-aventis, human African trypanosomiasis control activities have increased, raising the total number of people screened through active case-finding and subsequently increasing the access to diagnosis and treatment of affected populations. These constant efforts have led to a substantial and regular decline in the number of new cases. The number of people infected, which were estimated at 300,000 cases in 1995, has been reduced to 50,000–70,000 in 2005 [3].

In other words, the area of NTDs is not only an area lacking drugs and tools that can effectively treat affected individuals and communities, but an area of action. As an example, praziquantel, a very effective, safe, and relatively cheap single-dose drug (approximately 20 Euro cents per dose) to treat schistosomiasis, affecting in Africa alone at least 160 million people, is not accessible to those in need due to lack of financial resources to purchase and deliver it. We also have a series of other effective antischistosomal drugs, such as oxamniquine and metrifonate, that could again be made available in case resistance to praziquantel were to develop. Triclabendazole, the only effective drug against fascioliasis, has been on the market for veterinary use for over 20 years and is still not widely available for human use. Other drugs to tackle onchocerciasis and lymphatic filariasis are generously given free by the producers, Merck and GlaxoSmithKline, but more funds are required to deliver them to the millions in need.

These and many other highly effective drugs developed in the late 1970s are now out of patent but still not available to poor communities. We are well aware that "market mechanisms" will never solve the problem of access to effective drugs in the poorest communities of the low-income countries. Therefore, drug donations and funds for drug delivery are needed to tackle a problem that is intimately linked to underdevelopment and marginalization.

Global health development policies must also be more balanced in allocating resources to research and control. For instance, the recent resolution of the European Parliament [4] is indeed a sign of great progress. However, this document tackles disproportionately the lack of tools and the need for research in drug development. We believe that—above all—priority should be given to generating resources to deliver the drugs already available to those in need while monitoring their use and efficacy.

WHO is expanding activities in this area. WHO has very recently developed guidelines towards effective integrated implementation of large-scale preventive chemotherapy strategies in consultation with Member States, academic organizations, and other partners. We believe these guidelines will be essential for Member States and interested non-governmental organizations to tackle the problem of NTDs in their countries on a large scale.

We agree that this need for immediate action in the medium- and long-term must be backed up by research and development of new drugs, vaccines (like those presently developed against hookworms), diagnostics, and other tools. We believe that focusing mainly on research and development at this stage is overshadowing the importance of reducing mortality, morbidity, and disability now with the existing technology. ■

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Merck's Actions Surrounding Vioxx

Michael Heinley

Merck has always been committed to the highest standards of scientific integrity, patient safety, and ethics. In his part of the *PLoS Medicine* Debate entitled "What Are the Public Health Effects of Direct-to-Consumer Drug Advertising," Richard Kravitz incorrectly characterizes Merck's actions surrounding Vioxx [1].

Any suggestion that Merck acted improperly in the development and marketing of Vioxx is simply false. Vioxx was a widely used medicine because it served as an effective therapy for patients for whom—in many instances—no other alternative medicine worked. Merck's marketing efforts for Vioxx provided balanced and accurate information about both the product's considerable benefits for patients living with chronic pain as well as its potential risks.

Merck remains committed to producing innovative, safe, and therapeutic medicines for patients and to upholding the highest standards of scientific integrity. Our reputation in the industry, with patients and our community, is that of a company that puts patients first. We intend to keep it that way.

To learn more about Merck's actions, please visit the Vioxx Information Center on our Web site at http://www.merck.com/newsroom.

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Author's Reply

In my section of the *PLoS Medicine* Debate entitled "What Are the Public Health Effects of Direct-to-Consumer Drug Advertising?" [1], I noted that a two-year moratorium on direct-to-consumer (DTC) advertising of new drugs could "avoid another Vioxx tragedy, in which drug marketing got well ahead of the science." Contrary to Michael Heinley's complaint [2], I did not suggest that Merck acted improperly. That is a matter for the courts to decide. My only point was that obtaining more information on the risk:benefit ratio of Vioxx prior to mass marketing would have resulted in more informed prescribing.

From the time of its approval on May 21, 1999, until its voluntary withdrawal on September 30, 2004, Vioxx was prescribed to more than 80 million patients [3]. During much of that time, Merck conducted a vigorous and highly successful DTC marketing campaign. Whatever one believes about early signals of excess cardiovascular risk, by 2004 the results of the APPROVe trial had convinced everyone, including Merck, that Vioxx represented a potential threat to public health [4,5]. In the meantime, hundreds of thousands of patients sought and received Vioxx prescriptions as a result of watching DTC advertisements on television, and up to 16 per 1,000 may have suffered untimely myocardial infarctions or strokes as a result [3]. If there had been a DTC advertising moratorium in place beginning in 1999, the science of adverse-event monitoring might have had a fighting chance to catch up. ■

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