International Journal of Biomedical and Health Sciences
Vol. 9, No. 4, December 31, 2013
Printed in Nigeria

0794-4748/2013 $5.00 + 0.00

http://www.asopah.org

IJBHS 9402

Tropical Diseases Targeted for Elimination: Chagas Disease, Lymphatic Filariasis, Onchocerciasis, and Leprosy

Jan H. F. Remme, Piet Feenstra, P. R. Lever, Andre C. Medici, Chantal M. Morel, Mounkaila Noma, K. D. Ramaiah, Frank Richards, A. Seketeli, Gabriel Schmunis, W. H. van Brakel, and Anna Vassall.

Introduction

Tropical diseases are infectious diseases that are found predominantly in the tropics, where ecological and socioeconomic conditions facilitate their propagation. Climatic, social, and economic factors create environmental conditions that facilitate transmission, and the lack of resources prevents affected populations from obtaining effective prevention and adequate care. Tropical diseases are diseases of the poor, and investments in control and research to develop more effective intervention tools and strategies have been minimal (Gwatkin, Guillot, and Heuveline 1999; Remme and others 2002). For some, however, effective intervention methods have been developed, and successful control has been achieved.

This article focuses on four tropical diseases—Chagas disease, lymphatic filariasis (LF), onchocerciasis, and leprosy—for which effective means of control are available. All four diseases are targeted for elimination as a public health problem. Control strategies are being implemented at scale and have already achieved a major reduction in the burden of disease, and the causative agent has even been eliminated in some previously endemic areas. Those successes have not come easily, and much remains to be done to ensure complete and sustained control of the diseases.

Disease Characteristics and Transmission

Chagas disease, LF, onchocerciasis, and leprosy are all parasitic infections, but their causative agents, modes of transmission, and geographic distribution differ. Chagas disease is caused by infection with a protozoan, leprosy by a mycobacterium, and LF and onchocerciasis by filarial nematodes. Three are vector-borne diseases, but leprosy is transmitted directly from person to person. Chagas disease occurs only in the Americas, onchocerciasis is found predominantly in Africa, and LF and leprosy occur in all tropical regions.

Chagas Disease

Chagas disease—also known as American trypanosomiasis—is a zoonotic disease caused by the protozoan hemoflagellate *Trypanosoma cruzi* that is mainly transmitted by large, bloodsucking, reduviid bugs of the subfamily *Triatominae* (known as *kissing bugs*). Infection with this blood parasite has been recorded in more than 150 species of 24 families of domestic

and wild mammals as well as in humans. In the vertebrate host, *T. cruzi* usually infects macrophage, muscle, and nerve cells.

Human infection with *T. cruzi* most commonly originates through contact of broken skin or mucosa with the excretion of infected insect vectors. The incubation period ranges from 7 to 15 days, leading to the acute phase of infection—characterized by patent parasitemia—which may last up to four weeks. The acute phase may be without obvious symptoms. Romaña's sign—that is, uniocular, bipalpebral edema with regional lymphadenopathy—is diagnostic of the acute infection but occurs in less than 5 percent of infections.

If a recent infection is untreated, the individual will remain infected for life. After an asymptomatic period of 10 years or more, some 10 to 40 percent of those infected will develop cardiac or digestive complications that are characteristic of the chronic stage of the disease. In chagasic myocardiopathy the most common symptoms are dyspnea and arrhythmias. Electrocardiographic alterations can occur, such as right bundle branch block, left anterior hemiblock, or both, which may require a pacemaker implant. Apical aneurisms are also typical of advanced chagasic cardiopathy, which may rupture on excessive exercise, leading to sudden death. Chagas disease can also involve intestinal complications characterized by severe dilatations of parts of the digestive tract known as megasyndromes. Megaesophagus and megacolon are the most common. Symptoms of megaesophagus are dysphagia and odinophagia and subsequent malnutrition. Chagasic megacolon is characterized by constipation and meteorism. As a result of colon distension and contractions, abdominal pain is frequent, and fecalomas are a complication.

More than 120 species of *Triatominae* and three transmission cycles are recognized. The domestic cycle, responsible for maintaining infection in humans, occurs mostly in rural or periurban areas where houses have adobe walls and thatched roofs. Humans, dogs, cats, and in some countries guinea pigs are the main parasite reservoirs in this cycle. The vector lives and multiplies in cracks in the walls, holes in the roof, under and behind furniture and pictures, and so on. The sylvatic cycle involves sylvatic triatomine bugs that become infected and in turn infect rodents, marsupials, and other wild animals. The third is the peridomestic cycle in which mammals participate (domestic rodents, marsupials, livestock, cats, dogs) by moving freely in and out of human dwellings, and sylvatic bugs are attracted to lights in houses and to food. This peridomestic cycle acts as a link between the domestic and sylvatic cycles. Occasionally, infected sylvatic species of *Triatominae* fly into houses and contribute to transmission either by feeding and defecating on the people or their domestic animals or (indirectly) by contaminating food and drink in which the parasites can survive. In the Amazon region, cases of acute Chagas disease have been associated with sylvatic *Triatominae* contaminating sugarcane or fruit juice.

Transmission by blood transfusion is the second-most common way of acquiring *T. cruzi* infection. The true incidence of infection through blood transfusion is unknown, because most cases are not recognized. In transfusionally acquired *T. cruzi* infection, the incubation period is 30 or more days, and the most common symptoms are fever, general lymph node enlargement, and splenomegaly (Schmunis and others 2001).

Transplacental transmission of *T. cruzi* can occur, and estimates indicate that 5 percent of newborns born to chagasic mothers will become infected. Less common routes of transmission are by transplantation with an infected organ or, more rarely, through contaminated food or infection in the laboratory (WHO 2002a).

Lymphatic Filariasis

LF is caused by species of nematode parasites—*Wuchereria bancrofti*, *Brugia malayi,* and *Brugia timori*—and is transmitted by mosquitoes (WHO 2002c). The adult filarial parasites live in the lymphatics of humans. After mating, each female worm produces several thousand offspring, microfilariae, during its lifetime. The microfilariae are found in humans' internal organs and appear in peripheral blood at times that coincide with the vector's biting activity. The biting mosquito ingests the microfilariae along with the blood meal, and they develop into infective-stage larvae in 10 to 12 days. When an infective mosquito bites a human, the infective-stage larvae are transmitted to the human host and develop into the adult stage in about one year. The adult parasites live 5 to 10 years, of which the fecund life span is 4 to 6 years. Several hundreds to thousands of infective mosquito bites are necessary to establish infection.

Of the three parasite species, *W. bancrofti* accounts for nearly 90 percent of LF infections worldwide. *B. malayi* is prevalent only in some parts of South and Southeast Asia, and *B. timori* is found only in Indonesia. Several species of *Culex, Anopheles*, *Aedes*, and *Mansonia* mosquitoes are involved in the transmission of LF. *C. quinquefasciatus* is the major vector in Africa, Asia, and South America and transmits nocturnally periodic *W. bancrofti*. Among anophelines, *An. gambiae* and *An. funestus* play a significant role in Africa. Several *Aedes* species, particularly *Ae. polynesiensis*, are the major vectors in the South Pacific islands, where diurnally subperiodic *W. bancrofti* is common. *B. malayi* is primarily transmitted by *Mansonia* and *Anopheles* species.

Infected people can harbor microfilaremia without overt clinical manifestations. The disease process is determined primarily by living adult worms, inflammatory responses caused by the death of adult worms, and secondary bacterial infections. The inflammatory response begins with the death of or damage to adult worms, which leads to host reaction and acute filarial lymphangitis. A heavy worm burden and the presence of worms in the scrotal area precipitate the development of hydrocele, chyluria, chylocele, and lymph scrotum. Lymphatic dysfunction caused by dilatation of the lymphatic vessels makes the patient more prone to repeated secondary bacterial infection, which precipitates lymphedema and elephantiasis. Microfilariae play an important role in the pathogenesis of tropical pulmonary eosinophilia (Dreyer and others 2000).

Onchocerciasis

Onchocerciasis is an infection with the filarial parasite *Onchocerca volvulus*. The main complications are severe eye disease that can lead to blindness and severe skin disease with unsightly lesions and intense itching (WHO 1995a). *O. volvulus* is transmitted by vector blackflies of the genus *Simulium*, whose larvae and pupae develop in rapidly flowing, well-oxygenated streams and rivers. As a result, onchocerciasis is often known as *river blindness*. The most important vectors are members of the *S. damnosum* complex in Africa and the Middle East and *S. neavei* in parts of East Africa. Of the many vectors in the Americas, the most important are *S. ochraceum, S. metallicum, S. oyapockense, S. guianense,* and *S. exiguum*.

When taking a blood meal, infected *Simulium* vectors deposit one or more infective (third-stage) *O. volvulus* larvae, which reach adulthood in the human host after about a year but may live as long as 14 years. The adult worms typically entwine in nodules where they mate, producing microfilariae that migrate into the skin, eyes, and other organs. These microfilariae are unable to develop into adult worms without first being ingested in the blood meal of a blackfly vector. The microfilariae transform in the vector over a period of 6 to 12 days to produce the third-stage larvae that are infective to humans.

The thousands of microfilariae that do not succeed in reaching a blackfly vector die in the human body, provoking inflammatory reactions in tissues. Inflammation in the eyes leads to irreversible ocular lesions, resulting first in impaired vision and finally in total blindness (WHO 1995a). The death of microfilariae in the skin gives rise to intense itching, dermatitis, depigmentation, and atrophy of the skin (Murdoch and others 2002). A less common complication is lymphadenitis, which may lead to hanging groin and elephantiasis of the genitals, and increasing evidence indicates that onchocerciasis is a risk factor for epilepsy and hyposexual dwarfism in certain areas (Boussinesq and others 2002). The greater is the body load of adult worms and microfilariae, the greater is the risk of developing skin and eye disease.

The disease pattern of onchocerciasis—in particular the severity of ocular disease—varies considerably between geographic zones. Onchocercal blindness can be extensive in hyperendemic communities of the West African savannas, whereas in forest villages with a comparable intensity of infection, the skin manifestations tend to be the main complications of the disease (Dadzie and others 1989; Murdoch and others 2002). These differences may reflect the existence of different vector-parasite complexes, with strains of *O. volvulus* that differ in pathogenicity (Zimmerman and others 1992). The vector-parasite complex in the West African savanna is responsible for the most severe form of ocular onchocerciasis in the world: in the most affected villages, more than 10 percent of the population may be blind because of onchocerciasis.

Leprosy

Leprosy is caused by *Mycobacterium leprae*, a gram-positive, strongly acid-fast bacterium. *M. leprae* is an obligate, intracellular parasite that resides predominantly in macrophages. It is the only bacterium that infects peripheral nerves, showing a preference for Schwann cells, particularly of unmyelinated fibers.

The disease spectrum of leprosy ranges from a single self-healing, hypopigmented macule to a generalized illness causing widespread peripheral nerve damage and affecting even bones and internal organs. Skin lesions may be well- or ill-defined hypopigmented macules, plaques, or nodules that are localized or distributed over the whole skin. They may be hypaesthetic, anesthetic, hyperaesthetic, or have normal sensibility. Nerve lesions occur in dermal nerves as well as in superficial sensory nerves and mixed nerve trunks. One or more nerves may be enlarged on palpation. Signs such as clawing of fingers and toes, "absorption" of digits caused by repeated injury, and dry skin are secondary to impairment of motor, sensory, and autonomic nerve function.

A diagnosis of leprosy is based on finding at least one of three so-called cardinal signs (ILA 2002):

- diminished sensibility in a typical macule or plaque in the skin
- palpable enlargement of one or more peripheral nerve trunks at specific sites
- demonstration of acid-fast mycobacteria in a slit skin smear.

Currently, patients are classified based on clinical signs only, but skin smear results are taken into account when available. Patients who have more than five skin lesions or who have a positive skin smear are classified as *multibacillary;* others are classified as *paucibacillary*.

The skin signs of leprosy are relatively harmless, but complications of the disease may lead to severe consequences, such as blindness, infertility, disfigurement, and severe sensory and

motor disability. Reactions—that is, episodes of acute inflammation caused by hypersensitivity to bacterial antigens—can be particularly severe. Patients can develop nerve damage without any obvious sign of these reactions, but after neuropathy has become irreversible, it may lead to secondary impairments, such as wounds, contractures, and shortening of digits. As a result of visible impairments or activity limitations—or simply because of the diagnosis of leprosy—many people experience psychosocial problems (van Brakel 2000).

The exact mode of transmission of *M. leprae* is still not fully understood, but the respiratory tract seems to play an important role. The primary reservoir of infection is the human host. Untreated multibacillary leprosy patients are able to shed large amounts of *M. leprae* from the nose, and household and social contacts of such patients are at a higher risk of developing leprosy than the general population (van Beers, Hatta, and Klatser 1999). *M. leprae*–specific DNA sequences have been isolated from the noses of apparently healthy individuals, and widespread seropositivity against *M. leprae*–specific antigens has been demonstrated in endemic areas, although the role of these individuals in transmitting leprosy is not fully understood. Effective antileprosy treatment usually renders a patient noninfectious within a few days.

Disease Burden

Information on the number of people infected is often difficult to obtain for tropical diseases. Many infected people may be without obvious symptoms, those with symptoms may not seek care at public health facilities, and those who do may not be reported. Routine health information systems provide little information on the number of people infected in the population. Surveys are more informative but are rarely done. A better picture emerges only when control programs need to map the distribution of the disease as a basis for targeting large-scale interventions. Hence, the apparent paradox is that intensification of disease control may result in a significant initial increase in estimates of the burden of disease through better epidemiological data.

Chagas Disease

Chagas disease is an important public health problem in 17 countries in Latin America. Estimates from the 1980s indicated that some 16 million to 18 million individuals were infected (WHO 1991), and in the 1990s, a series of multinational control initiatives was launched that was designed to interrupt transmission by eliminating domestic insect vectors and improving the serological screening of blood donors. As a result, estimates of the number of infected people were revised to 9.8 million in 2001 (Schmunis 2000). The estimated burden of disease in terms of disability-adjusted life years (DALYs) declined from 2.7 million in 1990 (World Bank 1993) to 586,000 in 2001 (Mathers and others 2006). Because of migration, *T. cruzi*–infected individuals can be found outside Latin America (for example, in Spain or the United States).

Estimates from the 1980s suggested that 5 million people in the Americas had symptoms of Chagas disease (WHO 1991). These estimates decreased to 1.2 million to 2.8 million in the 1990s. The World Health Organization (WHO) attributed 45,000 yearly deaths to Chagas disease (WHO 1991). WHO decreased its mortality estimates to 13,000 in 2001 (WHO 2002d).

In all affected countries, Chagas disease has been responsible for a high burden of disease and significant direct and indirect costs. Reports from Brazil in the late 1980s suggested that the aggregate costs for pacemakers and intestinal surgeries for Chagas disease were US$250 million per year, excluding the costs of consultations, care, and supportive treatment for chronic chagasic patients, which amounted to US$1,000 per year per patient, and disability awards, which in one

state accounted for US$399,600 (Dias 1987; Schofield and Dias 1991). In Bolivia, in 1992, aggregate treatment costs were estimated at US$21 million. In Chile, in 1997, aggregate treatment costs for Chagas disease were estimated at US$14 million to US$19 million (Schenone 1998), and in Uruguay, in 1996, costs were estimated at US$15 million (Salvatella and Vignolo 1996).

Lymphatic Filariasis

LF is endemic in 83 countries, with 1.1 billion people living in known endemic areas. In 1992, the WHO Expert Committee estimated that 78 million people were infected (WHO 2002c). This estimate was later revised to 119 million, and current estimates indicate that LF is responsible for the loss of 4.6 million DALYs per year. Many endemic areas lack reliable data on the prevalence of LF, and estimates of the number infected may increase when more precise data become available from epidemiological mapping. Nationwide mapping in four neighboring countries in West Africa showed that LF was endemic in a much wider area than expected, and the findings resulted in a dramatic increase in the estimated number infected (Gyapong and others 2002).

Epidemiological trends have varied widely among different regions in recent decades. LF was controlled or eliminated from several islands in the Pacific, and China has seen a dramatic reduction in infection levels. Unfortunately, in India and Africa, the most endemic areas of the world, recent decades have witnessed little change (WHO 2002c).

The acute form of the disease is common and causes severe hardship in endemic communities. Infected individuals suffer from one to eight acute episodes per year, and during each episode, affected patients are bedridden for three to five days.

Morbidity caused by chronic LF is mostly lifelong, and the disease is considered the second leading cause of disability in the world (WHO 1995b). Patients affected by elephantiasis or hydrocele are often victims of societal discrimination, and the disease impairs their educational and employment opportunities, marriage prospects, and sexual life. Case-control studies in India revealed that affected individuals are 27 percent less productive than their uninfected counterparts (Ramu and others 1996). The patients work less and often switch to lighter jobs, leading to a loss of more than 1 billion person-days per year in India alone (Ramaiah and others 2000), which translates into an annual economic loss equivalent to 0.63 percent of gross national product.

Onchocerciasis

More than 99 percent of those infected with *O. volvulus* reside in 30 endemic countries in Africa, with the remainder living in the Republic of Yemen and six countries of the Americas. In 1995, the WHO Expert Committee on Onchocerciasis estimated that 17.7 million people were infected, of whom about 270,000 were blind and another 500,000 were severely visually impaired (WHO 1995a). However, more recent information from rapid epidemiological mapping of onchocerciasis (Noma and others 2002) by the African Programme for Onchocerciasis Control (APOC) indicates that the number of those infected is twice as high and that some 37 million people were infected in 1995. This revised estimate corresponds to an estimated 1.99 million DALYs lost because of onchocerciasis in 1995.

Using the most recent rapid epidemiological mapping data and the latest APOC data on treatment coverage and assuming that four rounds of ivermectin treatment will reduce the prevalence of troublesome itching by 85 percent and the burden of visual impairment and

blindness by 35 percent give a DALY estimate of 1.49 million DALYS lost for 2003 (see Table 1).

In addition to the burden of blindness and severe itching, onchocerciasis has important socioeconomic consequences. In the West African savanna, fear of blindness has resulted in the depopulation of fertile river valleys, severely affecting agricultural production. It was this socioeconomic impact, and not just the health impact, that led to the creation of the Onchocerciasis Control Program (OCP) in West Africa in 1975 (Remme 2004b).

Even though the importance of onchocercal blindness has long been recognized, only in 1995 did research demonstrate that the public health importance of onchocercal skin disease was even greater. Troublesome itching associated with dermal onchocerciasis makes working, studying, or interacting socially difficult (Murdoch and others 2002; Vlassoff and others 2000). Onchocercal itching now accounts for 60 percent of DALYs lost (Remme 2004a). Other skin manifestations, such as reactive skin lesions, are not included in the DALY estimates, even though they are highly prevalent and have major psychosocial and economic impacts. Onchocercal skin disease also diminishes people's income-generating capacity, and the school dropout rate is twice as high among children from households in which the head of household is affected by onchocercal skin disease (Benton 1998).

Table 1: DALYs Lost, by Disease and World Bank Region (thousands)

Disease (date of information)	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries	Total
Chagas disease (2001)	0	1	583	0	0	0	1	585
LF (2001)	373	1	9	4	2,412	1,656	212	4,667
Onchocerciasis (2003)	0	0	2	0.4	0	481	0	484
Onchocerciasis(latest APOC data)	0	0	2	0.4	0	1,487	0	1,490
Leprosy (2001)	34	0	18	2	113	24	1	192

Source: Mathers forthcoming; WHO 2004b; authors' calculations.

Leprosy

In May 2001, 10 years after the World Health Assembly had adopted a resolution to eliminate leprosy by the end of the millennium, the target—a prevalence rate of less than 1 per 10,000—had been achieved at the global level. The number of cases registered for treatment worldwide fell from 5.4 million in 1985 to 460,000 by the end of 2003 (WHO 2004a); however, this trend should not be taken at face value because the reduction is attributable mainly to such factors as the shortening of treatment duration for multibacillary patients and the cleaning up of patient registers.

Leprosy is reported from all regions of the world, but the burden of disease, which is estimated at 192,000 DALYs, is concentrated in a few countries. During 2003, 513,798 new cases were detected, of which more than 80 percent were in Brazil, India, Madagascar, Mozambique, Nepal, and Tanzania (WHO 2004a). India alone accounted for about 75 percent of the new cases. Case detection has remained remarkably stable over the past decade. Trends in

case detection rates should be analyzed in conjunction with the proportion of new patients with grade 2 impairment (an indicator of the delay between onset of the disease and diagnosis) and the proportion of children among new cases (an indicator of recent transmission).

Virtually all published data on leprosy-related disability concern impairments. In 1997, WHO estimated the global prevalence of patients with visible impairments (disability grade 2) as 2 million. A similar number may have sensory impairment without deformity. Sensory and motor impairment that are already present at diagnosis are important risk factors for developing additional impairment and disability. Evidence indicates that sensory impairment itself causes significant functional disability.

The prevalence of activity limitations among people affected by leprosy is unknown. Van Brakel and Anderson's (1998) survey in Nepal finds that among those with any impairment, about 20 percent had limitations in relation to one or more indoor activities and up to 34 percent had significant limitations in relation to common outdoor activities. Even less is known about the prevalence of restrictions on social and economic participation. Surveys are urgently needed to assess the extent of patients with leprosy-related disabilities who require intervention.

Two difficulties affect the validity of DALY estimates for leprosy. The first is the lack of data, particularly on the burden of functional and psychosocial disability caused by leprosy. The second is that the effect of leprosy often goes well beyond the affected individual; the psychosocial consequences may affect the whole family. People without any visible signs of leprosy may be stigmatized simply because they are known to be a leprosy patient. Even after completing treatment, people may remain stigmatized.

Summary of DALY Estimates

Table 1 summarizes the DALY estimates for each of the four diseases by World Bank region. The high estimate for LF reflects not only its wider distribution and the larger number of people affected, but also the reduction in the burden for the other three diseases as a result of control efforts. For those diseases for which there has been significant progress toward elimination, public health officials should remain aware of the burden of disease that is currently averted but that might return if control were not to be sustained before transmission has been completely eliminated.

Interventions and Their Effectiveness

For each of the four diseases in this article, effective interventions are available.

Chagas Disease

The primary approaches to control of Chagas disease are halting transmission and providing adequate treatment for those infected. The two most important routes of transmission are insect vectors and blood transfusion from infected donors; thus, control programs focus on eliminating domestic vector populations and improving the serological screening of blood donors.

Vector Control

Triatoma infestans lives only inside houses and in the peridomestic area. Work during the late 1940s suggested that spraying houses with residual insecticides could eliminate vectors' domestic populations. The effect and sustainability of such vector control programs can be enhanced when they are combined with improved housing and when communities are well informed and closely involved in vector surveillance activities.

Argentina and Brazil initiated programs for nationwide vector control in the 1960s, and Chile and Uruguay did so in the 1970s. These programs were strengthened in 1991 by the Southern Cone Initiative, a multinational effort to eliminate infestation by *T. infestans* launched by the ministries of health of Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay and coordinated by the WHO Regional Office for the Americas. Similar regional initiatives for Central America and the Andean Pact regions, targeted primarily against *Rhodnius prolixus,* followed in 1997.

The results in the Southern Cone region have been impressive, with vast areas now free of domestic infestation with *T. infestans* and other vector species. In Argentina, seroprevalence rates among men age 18 to 20 drafted for military service decreased from 5.8 percent in 1981 to 1.2 percent in 1993. The number of cases of Chagasic cardiomyopathy, when compared with the number expected in the absence of control, indicates a decrease of 81 percent in the population up to 18 years of age. In 2001, a WHO commission certified that 4 of the 18 endemic provinces were free of vectorial transmission. In Brazil, domestic infestation rates decreased by 98.3 percent between 1991 and 2000. Of the 11 Brazilian states that were originally endemic for *T. infestans,* 9 have been certified as free of vectorial transmission. In Chile, house infestation rates decreased from 28.80 percent in 1982 to less than 0.01 percent in 1999, when the country was certified free of vectorial transmission. Uruguay also achieved a dramatic reduction in house infestation rates, from 5.7 percent in 1983 to 0.3 percent in 1997, when it too was certified as free of vectorial transmission. Bolivia and Paraguay have not yet eliminated transmission, but thousands of houses have been sprayed since 1991.

Blood Transfusion Control

The purpose of screening for *T. cruzi* in blood banks is to eliminate all units of potentially infected blood. Argentina and Brazil require screening to be done using two serological tests to reduce the risk of false negatives; however, the cost-benefit ratio of the two-test approach may be questionable in countries where prevalence is low and the reagents used for diagnosis are highly sensitive.

In 1993, the national coverage of blood donor screening was analyzed in four Central American and six South American countries (Schmunis and others 1998). At that time, only Honduras, Uruguay, and República Bolivariana de Venezuela screened 100 percent of donors, and even in those countries infected transfusions were possible because of the lack of sensitivity of the reagents used. Since then, the sensitivity and specificity of serological tests have improved, and more countries have passed legislation requiring the screening of all blood donors. By 2001, seven endemic countries were screening 100 percent of blood donors for *T. cruzi,* four were screening more than 99 percent of donors, 0and two were screening about 90 percent; but four countries were still screening fewer than 25 percent of donors. In countries with a high number of immigrants from Latin America, such as Spain and the United States, thousands of individuals are potentially infected, and screening of blood donors for *T. cruzi* infection may be indicated in these countries.

Treatment

If untreated, most individuals infected with *T. cruzi* will remain infected for life. Spontaneous cure is rare. Only two drugs, nifurtimox and benznidazole, are effective for treating *T. cruzi*. Both are highly effective for acute infections and can be used in cases of congenital Chagas disease. Their effectiveness for treating chronic cases remains unclear, but increasing

evidence indicates that they are effective in clearing parasitemia when administered to young cases, which may impede the development of chronic lesions. Both drugs may cause serious side effects and should be administered under medical supervision.

Lymphatic Filariasis

In recent years, new control tools and strategies have become available for LF (Ottesen and others 1997), and the World Health Assembly has adopted a resolution on the global elimination of LF. The Global Programme for the Elimination of Lymphatic Filariasis was launched in 2000 with the primary goals of interrupting transmission and preventing suffering and disability caused by the disease (Ottesen 2000).

The core strategy for interrupting transmission is annual mass drug administration (MDA) to treat the entire at-risk population for a period long enough to ensure that levels of blood microfilariae remain below those necessary to sustain transmission. Two annual, single-dose, two-drug regimens are recommended for MDA: ivermectin plus albendazole in African countries that are coendemic for onchocerciasis, and diethylcarbamazine plus albendazole for all other endemic countries. Where feasible, diethylcarbamazine-fortified salt as the only source of domestic salt for a period of at least six months would be an alternative strategy to MDA.

The principal strategy for alleviating suffering and decreasing the disability caused by LF focuses on decreasing secondary bacterial and fungal infection of limbs or genitals whose lymphatic function has already been compromised by filarial infection. Operationally, a regimen of meticulous local hygiene of affected areas and the creation of hope and understanding among patients and their communities are the principal strategic approaches (Dreyer, Dreyer, and Noroes 2002).

Mass Treatment

It is not yet known how many years of MDA are needed to eliminate LF transmission, but empirical evidence on the effect of MDA on transmission is progressively becoming available. In *Anopheles*-transmitted *W. bancrofti* in Papua New Guinea, four rounds of MDA with diethylcarbamazine or diethylcarbamazine plus ivermectin that reached about 88 percent of the target population reduced the annual transmission potential (the estimated number of infective-stage larvae inoculated per person per year) by 97 percent and 84 percent in low- and high-transmission areas, respectively. In India, where *W. bancrofti* is transmitted by *C. quinquefasciatus,* six rounds of MDA that reached 54 to 75 percent of the target population reduced the annual transmission potential by 95 and 80 percent in diethylcarbamazine- and ivermectin-treated villages, respectively (Ramaiah and others 2003). Modeling studies indicate that the required duration of treatment will depend largely on the treatment coverage achieved and the extent of systematic noncompliance to treatment—that is, noncompliance by the same individuals during successive treatment rounds (Stolk and others 2003). The physiology of the vectors also plays a role, because with *Culex*-transmitted LF, the critical microfilariae density required to interrupt transmission is thought to be lower than in areas where *Anopheles* is the vector.

The addition of albendazole to the two established anti-filarial drugs—diethylcarbamazine and ivermectin—is based on clinical trials indicating that the combination therapy is as good as or better than single-drug therapy and that albendazole may enhance the macrofilaricidal action of diethylcarbamazine. Albendazole is also effective and safe against intestinal helminth infections, and its inclusion may enhance compliance with MDA. However, clinical trials have

not yet been conclusive, and more robust evidence on the advantages of combination therapy is needed (Addiss and others 2004; Gyapong and others 2005). Community trials are ongoing in India and Africa, and preliminary results of a trial in south India suggest that the combination of diethylcarbamazine and albendazole may indeed achieve greater reduction in the prevalence of antigenemia than diethylcarbamazine alone (Rajendran and others 2002). A study in Nigeria showed that the addition of albendazole to ivermectin had an additive effect on reducing LF mosquito infection rates. (Richards and others 2005).

Vector Control

Vector control has sometimes been extremely effective against LF. In the Solomon Islands, 9 to 10 years of vector control virtually eliminated LF. In India, five years of integrated vector control in an urban area reduced the overall prevalence of microfilariae by 28 percent and the prevalence in children by 92 percent. Studies suggest that 11 to 12 years of effective vector control may eliminate LF (Ramaiah, Das, and Dhanda 1994). Vector control combined with chemotherapy produced the best results. The introduction of polystyrene beads in vector breeding habitats and treatment with diethyl-carbamazine reduced the annual infective biting rate in Tanzania by 99.7 percent (Maxwell and others 1990). In India, vector control combined with single-dose treatment with diethylcarbamazine plus ivermectin reduced the annual transmission potential by 96 percent, compared with 60 percent using chemotherapy alone (Reuben and others 2001).

Such results, along with the limitations of MDA for completely eliminating microfilariae in some situations, have reactivated the debate on the role of vector control in LF elimination (Burkot and Ichimori 2002). However, few endemic countries have an adequate vector control infrastructure.

In some African countries, the same vector species transmit both LF and malaria. In such situations, the effect of malaria control measures, particularly insecticide-treated bednets, on LF vector densities and transmission needs further evaluation. A review of the role and feasibility of community-based vector control strategies and large-scale application of biological control agents is also needed.

Morbidity Management

The second objective of the Global Programme for the Elimination of Lymphatic Filariasis is to decrease the disability caused by LF. Simple and cheap methods have been developed for managing lymphedema, using water and soap occasionally supplemented with antibiotics. Studies in India, Africa, and the Americas have shown that such methods can significantly improve the quality of life of those affected, but implementation of this strategy has greatly lagged behind the MDA campaigns.

Onchocerciasis

Onchocerciasis control is based on vector control and large-scale ivermectin treatment.

Vector Control

Vector control used to be the only feasible intervention when available drugs were too toxic for large-scale use. Following success with vector control in Kenya, where the application of larvicides resulted in local elimination of the vector *S. neavei,* and in selected locations in West Africa, where the application of larvicides effectively stopped local vector breeding but could not

prevent reinvasion of infective vectors from elsewhere, vector control was considered feasible in the West African savanna if carried out on a large scale. In 1975, the OCP started large-scale vector control operations using helicopters for weekly spraying of larvicides over the vector breeding sites in river rapids (Molyneux 1995). The operation ultimately covered some 50,000 kilometers of rivers over a geographic area of 1,235,000 square kilometers. The OCP's strategy was to maintain vector control for at least 14 years to interrupt transmission and eliminate the parasite reservoir. Despite initial problems with reinvasion by infective flies, the strategy proved effective, eliminating onchocerciasis as a public health problem throughout the OCP area. The OCP was successfully concluded in 2002, but concerns remain about the possible recrudescence of onchocerciasis through reinvasion by infected blackflies or migration of infected persons into OCP areas. The OCP countries, therefore, need to maintain effective surveillance to identify any recurrences of infection (Richards and others 2001).

Treatment with Ivermectin

In 1987, Merck & Co., the manufacturer of ivermectin, agreed to donate the drug for onchocerciasis control for as long as needed (Peters and Phillips 2004). Clinical and community trials involving more than 70,000 people showed that annual ivermectin treatment was safe, prevented ocular and dermal morbidity, and significantly reduced transmission; however, ivermectin is a microfilaricide and does not kill the adult worms, and long-term treatment is needed to sustain suppression of the microfilarial load (Remme 2004b). Additional research is needed to determine the extent to which repeated treatments reduce the reproductive capacity of the adult worm population over time.

The introduction of ivermectin allowed the OCP to achieve its objective in 12 years instead of 14 by combining vector control with ivermectin treatment, but most important, it also provided an opportunity to control onchocerciasis in endemic areas outside the OCP where vector control was not feasible. This ability led to the creation of two other regional programs for controlling onchocerciasis in endemic areas of Africa and the Americas: APOC (Remme 1995) and the Onchocerciasis Elimination Program for the Americas (OEPA) (Richards and others 2001).

The World Bank and WHO launched APOC in 1995 to serve 19 onchocerciasis-endemic countries outside the OCP. APOC's principal strategy is to establish annual ivermectin distribution in highly endemic areas to prevent eye and skin morbidity. In partnership with ministries of health and nongovernmental organizations, APOC currently provides more than 35 million ivermectin treatments per year and aims to reach 65 million treatments per year before its scheduled termination in 2010. APOC uses an approach referred to as *community-directed treatment with ivermectin*, whereby local communities rather than health services direct the treatment process (Amazigo and others 2002). A community decides collectively whether it wants ivermectin treatment, how it will collect ivermectin tablets from the medical supply entity, when and how the tablets will be distributed, who will be responsible for distribution and recordkeeping, and how the community will monitor the process. Health workers provide only the necessary training and supervision. To date, communities have responded enthusiastically to this approach (Seketeli and others 2002), and interest is now growing in exploring this strategy for interventions against other diseases (Homeida and others 2002).

In the Americas, *O. volvulus* transmission occurs only in a few small areas in six endemic countries. Accordingly, OEPA's strategy is based on intense ivermectin treatment twice a year that should allow eventual cessation of ivermectin delivery without the risk of recrudescence

(Richards and others 2001). OEPA was launched in 1992 and is currently reaching more than 85 percent of its intended target population.

Leprosy

The objectives of leprosy control are to interrupt transmission, to cure patients, to prevent the development of associated deformities, and to rehabilitate those patients already afflicted with deformities. The strategy involves early case detection and the provision of adequate chemotherapy and comprehensive patient care (ILA 2002).

Multidrug Therapy

Dapsone therapy for leprosy was introduced in the late 1940s and successfully used as monotherapy for two decades. In the 1970s, resistance to dapsone emerged, and WHO introduced multidrug therapy (MDT) in 1982. Paucibacillary patients were to be given a six-month regimen of daily dapsone and supervised monthly rifampicin. Multibacillary patients were to be treated with a three-drug regimen for two years or, where feasible, until the skin smear had become negative. This regimen followed the paucibacillary regimen, adding a smaller daily dose of clofazimine and a larger supervised dose once a month.

These regimens have had good results, with a relapse incidence of less than 0.1 percent per year (ILA 2002). No multidrug-resistant leprosy has been reported so far, and reports of rifampicin-resistant *M. leprae* have been few. In 1998, the standard multibacillary MDT regimen was shortened to 12 months. Long-term relapse rates for the 12-month regimen are not yet available.

Public health specialists expected that wide application of MDT together with earlier diagnosis resulting from the upgrading of leprosy services would have a considerable effect on transmission; however, by 2002, clear evidence of a reduction in transmission had not been seen.

Immunoprophylaxis and Chemoprophylaxis

Several randomized trials have shown that vaccination with the bacillus Calmette-Guérin (BCG) vaccine reduces the risk of developing leprosy (Fine and Smith 1996), with the level of protection varying from 20 to 80 percent. Chemoprophylaxis based on dapsone or intramuscular acedapsone conferred overall protection against leprosy of about 60 percent (Smith and Smith 2000). Two large trials are currently under way in Bangladesh and Indonesia to investigate the efficacy of one or two doses of rifampicin in preventing leprosy, with preliminary results from the Indonesian trial indicating a significant protective effect.

Prevention of Disabilities

As concerns primary prevention, leprosy-related disability is preventable, but when peripheral neuropathy has become established, it is irreversible and leads to lifelong morbidity and disability (Bekri and others 1998; Meima and others 1999). Early case detection and treatment are therefore likely to be the most effective interventions in relation to preventing disability. When detected and treated in time with corticosteroids, primary impairments may be reversible, but because many patients present late, some 11 to 51 percent do not recover or get worse.

In relation to secondary prevention, the main strategy is self-care to prevent worsening of impairments in people who already have irreversible neural impairment or secondary impairments such as wounds and contractures. The role of health care workers is to educate

patients so that they can be responsible for the daily management of the effects of nerve function impairment. An essential part of secondary prevention is the use of protective footwear by people with anesthetic feet. Several studies have shown that the use of locally acceptable, appropriate footwear is a cost-effective intervention for those with a loss of plantar sensation (ILA 2002). Reconstructive surgery, protective footwear for people with insensitive feet, and assistive devices to correct or prevent activity limitations are also used in secondary prevention.

As concerns tertiary prevention, the stigma attached to leprosy often prevents patients from participating in normal community activities. Strategies include counseling of those affected and their families, neighbors, and communities; vocational training; and advocacy work.

Rehabilitation

Impairments often lead to activity limitations and restrictions on social participation, which can be prevented by correcting the underlying impairment if it is not yet irreversible. After impairment is established, activity limitations can still be minimized with the help of reconstructive surgery or appropriate assistive devices, such as orthoses, grip aids, calipers, or prostheses. A large but unknown percentage of people succeed in overcoming activity limitations by themselves. Some require rehabilitation interventions, such as physical or occupational therapy, reconstructive surgery, or temporary socioeconomic assistance.

Intervention Effectiveness

For all four diseases covered in this article, interventions are available that are effective under routine control conditions. The feasibility of eliminating these diseases as public health problems from most endemic areas is therefore not in doubt; however, questions remain about the effectiveness and sustainability of control under specific conditions and about the feasibility of eliminating the parasites and transmission. The vector control strategy for Chagas disease worked well in the Southern Cone countries, but the sylvatic reservoir of *T. cruzi* remains unaffected, and continued surveillance will be essential. Vector control is more challenging in the Andean and Central American countries, where some of the vectors are not domiciliated. For LF, the number of years of MDA and the treatment coverage required to interrupt transmission remain unknown, just as the epidemiological conditions and the number of rounds of ivermectin treatment required to achieve the same for onchocerciasis are not yet known. For leprosy, the key questions remain how much effect MDT has on transmission and when the incidence of new cases can be expected to decline significantly. Hence, the sustainability of control remains a critical issue.

The control programs for three of the diseases depend on drug donations. To date, the pharmaceutical companies donating the drugs and the donors supporting drug distribution have shown impressive commitment to the programs, but if their commitment were to lapse, the control programs would collapse and the diseases would return as public health problems. Another risk is drug resistance. The control programs rely on just a few drugs, and even though drug resistance is not currently apparent, if it were to emerge, the essential tools for control would be lost. Hence, although elimination is in sight, the battle has not yet been won, and research to develop new and improved interventions and strategies for these tropical diseases remains important.

Costs and Cost-Effectiveness of Interventions

The published information on cost-effectiveness of interventions for the four diseases is incomplete, and this section provides some new data on the cost per DALY averted that is not available in the literature.

Chagas Disease

For the Southern Cone countries, investment in the control of Chagas disease since 1991 has been about US$320 million, well within the original estimates of US$190 million to US$350 million (Schofield and Dias 1991). Initial predictions of cost-effectiveness suggested an internal rate of return (IRR) for the initiative of about 14 percent, but point studies during the course of the interventions suggest actual IRRs of about 30 percent for Brazil (Akhavan 1998) and more than 60 percent for the province of Salta, Argentina (Basombrio and others 1998).

Brazil had an estimated 2 million infected individuals in 1995. Annual follow-up of the 1.6 million asymptomatic cases would have cost US$98 million. Diagnosis of megasyndromes for 6 percent of infected individuals at an average cost of US$141 each would add US$16.9 million, and corrective surgery for 3 percent of the latter would add US$60 million. Cardiac pacemakers for 5 percent of infected individuals at US$3,000 each would add another US$30 million, so that the partial direct costs for medical attention in Brazil in 1995–96 would have been US$205 million.

In Argentina, the costs for medical attention in 1992 were US$435 for acute cases, US$122 per patient for asymptomatic cases, US$336 for moderate cardiopathy, and US$1,135 for severe cardiopathy. Given that Argentina had 2 million infected individuals, and assuming that 85 percent of them would have been asymptomatic,9 percent would have had mild cardiopathy, 4 percent would have had moderate cardiopathy, and 2 percent would have had severe cardiopathy, then total expenditures for medical attention would have amounted to US$457 million.

In Chile, aggregate treatment costs were estimated at US$37 million in 1991. New estimates in 1997 using the government payment schedule and an estimate of 142,000 people infected, including 26,545 with myocardiopathy of which 9,652 were severe cases, resulted in an estimated cost of US$14 million to US$19 million. In Uruguay, annual costs for treatment were estimated at US$15 million for 1996.

These treatment costs are significantly higher than the costs of vector control, which for 1996 were US$13 million in Argentina, US$28 million in Brazil, US$650,000 in Chile, and US$4,000 in Uruguay. Akhavan's (1998) study in Brazil estimates a cost of US$260 per DALY prevented, and Robles's (1997) study in Bolivia indicated a cost of US$362 to prevent one year of life lost.

Data on the cost-effectiveness of treating those infected are sparse; however, Robles's (1997) study in Bolivia estimates the costs of treating infected children under the age of five, coming up with a cost of US$3,009 per death averted or about US$100 per DALY averted.

Lymphatic Filariasis

The most widely used interventions for LF control are MDA, vector control, and administration of diethylcarbamazine-fortified salt. We estimate the cost-effectiveness of those strategies in terms of DALYs averted from studies in India on the costs and effectiveness of control and for different scenarios for the minimum duration of control required to achieve sustained interruption of transmission. These scenarios assume that all three strategies are

implemented in areas with similar levels of endemicity of *Culex*-transmitted Bancroftian filariasis and that the available cost data for India apply.

We consider three scenarios (Table 2). *Elim1* is an optimistic elimination scenario under which sustained interruption of transmission is achieved after a relatively short period of intervention (six annual rounds of MDA, 10 years of vector control, and 2 years of diethylcarbamazine-fortified salt). *Elim2* is a conservative elimination scenario under which sustained interruption is achieved only after a longer period of intervention (10 years of MDA, 15 years of vector control, and 4 years of diethylcarbamazine-fortified salt). *Control* is a scenario under which transmission is brought to low levels but not interrupted and where control efforts will have to continue.

Table 2: Costs per DALY Averted for LF

	Mass drug administration			**Vector control**			**Diethylcarbamazine-fortified salt**		
Scenario	**Elim1**	**Elim2**	**Control**	**Elim1**	**Elim2**	**Control**	**Elim1**	**Elim2**	**Control**
Duration (years)	6	10	30	5	10	30	1	3	30
Costs of control operations per capita (US$)	0.35	0.65	2.22	2.92	6.64	22.74	0.09	0.29	3.56
Cost per DALY averted (US$)	4.40	8.10	29.00	47.50	84.30	302.50	1.10	3.62	46.48

Source: Authors' calculations.

Because of the slow dynamics of filariasis transmission and disease, the prevalence of the chronic disease manifestations (lymphedema and hydrocele) on which the DALY estimates are based will not fully reflect the effect of control for many years. We have therefore tried to predict the trend in chronic disease over a 30-year period. Recent findings from a longitudinal study (Ramaiah and others 2003) of the effect of MDA in Pondicherry, India, showed that the prevalence of hydrocele and lymphedema had declined by 58 percent after seven annual treatment rounds with diethylcarbamazine. We assumed that from the seventh year of intervention, any further reduction in disease prevalence was attributable exclusively to reduced incidence as a result of reduced transmission, and that 30 years after the initiation of the intervention, the prevalence of disease would have fallen by 90 percent. We assumed that the effect of diethylcarbamazine-fortified salt was similar to that of MDA, whereas for vector control we assumed that prevalence would decline with a delay of seven years.

The predicted costs per DALY averted (Table 3) indicate that MDA and diethylcarbamazine-fortified salt are extremely cost-effective. Elimination with MDA costs about US$4 to US$8 per DALY averted, and even if transmission were not interrupted and MDA would have to be continued for 30 years (control scenario), the cost would be still only be around US$29 per DALY averted. Diethylcarbamazine-fortified salt would be the cheapest intervention, but governments rarely favor it, and compliance can be difficult to ensure. Vector control is at least 10 times more expensive in terms of DALYs averted, but it offers additional benefits in terms of malaria and dengue control and significant relief from mosquito nuisance.

Table 3: Cost-Effectiveness Estimates for the Main Interventions for Each Disease

Intervention	Cost per DALY averted (US$)	Internal rate of return (percent)
Chagas disease		
Vector control	260	30–60
Treatment (children under five)	100	—
LF		
MDA	4–29	—
Diethylcarbamazine-fortified salt	1–46	—
Vector control	48–303	—
Onchocerciasis		
MDA	7	17 (APOC)
Vector control	—	20 (OCP)
Leprosy		
Case detection and treatment	38	—
Prevention of disability	1–110	—

Source: Authors' calculations.
MDA = mass drug administration.

The effect of MDA on hydrocele and lymphedema is not yet well established and the results of the Indian trial on which the previous calculations are based may be too optimistic. However, even under much less favorable assumptions that the prevalence of hydrocele and lymphedema declines by 20 percent after 7 years of MDA and by 75 percent after 30 years, the estimated cost per DALY averted would be only 50 percent higher than those given in Table 3, and the interventions would still be very cost-effective.

The prevention of chronic disease also has direct economic benefits (Ramaiah and Das 2004). The cost of preventing one case of chronic disease through six rounds of MDA in India has been estimated at US$8.41. The economic benefits include savings of 58.24 working days per year per case, yielding wages of US$39.39 and treatment costs of US$1.44. On average, chronic patients lose 11 years of productive life; thus, the average economic benefits total US$449.13 per chronic case averted. This figure gives a benefit-cost ratio of 52.6, perhaps one of the highest for any disease control program.

Onchocerciasis

Investment in onchocerciasis control has included about US$570 million provided by donors to the OCP during 1975–2002, US$140 million provided and earmarked for APOC for 1996–2010, and US$10 million for OEPA for 1991–2003. The African onchocerciasis control programs are considered highly cost-effective. No cost-benefit analysis has yet been published for OEPA.

The OCP has been highly successful. More than 40 million people in the program's 11 countries are now considered free from infection and eye lesions, more than 1.5 million people are no longer infected, and more than 200,000 cases of blindness have been prevented. Sixteen million children born since the program began are free of onchocerciasis. The socioeconomic

effect has also been dramatic: 25 million hectares of fertile land in the river valleys were made available for resettlement and agriculture. A cost-benefit analysis of the OCP has estimated the net present value for the OCP over a 39-year project horizon from 1974 to 2002 as US$485 million (Kim and Benton 1995). This figure corresponds to an IRR of 20 percent, resulting mainly from increased labor because of prevention of blindness (25 percent of benefits) and increased land use (75 percent of benefits).

A similar cost-benefit analysis for APOC also considered benefits in terms of additional labor resulting from blindness prevention (Benton 1998). It did not consider land use because depopulation of river valleys is rarely seen in APOC countries, where the forest type of onchocerciasis predominates. Nevertheless, the estimated IRR for APOC remained almost as high as that for the OCP (17 percent), because the cost is lower but the number of people served is far greater.

The estimated rates of return for the OCP and APOC did not include the effects of control on onchocercal skin disease. Hence, these rates underestimate the benefits, because troublesome itching accounts for more than 50 percent of the DALYs attributable to onchocerciasis. The cost of ivermectin, which is donated by Merck, was not included in our analyses.

To estimate the approximate cost per DALY averted, we considered the burden of disease and treatment with ivermectin in APOC countries. Using the latest epidemiological mapping data, we estimate that, in 1995, 34.6 million people were infected in APOC countries and that 1.86 million DALYs were lost. Currently more than 44 percent of those infected are covered by community-directed treatment with ivermectin, and expectations are that treatment will be expanded to cover most of the remainder before the end of APOC in 2010. Information from areas where ivermectin treatment has been in effect for more than 15 years shows that the prevalence and intensity of onchocerciasis infection have fallen to low levels (Borsboom and others 2003), and computer simulations predict that the disease could not become a public health problem again for at least another 10 to 20 years if treatment were halted (Remme, Alley, and Plaisier 1995). We therefore estimate that 15 years of ivermectin treatment at 65 percent coverage will prevent at least 25 years of onchocercal disease. If we assume that 70 percent of endemic communities will ultimately be covered by community-directed treatment with ivermectin and that 80 percent of those communities will maintain annual treatment at 65 percent coverage for at least 15 years, at least 26 million DALYs would be prevented over a 25-year period.

The predicted cost of community-directed treatment with ivermectin in APOC countries is US$145 million by the international donor community plus US$64 million by ministries of health and collaborating nongovernmental organizations, giving a total of US$209 million. Therefore we estimate that the cost of community-directed treatment is approximately US$7 per DALY averted.

The ultimate cost-benefit of onchocerciasis control will depend on how long effective control programs will need to be maintained to keep the disease under control. National governments and ministries of health should plan to invest in ivermectin distribution and in surveillance activities for the foreseeable future. Thus, a case must continually be made with national decision makers that if investments do not continue, recrudescence of infection is likely. One strategy for sustaining national investment is to show that ivermectin distribution systems can be made polyfunctional. Treatment programs based on MDA for intestinal parasites, schistosomiasis, and LF and on vitamin A distribution can be integrated with ivermectin distribution programs and thereby further improve cost-benefit ratios. The use of community-

directed treatment with ivermectin is also envisaged as a way of strengthening peripheral and district health systems (Homeida and others 2002).

Leprosy

Costs associated with leprosy control include case detection, treatment, prevention of disability, and rehabilitation. We calculate the incremental health service cost to arrive at the average cost of curing a patient with leprosy. Our estimates are based on the limited published cost data available, program expenditure data, and expert opinion, although costs are likely to differ substantially by country.

As case-detection rates decrease, the average cost of detecting one case increases. The previous edition of this volume estimated a cost of US$2 per case detected based on a case-detection rate of about 300 per 100,000; however, case-detection rates are now considerably lower in most countries (Dharmshaktu and others 1999; Ganapati and others 2001; Smith 1999). Many leprosy control programs now rely on voluntary case finding supported by information, education, and communication activities to raise or maintain people's awareness of the early signs and symptoms of leprosy. We estimate the cost of this approach to be about US$1 per case detected. Nevertheless, if active methods are still used in areas where case-detection rates are low, the cost of case detection may be as high as US$108.

The costs of diagnosing and treating leprosy have fallen in the past decade, and diagnosis by clinical examination only is now recommended. We therefore exclude the cost of skin smears. In addition, a shortening of the treatment regimen has lowered drug costs to about US$12 for a multibacillary case and US$1 for a paucibacillary case. Globally, almost 40 percent of leprosy cases are classified as multibacillary cases, with the remaining 60 percent being paucibacillary cases. Thus, we estimate the average drug cost as US$5.40 per case.

The cost of treatment, however, is more than the cost of drugs alone. WHO guidelines recommend that a multibacillary case receive supervised treatment for 12 months and that a paucibacillary patient receive treatment for 6 months. Using cost data from Ethiopia and Pakistan, we estimate these treatment costs at US$20 to US$30 in low-income countries. Data from studies of tuberculosis interventions show that community-supervised treatment may reduce costs by up to 50 percent (Khan and others 2002), and this approach is being advocated as part of "flexible MDT delivery" (ILA 2002) and "accompanied MDT" (WHO 2002b). Reducing the nondrug costs of treating leprosy to about US$10 to US$20 per patient may, therefore, be possible. We thus estimate the costs of treating a case of leprosy with MDT to be between US$15.40 and US$35.40 per case, depending on the strategy used.

About 10 to 20 percent of new leprosy cases are likely to suffer a reaction during or after MDT. We estimate treatment of those reactions to cost US$25 per patient. Of these patients, 1 percent may develop severe complications requiring hospitalization, at an estimated cost of US$480 per patient. In addition, 10 percent of new cases will develop neural or secondary impairments and may require footwear and education about wound management. We estimate the lifetime cost of protective footwear at US$300 per patient (Seboka, Saunderson, and Currie 1998) and education at US$10 per patient. In 1 percent of cases, reconstructive surgery may be required at about US$455 per patient. We therefore estimate the average incremental cost of interventions for prevention of disability to be US$44.15 per new case of disability. Because about 3 percent of new patients will need rehabilitation, we estimate the average cost at under US$1 for each new case of leprosy detected (Jagannathan and others 1993). However, a backlog of old cases exists. Although data in this area are weak, up to a third of the 4 million people

living with leprosy globally (2 million with grade 1 disability and 2 million with grade 2 disability) could require rehabilitation.

Few data are available on the program costs associated with leprosy. A review of expenditure in Asia found that up to 40 percent of the total costs could be classified as programmatic costs, although this amount may now be less because leprosy programs have increasingly been integrated into general health services. Data from Indonesia demonstrate that program costs can be reduced by up to 35 percent by integrating them with tuberculosis programs (Plag 1995). We therefore estimate the average cost of finding, treating, and preventing disabilities and rehabilitating a new case of leprosy at US$76 to US$264.

In practice, many leprosy programs will also be providing disability prevention and rehabilitation interventions to a large backlog of patients, so the average cost per new case will be higher than here. Programs that face a high proportion of multibacillary cases and cases presenting with high levels of disability are also likely to have higher costs.

Assuming a cure rate of around 85 percent, we estimate the costs of curing one patient of leprosy to be about US$93 per new case. Using data from India (25 percent of those with leprosy will self-cure, an average age of onset of 27, a disability weighting of 0.152, and a life expectancy at age 25 to 29 of 44.75), we estimate the cost per DALY of detecting and treating a new case of leprosy to be US$38.

In addition, assuming a 90 percent success rate, we calculate a cost per DALY of US$7 for patients needing treatment for reactions and ulcers, US$75 for those needing footwear and self-care education, and US$110 for those needing reconstructive surgery. These estimates provide only a broad indication because data on the effectiveness of these interventions are scarce, and the application of the disability weight of 0.152 to all interventions may overestimate their benefits.

Data on the economic effect of leprosy at the national level are not available. However, leprosy affects those who are economically active, with a peak in incidence at 10 to 20 years of age and again at 30 to 50 years of age. Studies of the impact of leprosy on productivity show that deformity from leprosy can reduce the probability of obtaining employment and can reduce household income and expenditure on food (Diffey and others 2000; Kopparty 1995). In addition, leprosy can have a significant social impact because participation in the community may be restricted. This impact continues well beyond the actual treatment period because leprosy-related impairments have a tendency to get worse over time even after the infection has been arrested.

Summary

Available information indicates that interventions for the four diseases are highly cost-effective and that the benefit-cost ratio of control is high (Table 3).

Research Needs and Priorities

Because the diseases in this article are targeted for elimination as public health problems, it is sometimes assumed that research for these diseases is no longer necessary and that all available resources should be allocated to elimination efforts. However, research remains critical to address questions pertaining to how to achieve elimination with currently available tools and especially to how to optimize implementation in different epidemiological, sociocultural, and health system settings. Epidemiological questions on the required intervention coverage,

frequency, and duration need to be answered to guide elimination strategies, and research on the risk, prevention, and control of recrudescence is crucial to ensure sustained success.

The Special Programme for Research and Training in Tropical Diseases, a joint project of the United Nations Children's Fund, United Nations Development Programme, World Bank, and WHO, recently undertook a systematic analysis of research needs for each of the 10 tropical diseases in its portfolio (Remme and others 2002). This analysis involved assessing the burden of disease and recent epidemiological trends, reviewing current control strategies, and identifying the major problems and challenges for disease control and the research needed to address these challenges. Table 4 summarizes the results of this analysis for the four diseases discussed in this article.

Table 4: Control Strategies, Major Challenges, and Research Needs for Each Disease

Disease	Principal control strategy	Major problems and challenges	Major research needs
Chagas disease	Interruption of transmission through domestic vector control and improved blood transfusion	Control of nondomiciliated vectors Sustained vector control Millions of those infected still at risk of disease	Strategies for surveillance of nondomiciliated vectors Better drugs and diagnostics
LF	Interruption of transmission through periodic mass treatment Disability alleviation by local hygiene measures	Need for high treatment coverage Unknowns in elimination strategy Limited effect of current drugs	Strategies for high treatment coverage Evidence base for elimination strategies Drug that kills or sterilizes adult worms
Onchocerciasis	Periodic mass treatment to eliminate the disease as a public health problem	Need to sustain high coverage for decades Risk of ivermectin resistance Eradication not possible with current tools	Strategies for sustained high treatment coverage Feasibility of elimination with ivermectin Drug that kills or sterilizes adult worms
Leprosy	Case finding and multidrug treatment Rehabilitation and prevention of disability	Incomplete MDT coverage Need to integrate and sustain control Impact on transmission not known	Integration and sustainability of control Improved diagnosis of infection Prevention and management of nerve damage

Source: Remme and others 2002.

Chagas disease has two main research priorities. The first is the development of new vector control strategies that will allow the successful elimination campaign used in the Southern Cone countries to be extended to the Central American and Andean countries, where the vectors are often not domiciliated. The second is the development of effective and affordable treatment for the millions of people already infected and the prevention of chronic complications.

For onchocerciasis and LF, the main research priorities are similar: implementation research to improve MDA; epidemio-logical research to determine if, when, and with what treatment coverage the parasite reservoir can be locally eliminated for different vector-parasite complexes;

and research to develop a macrofilaricide and improved diagnostics that would facilitate elimination.

For leprosy, the research needs were further reviewed during a Scientific Working Group (Special Programme for Research and Training in Tropical Diseases 2003). The meeting arrived at a clear consensus of three top priorities for leprosy research: implementation research on sustainable and integrated residual leprosy control activities, improved diagnosis of infection, and improved approaches for preventing and managing nerve damage.

These are the current main priorities for research in support of elimination. Eradication is not currently anticipated for any of the diseases; thus, research on better tools and strategies that will allow a permanent solution for these infectious diseases is also needed. Furthermore, currently available control tools may be lost because of factors such as resistance, and research to develop replacement tools is essential now.

Conclusion

Tropical diseases are often viewed as neglected, because the investments made to fight them appear negligible compared with the massive amounts expended globally on the health problems of developed countries. Tropical diseases are truly diseases of the poor, but despite the limited resources available for research and control, simple and effective interventions have been developed and delivered to populations in need for the four tropical diseases discussed in this article. Thus, experience with these four diseases sends a powerful message: success is possible, even for neglected tropical diseases of poor populations in developing countries. Elimination of these diseases as public health problems can be achieved, and investments in tropical disease research and control can make a significant contribution to poverty reduction.

An important reason for the success was that the interventions were extremely cost-effective. The available cost-effectiveness data, though limited, show convincingly that intervention against these diseases is a good investment, and the argument for investment gets better when other economic benefits, not reflected in DALYs, are taken into account, such as increased food production when fertile land along river valleys became available for agriculture after the control of onchocerciasis in West Africa and increased labor productivity after effective filariasis control in India.

The pharmaceutical industry also played a major role through large drug donations, and the creation of intercountry control programs provided effective mechanisms for implementing interventions, technical support, and coordination. Another reason for the success was a focused research program that ensured the development of interventions based on simple and sustainable approaches that use cheap and "appropriate" technology and that are potentially multifunctional.

Chagas disease, LF, onchocerciasis, and leprosy are now on target for elimination as public health problems from large parts of the world. However, these diseases cannot be eradicated using current tools, and much remains to be done to expand and sustain the control efforts and undertake the necessary research to improve the control efforts as well as to develop more definite solutions. It will be essential, therefore, that donors and ministries of health not abandon these programs because of their success.

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