REVIEW ARTICLE

CURRENT CONCEPTS

Control of Neglected Tropical Diseases

Peter J. Hotez, M.D., Ph.D., David H. Molyneux, Ph.D., D.Sc., Alan Fenwick, Ph.D., Jacob Kumaresan, M.B., B.S., Ph.D., Sonia Ehrlich Sachs, M.D., Jeffrey D. Sachs, Ph.D., and Lorenzo Savioli, M.D.

THE NEGLECTED TROPICAL DISEASES ARE A GROUP OF 13 MAJOR DISABLING conditions that are among the most common chronic infections in the world's poorest people. A blueprint for the control or elimination of the seven most prevalent neglected tropical diseases — ascariasis, trichuriasis, hookworm infection, schistosomiasis, lymphatic filariasis, trachoma, and onchocerciasis — has been established by a group of private, public, and international organizations working together with pharmaceutical partners and national ministries of health. Through the newly established Global Network for Neglected Tropical Diseases, with updated guidelines for drug administration issued by the World Health Organization (WHO), partnerships are coordinating their activities in order to launch a more integrated assault on these conditions. If new resources are made available, as recommended by the Commission for Africa, a scaled-up approach to simple interventions could lead to sustainable decreases in poverty in some of the world's poorest countries. These decreases would represent a major success story for the United Nations Millennium Declaration.

From the Sabin Vaccine Institute, and George Washington University, Washington, DC (P.J.H.); Liverpool School of Tropical Medicine Lymphatic Filariasis Support Centre and the Global Alliance to Eliminate Lymphatic Filariasis, Liverpool, United Kingdom (D.H.M.); the Schistosomiasis Control Initiative, Imperial College London, London (A.F.); the International Trachoma Initiative, New York (J.K.); the Earth Institute at Columbia University, New York (S.E.S., J.D.S.); and the Department of Neglected Tropical Diseases, World Health Organization, Geneva (L.S.). Address reprint requests to Dr. Hotez at the Sabin Vaccine Institute and the Department of Microbiology, Immunology, and Tropical Medicine, George Washington University and Sabin Vaccine Institute, Ross Hall 736, 2300 Eye St., NW, Washington, DC 20037, or at mtmpjh@gwumc.edu.

N Engl J Med 2007;357:xxxx-xxxx.

"OTHER DISEASES"

The Millennium Declaration, adopted by world leaders at the United Nations in September 2000, establishes an ambitious set of eight millennium development goals to eliminate extreme poverty, hunger, and disease by 2015. The sixth goal, "to combat HIV–AIDS [human immunodeficiency virus infection–acquired immunodeficiency syndrome], malaria, and other diseases," specifically addresses the health and economic impact of infectious diseases. This goal has led to considerable and welcomed large-scale financial support through ambitious initiatives sponsored by the Group of Eight (G8) governments to fight HIV–AIDS and malaria. These initiatives include the U.S. President's Emergency Plan for AIDS Relief, the U.S. President's Malaria Initiative, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria.[1-5] However, programs to combat many of the "other diseases," particularly the neglected tropical diseases, have not yet benefited from such support.[1-5]

The 13 parasitic and bacterial infections known as the neglected tropical diseases include three soil-transmitted helminth infections (ascariasis, hookworm infection, and trichuriasis), lymphatic filariasis, onchocerciasis, dracunculiasis, schistosomiasis, Chagas' disease, human African trypanosomiasis, leishmaniasis, Buruli ulcer, leprosy, and trachoma.[2-4] An expanded list could include dengue fever, the treponematoses, leptospirosis, strongyloidiasis, foodborne trematodiases, neurocysticercosis, and scabies,[4] as well as other tropical infections. The parasitic and bacterial diseases identified as being neglected are among some of the most common infections in the

estimated 2.7 billion people who live on less than $2 per day. These diseases occur primarily in rural areas and in some poor urban settings of low-income countries in sub-Saharan Africa, Asia, and Latin America (Table 1). The neglected tropical diseases lead to long-term disability and poverty.[2-5,20] The poverty results from disfigurement or other sequelae of long-term illness, impaired childhood growth and development, adverse outcomes of pregnancy, and reduced productive capacity (Table 2).[3,21,22] These features contrast with those of emerging acute infections, such avian influenza, Ebola virus infection, and West Nile virus infection.[5]

In aggregate, the neglected tropical diseases cause approximately 534,000 deaths annually.[4] This substantial number of deaths is considerably less than that resulting from lower respiratory tract infections, diarrheal diseases, HIV–AIDS, or malaria. However, if metrics are applied to the disability and poverty associated with these diseases, the neglected tropical diseases can be shown to constitute large burdens on the health and economic development of low-income countries. In terms of disability-adjusted life-years, the neglected tropical diseases together rank closely with diarrheal diseases, ischemic heart disease, cerebrovascular diseases, malaria, and tuberculosis as

Table 1. The Major Neglected Tropical Diseases Ranked by Prevalence.*

Disease	Global Prevalence (millions)	Population at Risk	Regions of Highest Prevalence	Source
Ascariasis	807	4.2 billion	East Asia and Pacific Islands, sub-Saharan Africa, India, South Asia, China, Latin America and Caribbean	Bethony et al.,[6] de Silva et al.[7]
Trichuriasis	604	3.2 billion	Sub-Saharan Africa, East Asia and Pacific Islands, Latin America and Caribbean, India, South Asia	Bethony et al.,[6] de Silva et al.[7]
Hookworm infection	576	3.2 billion	Sub-Saharan Africa, East Asia and Pacific Islands, India, South Asia, Latin America and Caribbean	Bethony et al.,[6] de Silva et al.[7]
Schistosomiasis	207	779 million	Sub-Saharan Africa, Latin America and Caribbean	Steinmann et al.[8]
Lymphatic filariasis	120	1.3 billion	India, South Asia, East Asia and Pacific Islands, sub-Saharan Africa	Ottesen,[9] WHO[10]
Trachoma	84	590 million	Sub-Saharan Africa, Middle East and North Africa	International Trachoma Initiative,[11] Médecins sans Frontières[12]
Onchocerciasis	37	90 million	Sub-Saharan Africa, Latin America and Caribbean	Basáñez et al.[13]
Leishmaniasis	12	350 million	India, South Asia, sub-Saharan Africa, Latin America and Caribbean	Desjeux[14]
Chagas' disease	8–9	25 million	Latin America and Caribbean	WHO[15]
Leprosy	0.4	ND	India, sub-Saharan Africa, Latin America and Caribbean	International Federation of Anti-Leprosy Associations[16]
Human African trypanosomiasis	0.3	60 million	Sub-Saharan Africa	Févre et al.[17]
Dracunculiasis	0.01	ND	Sub-Saharan Africa	Carter Center[18]
Buruli ulcer	ND	ND	Sub-Saharan Africa	Global Buruli Ulcer Initiative[19]

* ND denotes not determined.

Table 2. Major Characteristics of the Most Prevalent Neglected Tropical Diseases.

Disease	Vulnerable Populations	Clinical Manifestations and associated Disabilities	Primary Interventions	Weaknesses of Current Approaches
Ascariasis	School-age children	Malnutrition, growth and cognitive delays	Single-dose albendazole or mebendazole (1–3 times/yr)	Limited access to essential medicines
Trichuriasis	School-age children	Inflammatory bowel disease, growth and cognitive delays	Single-dose albendazole or mebendazole (1–3 times/yr)	Limited access to essential medicines
Hookworm infection	School-age children, women of reproductive age	Anemia, malnutrition, growth and cognitive delays, poor pregnancy outcome	Single-dose albendazole or mebendazole (1–3 times/yr)	Limited access to essential medicines, low efficacy (mebendazole), rapid reinfection, drug resistance
Schistosomiasis	School-age children, women of reproductive age	Hematuria and urogenital disease, intestinal and liver fibrosis, growth and cognitive delays	Single-dose praziquantel	Limited access to essential medicines, potential drug resistance
Lymphatic filariasis	Adolescents, adults	Adenolymphangitis, lymphedema, hydrocele	Single-dose ivermectin or diethylcarbamazine (plus albendazole)	Limited access to essential medicines
Trachoma	Children, adults (especially women)	Trachomatous folliculitis and inflammation, trichiasis, blindness	Surgery, azithromycin, face washing, environmental control	Limited access to essential medicines, and public health interventions
Onchocerciasis	Adults	Onchocerca, skin disease, blindness	Single-dose ivermectin	Limited access to essential medicines, potential drug resistance
Leishmaniasis	Children, adults	Cutaneous and mucocutaneous disease, kala-azar	Case detection and management, antimonials, amphotericin B, pentamidine, miltefosine, vector control	Limited access to essential medicines, drug toxicity, drug resistance
Chagas' disease	Children, adults	Cardiomyopathy, megacolon, megaesophagous	Case detection and management, nifurtimox, benznidazole, vector control	Inadequate vector coverage, limited access to essential medicines, poor efficacy
Leprosy	Adults	Lepromatous leprosy, tuberculoid leprosy	Multidrug therapy: rifampicin, clofazimine, dapsone	Limited access to essential medicines
Human African trypanosomiasis	All ages	Sleeping sickness	Case detection and management, pentamidine, suramin, melarsoprol, eflornithine, vector control	Inadequate surveillance, limited access to essential medicines, drug toxicity
Dracunculiasis	All ages	Disfiguring ulcer, secondary bacterial infection	Provisions for safe water, water filtration, larvicides for copepod control, case containment and surveillance	Limited access to public health control measures in Ghana and Sudan
Buruli ulcer	Children	Disfiguring ulcer	Antibiotics, débridement and skin grafting	No preventive methods available, limited access to essential surgical interventions

being among the most important health problems in the developing world (Fig. 1).[4,5] In addition, the effect of the neglected tropical diseases on worker productivity causes annual losses of billions of dollars.[24-27]

PREVENTIVE CHEMOTHERAPY

Through the expanded use of mass drug administration as well as targeted treatments, we now have the opportunity to control or even eliminate some of the most important neglected tropical diseases in terms of prevalence and disease burden.[1-5,20,28-39] The use of mass drug administration for the control of neglected tropical diseases, or preventive chemotherapy, was pioneered in China. In that country, the prolonged and targeted use of salt containing diethylcarbamazine resulted in the elimination of lymphatic filariasis as a public health problem,[30] and the widespread use of praziquantel and other measures (including snail control and health education) is leading to the control of schistosomiasis.[31] Egypt has also succeeded in reducing the prevalence of lymphatic filariasis and schistosomiasis and their associated morbidity.[30,35]

Such successes have laid a foundation for the establishment of international partnerships to control or eliminate these infections.[1] A critical step occurred in the late 1980s, when Merck created the first partnership to control a neglected tropical disease; this partnership was formed to deliver donated ivermectin to treat onchocerciasis.[3] To date, more than 300 million treatments have been provided, initially through the Onchocerciasis Control Program and subsequently through the African Programme for Onchocerciasis Control and the Onchocerciasis Elimination Program for the Americas.[32] In addition, Pfizer has partnered with the International Trachoma Initiative to donate azithromycin as part of a comprehensive program to eliminate trachoma,[33] and GlaxoSmithKline is working with the WHO, Merck, and the Global Alliance to Eliminate Lymphatic Filariasis to add donated albendazole to mass-drug-administration regimens of either diethylcarbamazine or ivermectin.[34] These efforts have resulted in the near elimination of lymphatic filariasis as a public health problem in Egypt, Samoa, and Zanzibar[30,34,35] and of trachoma as a public health problem in Morocco.[36] Similarly, using donated generic formulations of praziquantel from Med-

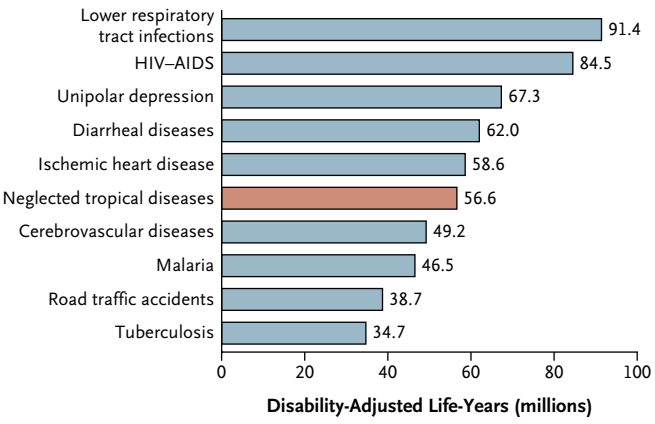

Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.

The number of years lost to disability and premature death (disability-adjusted life-years) for the 13 major neglected tropical diseases were calculated according to a method we described previously.[4] The disability-adjusted life-years for the other conditions are based on data from the World Health Organization.[23] The ranking of disease burdens is based on data in Hotez.[5]

Pharm and other organizations, the Schistosomiasis Control Initiative and African health ministries have significantly reduced the disease burden of urinary and intestinal schistosomiasis in schoolchildren in six countries in East and West Africa,[37,38] and the widespread use of albendazole and mebendazole is having an effect on school performance and the disease burden of soil-transmitted helminth infections,[6] especially ascariasis and trichuriasis, among children. Dracunculiasis is on the verge of being eradicated.[18,40,41] Many of these large-scale programs are being conducted in response to several World Health Assembly resolutions calling for the global control or elimination of the neglected tropical diseases with the greatest disease burden as a public health problem by the year 2020 or sooner.[42,43]

INTEGRATION OF CONTROL

Although great progress has been made in several countries,[1-5,20,30-37] it is unclear whether existing financial resources and global political commitments are sufficient to reach the World Health Assembly's ambitious goals. Instead, it is likely that enhanced efforts will be required to expand global coverage and integrate measures to control the neglected tropical diseases. These efforts will in-

volve harmonizing and coordinating the activities of the partnerships devoted to the control or elimination of the seven most prevalent neglected tropical diseases and linking them with national health ministries and the WHO. The rationale for integrating preventive chemotherapy measures is based on the observation that there is extensive geographic overlap and coendemicity among these seven diseases (Fig. 2).[2-5,20]

Populations in such regions are infected with several different parasites and have multiple neglected tropical diseases simultaneously.[2-5,20,46] Therefore, the delivery of a rapid-impact package of drugs is beneficial. The rapid-impact package is so named because the drugs can be quickly deployed by community-based distributors, with rapid reductions in disabilities, improvement in well-being, and, in some cases, interruption of disease transmission. This package includes a combination of four of six drugs: albendazole or mebendazole, praziquantel, ivermectin or diethylcarbamazine, and azithromycin.[2] Through coordination of the partnerships to control neglected tropical disease and the public health infrastructures they create, these drugs can be delivered at an estimated cost savings of 26 to 47%.[43] Because four of the six rapid-impact drugs are donated, the projected average total cost is as low as $0.40 to $0.79 per person per year in sub-Saharan Africa.[2,43,47] Thus, an entire at-risk population of approximately 500 million could be treated for $400 million or less annually. Such estimates are a fraction of the annual costs of treatments with antiretroviral agents or directly observed multidrug therapy for tuberculosis.[2] Moreover, the most prevalent neglected tropical diseases, especially hookworm infection and schistosomiasis, are frequently endemic with malaria and HIV–AIDS,[4,48-51] and they have considerable coexisting or synergistic effects.[49-51] Therefore, preventive chemotherapy could have an important collateral effect.[4]

To catalyze the integration of measures in order to control neglected tropical diseases, a group of partnerships that are committed to combatting the seven most prevalent of these diseases are cooperating with each other in the Global Network for Neglected Tropical Diseases. This network operates according to WHO treatment guidelines

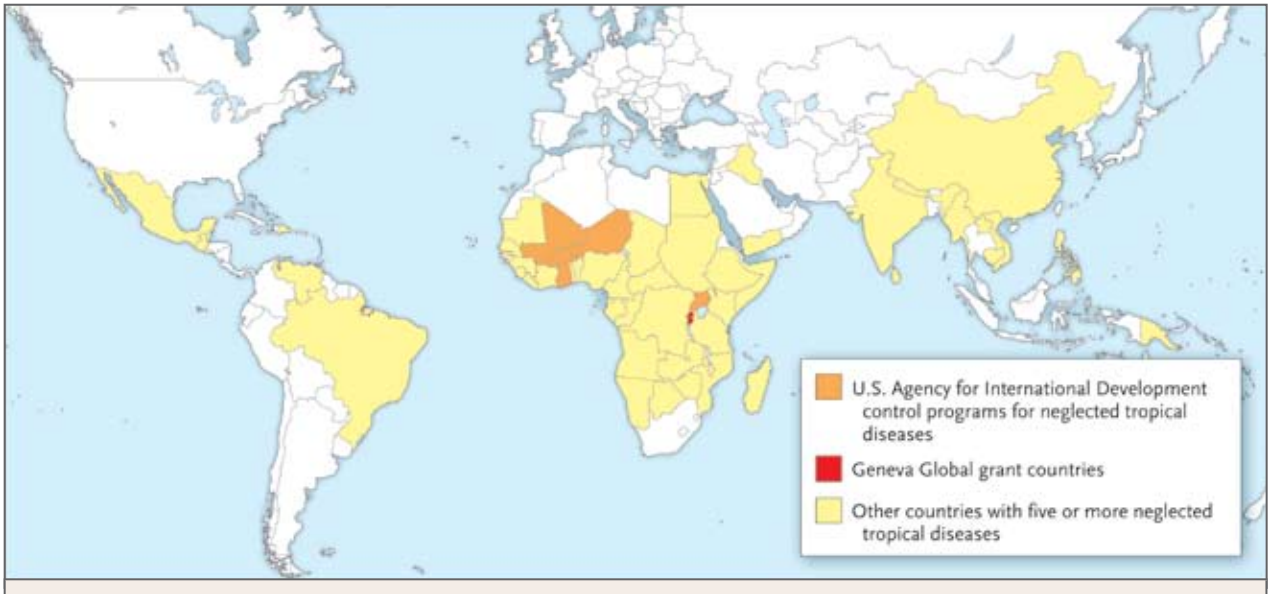

Figure 2. Nations with Five, Six, or Seven Neglected Tropical Diseases to be Targeted for Integrated Preventive Chemotherapy.

Of the 56 nations to be targeted with a rapid-impact package, shown in yellow, 37 are located in the World Health Organization (WHO) African region, 5 in the WHO region of the Americas, 5 in the WHO eastern Mediterranean region, 3 in the WHO Southeast Asia region, and 6 in the WHO Western Pacific region. Data regarding the occurrence of lymphatic filariasis, onchocerciasis, schistosomiasis, and the three soil-transmitted helminth infections are derived from the WHO.[44] Data regarding the occurrence of trachoma are derived from the WHO.[45] The five nations shown in orange — Burkina Faso, Ghana, Mali, Niger, and Uganda — will be targeted for integrated control in national programs through the support of the U.S. Agency for International Development Neglected Tropical Disease Control Program beginning this year. The two nations shown in red — Rwanda and Burundi — will be targeted for integrated control in national programs through the support of Geneva Global beginning this year.

and algorithms and with vector management and other environmental control measures (Table 3).[44]

Integrated control of these diseases at the national level will require substantial financial resources to expand coverage of community-based mass drug administration and targeted treatments. The U.S. Agency for International Development recently announced a 5-year, $100 million award to provide preventive chemotherapy for 40 million people, and Geneva Global has committed $8.8 million for preventive chemotherapy in Rwanda and Burundi (Fig. 2). The Bill and Melinda Gates Foundation has awarded $47 million to address critically important questions regarding operational research for effective integration. However, these awards constitute a fraction of the overall costs required to scale up programs in sub-Saharan Africa and elsewhere. It is estimated that a 5-year program to control or eliminate the major neglected tropical diseases in sub-Saharan Africa could cost approximately $1 billion to $2 billion. An estimated $2 to $9 per disability-adjusted life-year (i.e., per life year lost to disability or premature death) would be averted for deworming,[52] with up to 47% in cost savings through integration.[43] This cost for the coordinated control or elimination of the seven most prevalent neglected tropical diseases represents a relatively inexpensive but potent public health intervention. It also represents a priority investment in human capital and a reduction in global poverty.[53]

THE NEED FOR NEW TOOLS OF CONTROL

Despite its enormous benefits, preventive chemotherapy with the rapid-impact package will not affect the three neglected tropical diseases with the highest rates of death — Chagas' disease, human African trypanosomiasis, and visceral leishmaniasis. Strategies to control these diseases are based on surveillance, early diagnosis and treatment, and vector control.[17,54,55] These criteria for effective control present challenges because of the lack of appropriate diagnostic tools and safe drugs. To date, the greatest successes in the control of Chagas' disease and human African trypanosomiasis have occurred as a result of vector control. Vector control has dramatically reduced the transmission of Chagas' disease in five South American countries.[54] The transmission of human African trypanosomiasis has been reduced through the use of simple, impregnated tsetse traps that supplement surveillance and diagnostic measures.[17]

Although strategies to control and eliminate human African trypanosomiasis, leishmaniasis, and Chagas' disease are available,[56,57] ultimately, success will almost certainly depend on access to new and cost-effective products for improved control. However, in the absence of commercial markets for drugs for neglected tropical diseases, the pipeline of new drugs for these diseases has virtually dried up during the past three decades.[58] In response to this crisis, partnerships have been established to address product development for neglected tropical diseases. These partnerships for product development are either exploiting newly completed genome projects for protozoan parasites[59] in order to identify potential drug targets for high-throughput screening or taking more traditional approaches to drug development and clinical testing.[60] As a result of these activities, several new antiprotozoan drugs are under development for Chagas' disease, leishmaniasis, and human African trypanosomiasis, including miltefosine, paromomycin, sitamaquine, imiquimod, a pentamidine analogue known as DB289, and a vinyl sulfone known as K777, as well as combinations such as nifurtimox–eflornithine and paromomycin combined with antimonial agents.[55,60-62] Highly efficacious drugs for the treatment of Buruli ulcer have not been developed.

Even with regard to the proposed rapid-impact package, challenges remain. These challenges include integrated and rapid mapping of the seven targeted diseases; careful assessment of safety, compatibility, and compliance; integrated monitoring and evaluation that are compatible with the capacity of the health system, on the one hand, and with scientific need, on the other; cost-effectiveness and cost–benefit studies; and analyses to determine the effect of integrated control on health systems.[4,52] In countries such as Burkina Faso, Ghana, Niger, Nigeria, Togo, and Uganda, where integrated efforts to control neglected tropical diseases are under way, additional challenges have included limited access to drugs such as generic praziquantel (which is not yet donated on a large scale) and albendazole (which is currently donated only for the control of lymphatic filariasis), insufficient or fragmented funding, and a need for increased support from nongovernmental development organizations. In addition, African health ministries are beginning to struggle

Table 3. General Guidelines for Preventive Chemotherapy for the Seven Most Prevalent Neglected Tropical Diseases.*

Disease	Drug and Dosage	Threshold for Implementation	Eligible Population	Frequency of Administration
Lymphatic filariasis (in areas where onchocerciasis is also endemic)	Ivermectin, according to person's height (with use of a tablet pole for children) plus albendazole, 400 g	≥1% prevalence	Entire at-risk population except pregnant women, lactating women in the first week after birth, and children shorter than 90 cm (15 kg)	Once/yr
Lymphatic filariasis (in areas where onchocerciasis is not also endemic)	Diethylcarbamazine, 6 mg/kg of body weight (with age as criterion for dose) plus albendazole, 400 mg	≥1% prevalence	Entire at-risk population except pregnant women and children younger than 2 yr	Once/yr
Onchocerciasis	Ivermectin, according to person's height (with use of a tablet pole for children)	≥40% prevalence or ≥20% palpable nodules	Entire at-risk population except pregnant women, lactating women in the first week after birth, and children shorter than 90 cm (15 kg)	Once/yr
Schistosomiasis	Praziquantel, 40 mg/kg (with use of a tablet pole for children)	Presence of infection	School-age children and special-risk populations; exclude children younger than 4 yr	<10% community prevalence, twice during primary school; 10–50% prevalence, once/every 2 yr; >50% prevalence, every yr
Soil-transmitted helminth infections (ascariasis, hookworm infection, and trichuriasis)	Albendazole, 400 mg, or mebendazole, 500 mg	≥20% infection; once/yr for <50%, twice/yr for >50%	Preschool and school-age children, women of childbearing age, and adults at high risk; exclude children in first year of life and pregnant women in first trimester	Once or twice/yr depending on community prevalence (once/yr for low-risk communities with 20–50% prevalence; twice/yr for high-risk communities with ≥50% prevalence)
Trachoma	Azithromycin, 20 mg/kg (with use of a tablet pole for children) to a maximum dose of 1 g in adults	Active trachoma prevalence >5% in 1–9 yr at district level	Entire at-risk population except children ≤6 mo of age	Once/yr

* Data are from the World Health Organization.[44] A height pole shows the correct number of tablets according to a child's height as measured on the pole.

with the implementation of integrated control of neglected tropical diseases in the face of the demands of other disease-control programs, including G8-funded initiatives for HIV–AIDS, tuberculosis, and malaria. It is expected that these issues will pose particular challenges in areas that have experienced conflict and in fragile nation states.

Studies to determine the rates of post-treatment reinfection and to detect the emergence of anthelmintic drug resistance will be essential for monitoring and evaluation.[4,5] The possibility that resistance has already emerged is a serious concern, especially for the benzimidazole anthelmintic agents (e.g., albendazole and mebendazole) and ivermectin,[63,64] and without a new generation of tools for disease control and appropriate environmental control measures, the risk of repeating past mistakes remains.[3,4,65] Therefore, it is important to commit resources to the improvement of available diagnostic tests and surveillance tools, especially for lymphatic filariasis and onchocerciasis,[32,66] and to develop and test new, promising anthelmintic drugs such as tribendimidine for soil-transmitted helminth infections,[67,68] a new macrofilaricide, and antiwolbachia-based therapies for the elimination of onchocerciasis.[13] Although they are still experimental, medical therapies targeting wolbachia bacterial endosymbionts of filarial parasites offer new approaches to the reduction of parasite reproductive capacity and parasite-induced inflammation.[69] However, the best prospect for the sustainable control of the neglected tropical diseases is the development of vaccines.[21] Several vaccines against neglected tropical diseases, including vaccines against hookworm infection,[68] schistosomiasis,[70] and leishmaniasis,[71] are in phase 1 and phase 2 clinical trials by partnerships for product development.[4,21] In principle, it is possible to develop new "antipoverty vaccines" against all of the neglected tropical diseases[21]; these would be used as "vaccine-linked chemotherapy" alongside drugs in a comprehensive treatment and prevention framework.[72]

Drug and vaccine manufacturers from so-called innovative developing countries are assisting partnerships in their efforts to develop new products to control neglected tropical diseases. These middle-income countries, such as Brazil, China, and India, have the technical and industrial capacities to produce new drugs, vaccines, and diagnostic tests.[3,73,74] Enhanced support by the G8 governments would accelerate innovation and essential health research for the developing world.[75]

PUBLIC POLICY FOR INTEGRATED CONTROL

The High-Level Forum on the Health Millenium Development Goals has described partnership activities as best practices for moving forward a global agenda. Tackling neglected tropical diseases represents one of the "quickest wins" in terms of reducing the disease burden as well as developing new drugs and vaccines.[2] There are additional opportunities to bundle the control of neglected tropical diseases with the control of malaria and HIV–AIDS.[76] Such measures could exploit the geographic overlap of these conditions[48] as well as potential synergies in public health control, with resultant cost savings.[50,77] For example, a recent study showed that the administration of drugs for neglected tropical diseases by community distributors resulted in a ninefold increase in the distribution of antimalaria bed nets.[77]

Through partnerships to control the neglected tropical diseases and the Global Network for Neglected Tropical Diseases, a comprehensive framework is in place to provide preventive chemotherapy packages and to develop, test, and distribute a new generation of tools to control these diseases. This framework is an important model in disease control and poverty reduction. It also addresses important themes related to equity and ethics in developing countries[78] and critical elements of humanitarian assistance; these themes could be incorporated into a larger foreign-policy framework.[5] According to the United Nations Special Rapporteur on the right to the highest attainable standard of health, an effective and integrated program to control neglected tropical diseases strengthens local health systems, fosters community involvement in health, helps to ensure monitoring and accountability, and serves to destigmatize these conditions by dispelling myths and misconceptions about them through evidence-based information and education.[78] The global community is now well positioned to control or eliminate neglected tropical diseases in developing countries and to link these efforts to programs to combat HIV–AIDS and malaria.

Dr. Hotez reports being director of the Human Hookworm Vaccine Initiative, which receives support from the Bill and Melinda Gates Foundation; an inventor on an international patent application (PCT/US02/33106) for hookworm vaccine; and presi-

dent of the Sabin Vaccine Institute, which receives support for activities unrelated to control of neglected tropical diseases from Merck, Wyeth, and GlaxoSmithKline. Dr. Molyneux reports being director of the Global Alliance to Eliminate Lymphatic Filariasis and the Lymphatic Filariasis Support Centre, which receives support from the United Kingdom Department for International Development and GlaxoSmithKline, and participating in the Mectizan Expert Committee/Albendazole Coordination meetings, which receive support from the Mectizan Donation Program supported by Merck. Dr. Fenwick reports being director of the Schistosomiasis Control Initiative, which receives support from the Bill and Melinda Gates Foundation. All of the authors except Dr. Savioli report being member partners of the Global Network for Neglected Tropical Diseases, which receives funding from Geneva Global. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Molyneux DH. "Neglected" diseases but unrecognized successes — challenges and opportunities for infectious disease control. Lancet 2004;364:380-3.
2. Molyneux DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med 2005;2(11):e336.
3. Hotez PJ, Ottesen E, Fenwick A, Molyneux D. The neglected tropical diseases: the ancient afflictions of stigma and poverty and the prospects for their control and elimination. Adv Exp Biol Med 2006; 582:22-33.
4. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, malaria. PLoS Med 2006;3(5):e102.
5. Hotez PJ. The "biblical diseases" and U.S. vaccine diplomacy. Brown World Aff J 2006;12:247-58.
6. Bethony J, Brooker S, Albonico M, et al. Soil-transmitted helminth infections: ascariasis, and hookworm. Lancet 2006; 367:1521-32.
7. de Silva NR, Brooker S, Hotez PJ, Montresor A, Engels D, Savioli L. Soil-transmitted helminth infections: updating the global picture. Trends Parasitol 2003;19:547-51.
8. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: sytematic review, meta-analysis, and estimates of people at risk. Lancet Infect Dis 2006;6:411-25.
9. Ottesen EA. Lymphatic filariasis: treatment, control and elimination. Adv Parasitol 2006;61:395-441.
10. World Health Organization. Global programme to eliminate lymphatic filariasis. WHO Wkly Epidemiol 2006;81:221-32. (Accessed July 20, 2007, at http://www.who.int/WER.)
11. International Trachoma Initiative home page. (Accessed July 20, 2007, at http://www.trachoma.org.)
12. Médecins sans Frontieres. Campaign for access to essential medicines. (Accessed July 20, 2007, at http://www.accessmed-msf.org.)
13. Basáñez M-G, Pion SDS, Churcher TS, Breitling LP, Little MP, Boussinesq M. River blindness: a success story under threat? PLoS Med 2006;3(9):3371.
14. Desjeux P. The increase in risk factors for leishmaniasis worldwide. Trans R Soc Trop Med Hyg 2001;95:239-43.
15. WHO Expert Committee. Control of Chagas disease. World Health Organ Tech Rep Ser 2002;905:i-vi, 1-109.
16. International Federation of Anti-Leprosy Associations (ILEP) home page. (Accessed July 20, 2007, at http://www.ilep.org.uk.)
17. Févre EM, Picozzi K, Jannin J, Welburn SC, Maudlin I. Human African trypanosomiasis: epidemiology and control. Adv Parasitol 2006;61:167-221.
18. The Carter Center home page. (Accessed July 20, 2007, at http://www.cartercenter.org.)
19. Global Buruli Ulcer Initiative (GBUI) Geneva: World Health Organization. (Accessed July 20, 2007, at http://www.who.int/buruli/en.)
20. Lammie PJ, Fenwick A, Utzinger J. A blueprint for success: integration of neglected tropical disease control programmes. Trends Parasitol 2006;22:313-21.
21. Hotez PJ, Ferris MT. The antipoverty vaccines. Vaccine 2006;24:5787-99.
22. Alvar J, Yactayo S, Bern C. Leishmaniasis and poverty. Trends Parasitol 2006; 22:552-7.
23. Annex Table 3: burden of disease in DALYs by cause, sex and mortality stratum in WHO regions, estimates for 2002. In: The world health report 2004 — changing history. Geneva: World Health Organization, 2004.
24. Remme JHF, Feenstra P, Lever PR, et al. Tropical diseases targeted for elimination: Chagas disease, lymphatic filariasis, onchocerciasis, and leprosy. In: Jamison DT, Breman JG, Measham AR, et al., eds. Disease control priorities in developing countries. 2nd ed. Oxford, England: Oxford University Press, 2006:433-50.
25. Bleakley H. Disease and development: evidence from hookworm eradication in the American South. Q J Econ 2007;122:73-117.
26. Ramaiah KD, Das PK, Michael E, Guyatt H. The economic burden of lymphatic filariasis in India. Parasitol Today 2000;16:251-3.
27. Frick KD, Hanson CL, Jacobson GA. Global burden of trachoma and economics of disease. Am J Trop Med Hyg 2003; 69:5 Suppl:1-10.
28. Engels D, Savioli L. Public health strategies for schistosomiasis control. In: Secor WE, Colley DG, eds. World class parasites: Vol. X, schistosomiasis. New York: Springer, 2005:207-22.
29. Savioli L, Montresor A, Albonico M. Control strategies. In: Holland CV, Kennedy MW, eds. World class parasites: Vol. II, the geohelminths, ascaris, trichuris, and hookworm. New York: Springer, 2002: 25-37.
30. Molyneux DH. Elimination of transmission of lymphatic filariasis in Egypt. Lancet 2006;367:966-8.
31. Utzinger J, Zhou XN, Chen MG, Bergquist R. Conquering schistosomiasis in China: the long march. Acta Trop 2005; 96:69-96.
32. Boatin BA, Richards FO Jr. Control of onchocerciasis. Adv Parasitol 2006;61:349-94.
33. Kumaresan J. Can blinding trachoma be eliminated by 20/20? Eye 2005;19:1067-73.
34. Mohammed KA, Molyneux DH, Albonico M, Rio F. Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme. Trends Parasitol 2006;22: 340-4.
35. Ramzy RMR, El Setouhy M, Helmy H, et al. Effect of yearly mass drug administration with diethylcarbamazine and albendazole on bancroftian filariasis in Egypt: a comprehensive assessment. Lancet 2006;367:992-9. [Erratum, Lancet 2006; 367:1980.]
36. Levine R, What Works Working Group. Controlling trachoma in Morocco. In: Millions saved: proven successes in global health. Washington, DC: Center for Global Development, 2004:83-9.
37. Kabatereine NB, Fleming FM, Nyandindi U, Mwanza JCL, Blair L. The control of schistosomiasis and soil-transmitted helminths in East Africa. Trends Parasitol 2006;22:332-9.
38. Fenwick A. New initiatives against Africa's worms. Trans R Soc Trop Med Hyg 2006;100:200-7.
39. World Health Organization. Global leprosy situation, 2005. Wkly Epidemiol Rec 2005;80:289-95.
40. World Health Organization. Dracunculiasis eradication. Wkly Epidemiol Rec 2006;81:173-83.
41. Ruiz-Tiben E, Hopkins DR. Dracunculiasis (Guinea worm disease) eradication. Adv Parasitol 2006;61:275-309.
42. World Health Organization. Deworming for health and development: report of

the Third Global Meeting of the Partners for Parasite Control. Geneva: World Health Organization, 2005.
43. Brady MA, Hooper PJ, Ottesen EA. Projected benefits from integrating NTD programs in sub-Saharan Africa. Trends Parasitol 2006;22:285-91.
44. Preventive chemotherapy in human helminthiasis. Geneva: World Health Organization, 2006.
45. WHO global health atlas. Geneva: World Health Organization. (Accessed July xx, 2007, at http://globalatlas.who/int.)
46. Raso G, Luginbuhl A, Adjoua CA, et al. Multiple parasite infections and their relationship to self-reported morbidity in a community of rural Côte d'Ivoire. Int J Epidemiol 2004;33:1092-102.
47. Fenwick A, Molyneux D, Nantulya V. Achieving the Millennium Development Goals. Lancet 2005;365:1029-30.
48. Brooker S, Clements AC, Hotez PJ, et al. The co-distribution of *Plasmodium falciparum* and hookworm among African schoolchildren. Malar J 2006;5:99.
49. Druilhe P, Tall A, Sokhna C. Worms can worsen malaria: towards a new means to roll back malaria? Trends Parasitol 2005;21:359-62.
50. Kjetland EF, Ndhlovu PD, Gorno E, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. AIDS 2006;20:593-600.
51. Borkow G, Bentwich Z. HIV and helminth co-infection: is de-worming necessary? Parasite Immunol 2006;28:605-12.
52. Laxminarayan R, Mills AJ, Breman JG, et al. Advancement of global health: key messages from the Disease Control Priorities Project. Lancet 2006;367:1193-208.
53. Canning D. Priority setting and the 'neglected' tropical diseases. Trans R Soc Trop Med Hyg 2006;100:499-504.
54. Yamagata Y, Nakagawa J. Control of Chagas disease. Adv Parasitol 2006;61:129-65.
55. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. Adv Parasitol 2006;61:223-74.
56. World Health Organization. Human African trypanosomiasis (sleeping sickness): epidemiological update. Wkly Epidemiol Rec 2006;81:71-80.
57. Pan American Health Organization. XVth Meeting of the Southern Cone Intergovernmental Commision to Eliminate *Triatoma infestans* and Interrupt the Transmission of Transfusional Trypanosomiasis (INCOSUR-Chagas), Brasília, Brazil, 6–9 June 2006. (Accessed July 20, 2007, athttp://www.paho.org/English/AD/DPC/CD/dch-incosur-xv.htm.)
58. Chirac P, Torreele E. Global framework on essential health R&D. Lancet 2006; 367:1560-1.
59. El Sayed NM, Myler PJ, Blandin G, et al. Comparative genomics of trypanosomatid parasitic protozoa. Science 2005; 309:404-9.
60. Renslo AR, McKerrow JH. Drug discovery and development for neglected parasitic diseases. Nat Chem Biol 2006;2: 701-10.
61. Croft SL, Barrett MP, Urbina JA. Chemotherapy of trypanosomiases and leishmaniasis. Trends Parasitol 2005;21:508-12.
62. Croft SL, Seifert K, Yardley V. Current scenario of drug development for leishmaniasis. Indian J Med Res 2006;123:399-410.
63. Albonico M, Engels D, Savioli L. Monitoring drug efficacy and early detection of drug resistance in human soil-transmitted nematodes: a pressing public health agenda for helminth control. Int J Parasitol 2004;34:1205-10.
64. Osei-Atweneboana MY, Eng JKL, Boakye DA, Gyapong JO, Prichard RK. Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin after 19 years of treatment in endemic communities in Ghana. Lancet 2007;369: 2021-9.
65. Hotez PJ. The National Institutes of Health roadmap and the developing world. J Investig Med 2004;52:246-7.
66. Weil GJ, Ramzy RMR. Diagnostic tools for filariasis elimination programs. Trends Parasitol 2007;23:78-82.
67. Xiao SH, Hui-Ming W, Tanner M, Utzinger J, Chong W. Tribendimidine: a promising, safe and broad-spectrum anthelmintic agent from China. Acta Trop 2005; 94:1-14.
68. Hotez PJ, Bethony J, Bottazzi ME, Brooker S, Diemert D, Loukas A. New technologies for the control of human hookworm infection. Trends Parasitol 2006;22: 327-31.
69. Taylor MJ, Bandi C, Hoerauf A. *Wolbachia* bacterial endosymbionts of filarial nematodes. Adv Parasitol 2005;60:247-86.
70. Capron A, Riveau G, Capron M, Trottein F. Schistosomes: the road from host-parasite interactions to vaccines in clinica trials. Trends Parasitol 2005;21:143-9.
71. Coler RN, Reed SG. Second-generation vaccines against leishmaniasis. Trends Parasitol 2005;21:244-9.
72. Bergquist NR, Leonardo LR, Mitchell GF. Vaccine-linked chemotherapy: can schistosomiasis control benefit from an integrated approach? Trends Parasitol 2005; 21:112-7.
73. Morel CM, Acharya T, Broun D, et al. Health innovation networks to help developing countries address neglected diseases. Science 2005;309:401-4.
74. Rabinovich NR. The renaissance in global health. Trends Parasitol 2006;22: 277.
75. Fifty-Ninth World Health Assembly. Agenda item 11.11: Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action, 27 May 2006. Geneva: World Health Organization. (Accessed July 20, 2007, at http://www.who.int/mediacentre/events/2006/wha59/en/index.html.)
76. Sachs JD, Hotez PJ. Fighting tropical diseases. Science 2006;311:1521.
77. Blackburn BG, Eigege A, Gotau H, et al. Successful integration of insecticide-treated bed net distribution with mass drug administration in central Nigeria. Am J Trop Med Hyg 2006;75:650-5.
78. Hunt P. The human right to the highest attainable standard to health: new opportunities and challenges. Trans R Soc Trop Med Hyg 2006;100:603-7.