

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. ■

Jocelyn E. Mackie

Andrew D. Taylor

University of Toronto
Joint Centre for Bioethics
Toronto, Ontario, Canada

David L. Finegold

Keck Graduate Institute of Applied Life Sciences
Claremont, California, United States of America

Abdallah S. Daar

Peter A. Singer (E-mail: peter.singer@utoronto.ca)

University of Toronto
Joint Centre for Bioethics
Toronto, Ontario, Canada

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

Els Torrele, 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. ■

Els Torrelee

Catherine Royce

Robert Don

Ann-Marie Sevcsik (E-mail: amsevcsik@dndi.org)

Simon Croft

Drugs for Neglected Diseases Initiative
Geneva, Switzerland

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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 Torrelee 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 Torrelee 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. ■

Peter J. Hotez (E-mail: mtmpjh@gwumc.edu)

The George Washington University
Department of Microbiology and Tropical Medicine
Washington, District of Columbia, United States of America

David H. Molyneux

Liverpool School of Tropical Medicine
Lymphatic Filariasis Support Centre
Liverpool, United Kingdom

Alan Fenwick

Imperial College London
Infectious Disease Epidemiology
St. Mary's Campus
London, United Kingdom

Eric Ottesen

Emory University
Rollins School of Public Health
Atlanta, Georgia, United States of America

Sonia Ehrlich Sachs

Jeffrey D. Sachs

Columbia University
The Earth Institute
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 Torrele 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. ■

Lorenzo Savioli (E-mail: saviolil@who.int)

Dirk Engels

Denis Daumerie

Jean Jannin

Jorge Alvar

Kingsley Asiedu

Marc Gastellu-Etchegorry

Pere Simarro

World Health Organization
Department of Control of Neglected Tropical Diseases
Geneva, Switzerland

Silvio P. Mariotti

World Health Organization

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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>.

Michael Heinley (E-mail: michael_heinley@merck.com)

Merck & Company

Whitehouse Station, New Jersey, United States of America

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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. ■

Richard L. Kravitz (E-mail: rlkravitz@ucdavis.edu)

University of California Davis

Davis, California, United States of America

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