Turning Neglected Tropical Diseases Into Forgotten Maladies

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Turning Neglected Tropical Diseases Into Forgotten Maladies

Concerted efforts—from mass drug administration to nondrug interventions—could conquer several of these diseases of poverty.

by Philip Musgrove and Peter J. Hotez

ABSTRACT: Because they afflict mostly poor people in poor countries, killing relatively few compared to the many who suffer from severe chronic disabilities, a large cluster of infections deserve the label of neglected tropical diseases (NTDs). That is changing as these diseases’ enormous health, educational, and economic toll is better understood, including how they interact with HIV/AIDS, malaria, and other illnesses. Several NTDs could be controlled or even eliminated within a decade, using integrated, highly cost-effective mass drug administration programs together with nondrug interventions. Research is needed to provide additional means of control for these conditions and make elimination feasible for still others. [Health Aff (Millwood). 2009;28(6):1691–706]

Among the eight United Nations Millennium Development Goals (MDGs) for sustainable poverty reduction, only MDG 6, “to combat HIV/AIDS, malaria and other diseases,” mentions infectious diseases. Two of three specific targets for MDG 6 focus on HIV/AIDS; the third is to “have halted by 2015 and begun to reverse the incidence of malaria and other major diseases.” Malaria qualifies among the “big three” for the Global Fund to Fight AIDS, Tuberculosis, and Malaria.

However, more than thirty “other diseases” collectively cause as much health burden in many countries as do one or more of these big three. Some are among the world’s most widespread illnesses both geographically and by the number of people affected.

These neglected tropical diseases (NTDs) are heterogeneous in many ways, but they share several common features including the degree of neglect. Several are caused by helminths—worms or flukes—and others by protozoa, bacteria, fungi, or viruses. A few can pass directly from person to person; others are transmitted...
by the bites of insects or through contaminated soil or water (some species of snails can also be vectors). These are typically ancient diseases, not emerging infections like severe acute respiratory syndrome (SARS), AIDS, or avian influenza. They afflict mostly poor people in low- or middle-income countries, and they promote poverty by damaging children’s cognitive development and adults’ physical productivity. Although some can kill, they mostly cause chronic disability, including blindness. Several disfigure and stigmatize sufferers. Together, the effects often match Thomas Hobbes’ description of life in the state of nature—“solitary, poor, nasty, brutish and short.” This situation need not continue. For several of these neglected diseases, near-universal control, or even elimination, is possible at low cost—and should be actively pursued.

**Diseases, Pathogens, Prevalence, And Health Damage**

Several NTDs are especially important to tackle because of high current prevalence and disease burden, or because they could be controlled or eliminated through simple measures such as mass drug administration. Exhibit 1 shows modes of transmission, the type of health damage, and estimated prevalence for fourteen NTDs. Dengue, a viral disease spread by mosquitoes, differs from the others in not causing chronic disease. Rather, it causes acute illness, including a sudden high fever. People either recover or risk death from a hemorrhagic form that causes bleeding and death from shock. (Thus, Exhibit 1 shows incidence [new

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**EXHIBIT 1**

Fourteen Neglected Tropical Diseases: Mode Of Transmission, Health Damage, And Estimated Prevalence

<table>
<thead>
<tr>
<th>Disease and mode of transmission</th>
<th>Health damage</th>
<th>Estimated prevalence (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmitted by insect bites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ordinary acute case</td>
<td>Fever, pain, other symptoms</td>
<td>Incidence estimated at 50/year</td>
</tr>
<tr>
<td>Hemorrhagic fever</td>
<td>Frequently fatal</td>
<td>Incidence estimated at 0.075/year</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>Pancytopenia usually fatal if untreated</td>
<td>12 infected</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>Disfigurement, mutilation; risk of death from secondary complications</td>
<td>No estimate available</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Ulceration, disfigurement</td>
<td>2.2 severe disease</td>
</tr>
<tr>
<td>Human African trypanosomiasis (HAT, sleeping sickness)</td>
<td>Central nervous system damage; fatal if untreated</td>
<td>0.05–0.07</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>40% risk of cardiac or digestive complications, including risk of death from heart problems</td>
<td>8–9 infected, 1.2–2.8 severe disease</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Inflammation, secondary bacterial infection, swelling of lymphatics and tissues, including elephantiasis</td>
<td>128</td>
</tr>
<tr>
<td>Onchocerciasis (river blindness)</td>
<td>Severe skin diseases with itching; severe eye disease causing blindness</td>
<td>37 infected, 0.35 blindness, 0.60 low vision, 1.35 itching</td>
</tr>
</tbody>
</table>
Many estimates are uncertain and probably often too low, reflecting the diseases’ neglected status. For the major three soil-transmitted helminth infections, estimates distinguish people with very high worm loads—a fraction of those infected, who suffer most of the illness. According to Andrew Hall and colleagues, “almost one in every two people in the developing world is infected with one or more types of intestinal nematode worms.” That makes these among the most common chronic human infections. Lymphatic filariasis and schistosomiasis, for example, each infect more than 100 million.

Most neglected diseases occur primarily in Africa, Asia, and tropical regions of the Americas, with lower prevalence in the Middle East. Only one, Chagas disease, is exclusive to the Americas. (Some NTDs and related neglected infections of pov-
erty also occur among the poorest in the United States and Europe, as noted in the paper by Peter Hotez in this issue. Extreme poverty is universally the most important determinant. This is true both for individuals and for countries too poor to fund control efforts fully, still less to undertake needed research.

Many NTD elimination efforts are among the well-documented long-term successes in global health. Progress against four diseases—Chagas; lymphatic filariasis, the infection that causes elephantiasis; onchocerciasis, the infection that causes river blindness; and leprosy—places them in a category known as “targeted for elimination.” But prevalence is still in the millions for the first three diseases and in the hundreds of thousands for leprosy. Another neglected disease, dracunculiasis (Guinea worm disease), may soon be eradicated. Trachoma, a bacterial infection causing blindness, has been eliminated in Morocco and other places. Three other diseases—dengue, leishmaniasis (a protozoan infection causing skin sores and life-threatening disease), and human African trypanosomiasis (HAT, or sleeping sickness)—are often treated as “lacking adequate control measures” and are far from elimination (although in West Africa, HAT was nearly eliminated a century ago through case detection and drug treatment). Soil-transmitted helminth infections and schistosomiasis are too widespread to consider eliminating soon, except for schistosomiasis in the Caribbean and in China.

Varieties Of Neglect

If some diseases are close to elimination, how can they be “neglected”? Control efforts can be inadequate in several ways relative to the corresponding health burden. The most basic is lack of research into the pathogen’s biology and the body’s response. This matters even when treatments are highly effective, as for two major helminthic diseases (ascariasis, a parasitic infection, and schistosomiasis, caused by parasitic worms) and trachoma. A second kind of neglect is inadequate effort to develop diagnostics, drugs, or vaccines, including second-line medications aimed at overcoming resistance to current drugs. There may also be a lack of sufficient effort to develop drugs that lack toxic side effects or that entail lower costs or treatment time. (Adel Mahmoud and Elias Zerhouni discuss these deficiencies elsewhere in this issue.) Absent a drug or vaccine for dengue, for example, only mosquito control is possible. The available drugs for Chagas disease, leishmaniasis, and sleeping sickness, meanwhile, are expensive or toxic. All varieties of neglect reflect failure to take these diseases seriously at the national or international policy level.

The word “neglect” is also relative. The Special Program for Research and Training in Tropical Diseases of the World Health Organization (WHO) has operated for three decades, starting with seven NTDs and malaria. Control of mosquito vectors transmitting yellow fever began much earlier and was largely successful in the Americas. Although a safe and effective yellow fever vaccine exists, that disease remains a major health problem in much of Africa and parts of the Americas.
All NTDs are neglected compared to HIV/AIDS, TB, and malaria, if judged by funding relative to disease burden. Confinement to the poorest people in predominantly rural tropical areas also means that NTDs do not now threaten rich countries as HIV/AIDS and TB do. But richer countries, notably the United States, formerly suffered from some of these diseases—especially hookworm—and succeeded in eliminating them by the mid-twentieth century (as Margaret Humphreys explains in another paper in this issue).

Disease Burden, Economic Damage, And Effects On Other Diseases

No NTD appears among the twenty leading causes of death or disability-adjusted life-years (DALYs) for 2002. Mortality is difficult to estimate. Schistosomiasis may lead to death attributed to bladder cancer, and the underlying cause for many deaths attributed to anemia may be an NTD. Uncertainty about prevalence and incidence means uncertainty about years of life lost to disability (YLD), with ranges of 2:1 or 3:1 between high and low estimates. As NTDs have gained increased attention, estimated burdens from hookworm and other soil-transmitted helminth infections, schistosomiasis, and leishmaniasis have been criticized as too low. Disability weights may undervalue chronic morbidities, such as anemia, malnutrition, pain, and inflammation. They may not always take into account more severe forms of these diseases. Cases are also underreported; as few as one case may be reported for every forty actual instances of disease.

A full revision of burden estimates for 2005 is under way. Meanwhile, estimates for 2002 attribute to twelve NTDs together at least 162,000 deaths annually and 14.8 million years lost to disability, causing a total burden of 19.0 million DALYs (Exhibit 2). Other estimates attribute to ascariasis alone at least 10,500 deaths annually—three or more times the WHO number. Deaths attributable to schistosomiasis number as high as 280,000 per year. Taking the high estimates for several NTDs would make them look as damaging as malaria; one estimate for the thirteen major NTDs indicates up to 56.6 million DALYs lost annually and 534,000 deaths.

Nonhealth losses. Estimates in Exhibit 2 measure only ill health; they omit other effects of death and disability, including economic losses. Critics have attacked the WHO assessment of burden for this reason. They also contend that because sufferers are often poor, even the disability captured in DALYs is understated, because it is harder for the poor to cope with.

NTDs cause economic burdens through two main channels. They reduce adult physical productivity via anemia and other disabilities. And by impairing children's cognitive development, they impede school attendance and learning and thus reduce future earnings. Children acquire chronic soil-transmitted helminth infections while very young, so they lose economic potential early and suffer it for decades. Lymphatic filariasis sufferers in India are 27 percent less productive.
than uninfected people and are numerous enough to reduce gross national product (GNP) per capita by 0.63 percent. If NTDs were not concentrated among the poorest, their economic impact would look appreciably larger.

Economic losses from some NTDs extend beyond the effects on individuals. Onchocerciasis provides the most dramatic example. Heavily infested areas are sometimes abandoned because the risk of blindness affects as much as 10 percent of the population. Drugs and larvicide spraying controlled the disease in ten African countries by 2002, allowing 25 million hectares of fertile land to be resettled and farmed.

### Effects on other diseases

Some NTDs may cause further damage by facilitating transmission of other diseases, exacerbating their clinical course, or undermining control measures. Just as sexually transmitted diseases may promote HIV transmission, female genital schistosomiasis infection increases HIV risk threefold. Preventing schistosomiasis might also prevent much HIV/AIDS, at very low cost.

#### EXHIBIT 2

**Burden Of Twelve Neglected Tropical Diseases: Deaths, Years Of Life Lost (YLL), Years Lost To Disability (YLD), Total Disability-Adjusted Life Years (DALYs) (All In Thousands), And Disability Weights, 2002**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths</th>
<th>YLL</th>
<th>YLD</th>
<th>DALYs</th>
<th>Disability weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue hemorrhagic fever</td>
<td>19</td>
<td>609</td>
<td>6</td>
<td>616</td>
<td>0.210</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>51</td>
<td>1,569</td>
<td>521</td>
<td>2,090</td>
<td>0.243 visceral; 0.023 cutaneous</td>
</tr>
<tr>
<td>Human African trypanosomiasis (sleeping sickness)</td>
<td>48</td>
<td>1,429</td>
<td>96</td>
<td>1,525</td>
<td>0.191 acute phase of illness</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>14</td>
<td>185</td>
<td>481</td>
<td>667</td>
<td>0.062-0.270 cardiomyopathy</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>&lt;1</td>
<td>10</td>
<td>5,768</td>
<td>5,777</td>
<td>0.073 hydrocele; 0.106-0.116 lymphedema</td>
</tr>
<tr>
<td>Onchocerciasis (river blindness)</td>
<td>0</td>
<td>0</td>
<td>484</td>
<td>484</td>
<td>0.600 blindness; 0.260 low vision</td>
</tr>
<tr>
<td>Ascariasis (roundworm)</td>
<td>3</td>
<td>121</td>
<td>1,696</td>
<td>1,817</td>
<td>0.006-0.024 cognitive impairment; 0.463 intestinal blockage</td>
</tr>
<tr>
<td>Trichuriasis (whipworm)</td>
<td>3</td>
<td>106</td>
<td>900</td>
<td>10,060</td>
<td>0.006-0.024 cognitive impairment; 0.116 dysentery</td>
</tr>
<tr>
<td>Hookworm</td>
<td>3</td>
<td>51</td>
<td>922</td>
<td>973</td>
<td>0.024 anemia or cognitive impairment</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>15</td>
<td>171</td>
<td>1,531</td>
<td>1,702</td>
<td>0.006</td>
</tr>
<tr>
<td>Trachoma</td>
<td>&lt;1</td>
<td>3</td>
<td>2,326</td>
<td>2,329</td>
<td>0.600 blindness; 0.278 low vision</td>
</tr>
<tr>
<td>Leprosy</td>
<td>6</td>
<td>86</td>
<td>113</td>
<td>198</td>
<td>0.152 disabling</td>
</tr>
</tbody>
</table>


**NOTES:** YLL and YLD include the effects of discounting at 3 percent per year; YLD includes the disability weights. Estimates for ascariasis, trichuriasis, and hookworm refer only to the effects of high-intensity infection (large worm load).

- Difference in the weight for low vision between onchocerciasis and trachoma is unexplained (Mathers CD, personal communication, 2009 Jun 8).
- Corrected from Note 16.
- Does not include mortality from bladder cancer, cirrhosis, or colon cancer that may be related to schistosomiasis.
Schistosomiasis, hookworm, and some other NTDs cause anemia, as does malaria. Coinfection with malaria in the same individual—a common occurrence in sub-Saharan Africa—causes additive, severe anemia, especially among children and pregnant women.\textsuperscript{24, 28} Some evidence indicates that soil-transmitted helminth infections, schistosomiasis, and lymphatic filariasis may suppress immune functioning, promoting susceptibility to several diseases, including TB and malaria as well as HIV/AIDS.\textsuperscript{29} In Senegal, deworming for soil-transmitted helminth infections provides as much protection from malaria as the sickle-cell trait does.\textsuperscript{30}

Pregnant women infected with NTDs can pass parasite antigens to the fetus, affecting the child’s immune system so that vaccination is less effective.\textsuperscript{31} This may help explain why polio vaccination in Uttar Pradesh and Bihar, Indian states with poor sanitation and high adult worm burdens, requires many more doses than usual to achieve immunity.\textsuperscript{32} These indirect effects on other diseases have only recently been seen as potentially significant.

**Control Measures, Costs, And Results**

Before effective drugs existed, vector-borne diseases were controlled in several ways. These included spraying insecticides to kill mosquitoes, the “kissing bugs” that transmit the parasite causing Chagas disease, blackflies, sandflies, and tsetse flies; collecting adult tsetse flies in baited traps; and eliminating breeding sites, especially near rivers or in urban areas. These remain the only interventions against dengue and are still important for Chagas disease, leishmaniasis, and human African trypanosomiasis. In contrast, onchocerciasis can be controlled by a drug, ivermectin, which prevents blindness and can interrupt transmission. Ivermectin is also effective against lymphatic filariasis. Four other drugs—albendazole and mebendazole for soil-transmitted helminth infections, albendazole together with diethylcarbamazine or ivermectin for lymphatic filariasis, and praziquantel for schistosomiasis—are comparably effective at deworming infected individuals. Azithromycin, an antibiotic, is effective for killing the trachoma bacterium. All are cheap to produce, and except for diethylcarbamazine, control programs still are relatively low cost because pharmaceutical makers donate enough to meet up to 100 percent of the need for some drugs.\textsuperscript{25} However, other drugs, including praziquantel and albendazole, are only partially donated for schistosomiasis and soil-transmitted helminth infections, respectively. Praziquantel shortage is particularly serious.

Five aspects to controlling NTDs with drugs are important, as follows.

- **Geographic concentration.** First, soil-transmitted helminth infections, schistosomiasis, lymphatic filariasis, and onchocerciasis are usually so concentrated in specific areas as to justify treating everyone, infected or not. The extra cost is offset by not having to test each person. Representative diagnostic sampling can identify the population infected or at high risk.

- **Treatment reduces transmission.** Second, mass drug administration pro-
vides large spillover effects by reducing transmission. Deworming all of the children in one school or village reduces infection in nearby untreated schools or villages. Analyses of only the treated population underestimate the benefits from control programs.33

■ Reinfecion after treatment. Lymphatic filariasis, trachoma, onchocerciasis, and leprosy have been eliminated in several places, and eventual global elimination is projected for some of these diseases.25, 34 However, while drugs can control illness, they often fail to eliminate a disease because of rapid reinfection. Other, nondrug interventions are also needed. For Chagas disease this means vector control and blood screening; preventing trachoma transmission usually requires the complete SAFE intervention (surgery for advanced eyelid damage, antibiotics, face washing, and environmental sanitation).35 Safe and abundant water supply and disposal of feces are required for long-run control of soil- and water-transmitted diseases, since “without a change in defecation habits, periodic deworming cannot attain a stable reduction in transmission.”23 Water matters when it is too scarce for washing (trachoma), carries an intermediate disease host (schistosomiasis, guinea worm), or comes from open sources where insect vectors breed (dengue, onchocerciasis, trypanosomiasis). Improved water supply plus sanitation can reduce schistosomiasis and guinea worm morbidity by three-fourths and that of trachoma by one-quarter.36

■ Long horizons. Fourth, elimination requires a long-term program. Mass drug administration is needed only once or twice a year, but it takes two to six treatment rounds to reduce lymphatic filariasis transmission significantly. For onchocerciasis, elimination is considered possible over periods of ten to fifteen years. Vector control for Chagas disease required more than twenty years to eliminate the disease in four of eighteen endemic provinces in Argentina.9 A schistosomiasis control program in Egypt reduced prevalence from 50 percent to 10 percent over fourteen years.22 If control efforts stop once a program appears successful, schistosomiasis prevalence can rebound within a decade, as occurred in Mali.37 Vector reinestation has occurred with dengue in the Americas and sleeping sickness in Africa.11 This last is particularly unfortunate. Tsetse flies breed slowly and are susceptible to ultra-low doses of insecticide, so eliminating them over large areas is possible, as with the vectors of onchocerciasis and Chagas disease.

■ Value for money. Fifth, given adequate control measures, NTD interventions are cost-effective or yield high benefit-cost ratios. Exhibit 3 summarizes estimates for thirteen diseases, with the three soil-transmitted helminths combined because they are often co-endemic and respond to the same drugs. Mass drug administration is extremely cost-effective for lymphatic filariasis, soil-transmitted helminth infections, onchocerciasis, and schistosomiasis, even when treating some uninfected or mildly infected people. This reflects the low cost of drugs—typically only a few cents a dose—so that even with distribution costs, people can be treated for one dollar or less. Individual treatment with drugs is cost-effective for visceral leishmaniasis and the second stage of sleeping sickness, because death is very likely oth-
erwise. This offsets the high treatment cost, including hospitalization. No comparable analysis exists for dengue hemorrhagic fever, which also is life-threatening.

Antibiotics alone are not always cost-effective for trachoma because of rapid re-infection if the intervention does not reduce transmission by flies. Surgery for people with advanced effects of trachoma who can still see is also cost-effective.\textsuperscript{38} Elimination with the full SAFE intervention is probably more cost-effective than indicated by individual costs and results.\textsuperscript{39} Drug management of leprosy has the same range of costs per DALY.

### Exhibit 3

Estimates of cost-effectiveness (dollars per disability-adjusted life-year, or DALY), benefit/cost ratios, or internal rates of return for interventions against selected neglected tropical diseases (NTDs)

<table>
<thead>
<tr>
<th>Disease and intervention</th>
<th>Cost per DALY (US$)</th>
<th>Benefit-cost ratio</th>
<th>Internal rate of return (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue: prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental management</td>
<td>1,992</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insecticides</td>
<td>3,139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue: case management</td>
<td>587</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral: case management</td>
<td>18.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human African trypanosomiasis</td>
<td>4–22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chagas disease: treatment</td>
<td>100 (child &lt;5)</td>
<td>260–362</td>
<td>30–60</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td></td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Mass drug administration</td>
<td>4–29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diethylcarbamazine-fortified salt</td>
<td>1–46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vector control</td>
<td>48–303</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass drug administration</td>
<td>7</td>
<td>17 (APOCH)</td>
<td>20 (OCP)</td>
</tr>
<tr>
<td>Vector control</td>
<td>7</td>
<td>17 (APOCH)</td>
<td>20 (OCP)</td>
</tr>
<tr>
<td>Soil-transmitted helminths: mass drug administration</td>
<td>3.14 (school-age children)</td>
<td>&gt;100</td>
<td></td>
</tr>
<tr>
<td>Schistosomiasis: one drug</td>
<td>3.36–6.92</td>
<td>8–19</td>
<td></td>
</tr>
<tr>
<td>Two-drug combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dracunculiasis (Guinea worm)\textsuperscript{a}</td>
<td>&gt;100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery for trichiasis</td>
<td>4–82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics alone</td>
<td>&gt;4,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leprosy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case detection and management</td>
<td>38</td>
<td></td>
<td>1–110</td>
</tr>
<tr>
<td>Prevention of disability</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Sources:** Notes 7, 9, 11, 22, 30, and 33 in text. Also, see below.

**Notes:** APOCH is the African Program of Onchocerciasis Control. OCP is the Onchocerciasis Control Program.


\textsuperscript{b} Not adequately defined in the only study undertaken.
Vector control gave very high returns on investment in the Onchocerciasis Control Program in West Africa, 1975–1987; adding treatment with ivermectin brought the program to a successful close in 2002. The current African Program of Onchocerciasis Control began in 1995, using ivermectin in nineteen countries outside the Onchocerciasis Control Program area where vector control was infeasible, and has given similar returns. The Onchocerciasis Elimination Program for the Americas, begun in 1992, has used ivermectin to interrupt transmission in several highly endemic areas; regional elimination by 2012 looks feasible. Vector control has also succeeded against Chagas disease and lymphatic filariasis, at a somewhat higher cost per DALY. Dengue control through insecticides or environmental management pays off economically much less well because vector control cannot be targeted to the life-threatening cases; most cases prevented would be brief and contribute little to burden.

Some NTDs offer opportunities for major health improvements and substantial long-run economic gains at low cost, sometimes among the most cost-effective of any health interventions. The current reevaluation of disease burdens may make these estimates look even better. Moreover, most analyses cited in Exhibit 3 consider diseases separately. Integrating control efforts could yield large health gains and cost savings.

**Partnerships And Integration**

Lymphatic filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminth infections, and trachoma are starting to lose the “N” from NTD. Specific preventive chemotherapy programs for their control have been created, treating the population at risk once or twice yearly. Exhibit 4 describes each program’s target population, drug regimen and goal. (These programs and the roles of pharmaceutical companies in them are discussed further by Ken Gustavsen in this issue.) In sub-Saharan Africa, soil-transmitted helminth infections and lymphatic filariasis have the largest target population: At least 60 percent of the target population for each disease is estimated to live in the lymphatic filariasis endemic zone. Four or five diseases, counting the soil-transmitted helminths as one, occur in thirty or more countries in Africa (and fifty-six countries worldwide). Integrating programs for all of these diseases makes sense in Africa, especially because two drugs for lymphatic filariasis (ivermectin and albendazole) also are effective against intestinal worms and onchocerciasis.

Implementing mass drug administration separately for each disease in sub-Saharan Africa in 2006 cost an estimated $110 million. Starting with the cost of a lymphatic filariasis control program, it is expected that additional diseases
EXHIBIT 4

Preventive Drug Therapy Programs For Selected Neglected Tropical Diseases (NTDs): Populations At Risk, Drug Regimens, And Goals

<table>
<thead>
<tr>
<th>Disease and program(s)</th>
<th>Endemic countries</th>
<th>Population at risk (millions)</th>
<th>Drug(s) and annual frequency</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic filariasis: Global Programme to Eliminate Lymphatic Filariasis</td>
<td>83: Africa, Asia, Americas, Western Pacific</td>
<td>1,303</td>
<td>Albendazole+ ivermectin (1)</td>
<td>Elimination as a public health problem by 2020</td>
</tr>
<tr>
<td>Onchocerciasis: Mectizan/ivermectin donation program; African Program for Onchocerciasis Control; Onchocerciasis Elimination Program for the Americas</td>
<td>37: 30 in Africa, Yemen, 6 in the Americas</td>
<td>87</td>
<td>Ivermectin (1)</td>
<td>Community-based sustainable treatment by 2010, moderate or high intensity (Africa); elimination (Americas)</td>
</tr>
<tr>
<td>Schistosomiasis: Partners for Parasite Control; Schistosomiasis Control Initiative</td>
<td>78: Africa, Middle East, Americas, Pacific</td>
<td>779</td>
<td>Praziquantel (1)</td>
<td>Regular treatment of 75% of at-risk school-age population by 2010</td>
</tr>
<tr>
<td>Soil-transmitted helminths: Partners for Parasite Control</td>
<td>Most countries: Africa, China, S and SE Asia, tropical Americas</td>
<td>1,264 (preschool and school-age children), 4,200 total</td>
<td>Albendazole + mebendazole (2)</td>
<td>Regular treatment of 75% of at-risk school-age population by 2010</td>
</tr>
<tr>
<td>Trachoma: International Trachoma Initiative</td>
<td>55: Africa, Asia, pockets in Americas and Australia</td>
<td>460-590</td>
<td>Azithromycin (1)</td>
<td>Elimination of blindness as a public health problem by 2020</td>
</tr>
</tbody>
</table>

SOURCES: Endemic countries: Note 45 in text. Population at risk: Note 57 in text, Table 3. Drug regimens: Note 34 in text.
transmission, and incorporating NTD control with that for malaria increases the adoption of nets.\textsuperscript{47} Proposals have been made since 2005 for bundling control for soil-transmitted helminth infections, schistosomiasis, lymphatic filariasis, and onchocerciasis into a “rapid-impact package” of anthelminthic drugs together with azithromycin for trachoma\textsuperscript{24, 29} or even linking the rapid-impact package with the control of malaria because it would yield both improved health and monetary savings within a year or two. Reductions in long-term disability would accrue only gradually.

**New Initiatives**

Through large-scale funding from the U.S. and U.K. governments, integrated NTD control efforts are under way in sub-Saharan Africa. These include programs in nine African nations supported by the U.S. Agency for International Development,\textsuperscript{48} with plans ultimately to increase the U.S. commitment for global NTD control to $350 million, as well as a £50 million (US$83 million) commitment made in 2008 from the U.K. Department for International Development.\textsuperscript{49} U.S. government programs are also under way in Bangladesh, Nepal, and Haiti. NTD control is also a potential element of U.S. foreign policy because these (and other) diseases are linked to war or internal conflict.\textsuperscript{50}

To further promote integration efforts, several public-private partnerships (PPPs) allied in 2006 to form a Global Network for Neglected Tropical Diseases. In 2009 the Bill and Melinda Gates Foundation provided support to this Global Network to launch an innovative financing mechanism for integrated NTD control and elimination. The initiative has created specialized regional hubs based in Latin America and the Caribbean, sub-Saharan Africa, and Asia.\textsuperscript{25} The creation of regional hubs presumes that approaches for NTD control and elimination will vary depending on each region’s unique infections, their vectors, and disease ecologies. (Ricardo Bitran and colleagues, in this issue, provide details on strategic approaches to NTD control in Latin American and the Caribbean.)\textsuperscript{51}

**What Is Still Neglected?**

Despite the recent surge of attention and research findings, and remarkable successes against several NTDs, neglect still poses important obstacles. Proposals for expanded or integrated programs are slow to be adopted, even with low costs and potentially large health improvements and economic gains. Perhaps this is not surprising, considering how long it took to reach accord on a global subsidy for artemisinin combination therapy for malaria—even more urgent because of the great risk of resistance to monotherapy.\textsuperscript{52} To reach even the mass chemotherapy goals described in Exhibit 4 will require increased supplies of drugs and improved systems for delivering them.\textsuperscript{7}

At the current level of effort, reaching near-universal coverage for all NTDs, especially for soil-transmitted helminth infections and schistosomiasis, may require
another decade or more. Rapid-impact measures and integrated control efforts can and should be expanded to reach all the “bottom billion” of the world’s population infected by NTDs. Few actions could accomplish as much, with comparable resources, for those people’s welfare.

Some expanded efforts may eliminate one or more diseases as a public health problem—keeping prevalence low and preventing death or severe disability. But by themselves, they will not always remove the disease or the need to maintain mass drug administration. Improved sanitation together with clean water will take much longer to achieve. And NTDs are not the only reason to promote safe water and waste disposal, since reductions in diarrheal incidence and deaths are likely to be equally important outcomes.36

**Research And Development**

Research and development (R&D) is needed on four fronts: for drugs where no cheap, effective ones exist; for backup drugs as protection against the development of resistance, which expanded mass drug administration may promote; for vaccines wherever feasible, particularly for hookworm, schistosomiasis and dengue; and for better understanding of the nonbiological obstacles to effective delivery.7 Some of this research can be undertaken collaboratively by the most affected countries (as Sarah Frew and colleagues describe in this issue).53

Compared to R&D spending on the “big three” diseases, all NTDs together account for a very limited share of resources. Of an estimated total of $2.56 billion in 2007, HIV/AIDS, TB, and malaria received more than three-fourths. Dengue accounted for 3.2 percent, and all helminths, including some not considered here, for 2.02 percent. Leprosy, Buruli ulcer, and trachoma together got 0.38 percent.34

The better news is that Chagas disease, leishmaniasis, and trypanosomiasis—for which drug research is especially needed—received 4.89 percent, or $125 million. The Tropical Disease Research program at the WHO received $32.7 million, and the Drugs for Neglected Diseases Initiative, $28.5 million.34 The published data do not distinguish basic research from development of drugs, diagnostics, or vaccines; they separate about $300 million for multiple diseases or expenditures that cannot be identified as to disease. Delivery technologies and devices received only $2.52 million—barely 0.1 percent.

Numerous proposals exist for stimulating more research. These include priority-review vouchers,55 advance-purchase agreements for vaccines,56 which could also apply to drugs; “patent pools” for sharing intellectual property with researchers or developers,57 and tax credits for early-stage research before human trials (see Gerard Anderson’s paper in this issue).38, 59 Several product development partnerships (PDPs) have been launched with the support of the Bill & Melinda Gates Foundation.42 None of these funding mechanisms is specific to NTDs, but they are as suitable for these diseases as for other health problems.

Control of NTDs faces many uncertainties: the payoff to research, the likelihood
of drug resistance, the pace of development to provide the nondrug inputs needed for disease elimination, and the willingness of governments and donors to continue supporting current effective interventions. But none of these uncertainties justifies continued neglect. In the short to medium term, most of these diseases present opportunities as cost-effective and as wide-reaching as any in global public health, particularly if control efforts are integrated across diseases and sustained long enough. In the longer run, several could finally be transformed from neglected diseases to forgotten maladies—a true advance for humankind.

NOTES
17. Humphreys M. How four once common diseases were eliminated from the American South. Health Aff (Millwood). 2009;28(6):1734–44.


39. Benderley BL. The end of blinding trachoma among the world’s poor is in sight [Internet]. Washington (DC): Disease Control Priorities Project; [cited 2009 Sep 15]. Available from: http://dcp2.org/features/75


