

Tropical Diseases Lacking Adequate Control Measures: Dengue, Leishmaniasis, and African Trypanosomiasis

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ABSTRACT: Dengue, leishmaniasis, and African trypanosomiasis (sleeping sickness) are serious diseases that the World Health Organization (WHO) characterizes as lacking effective control measures. They are transmitted by insect vectors and can result in epidemic outbreaks. Specific treatment is unavailable for dengue, although good supportive treatment can drastically reduce mortality. For the leishmaniasis and for sleeping sickness, treatment relies largely on antiquated drugs based on antimony and arsenic, respectively. Sustained control of the insect vectors is difficult for dengue and leishmaniasis because their high reproductive potential allows the vector populations to recover quickly after intervention wherever adequate breeding conditions exist. By contrast, tsetse flies, the vectors for sleeping sickness, have a much lower reproductive potential and could be eliminated over large areas, given adequate organization and surveillance. Through the African Union, African nations are developing a large-scale initiative for areawide elimination of tsetse flies, partly because of sleeping sickness, but also because of their importance as vectors of animal trypanosomiasis, which poses a serious constraint to livestock development and agriculture.

Disease Characteristics and Transmission

Dengue

Dengue is a mosquito-borne viral disease with a high capacity for epidemic outbreaks. Infection can be asymptomatic or can present with symptoms ranging from mild, self-limiting, febrile illness to severe, life-threatening disease. Two clinical pictures are recognized: (a) dengue fever (DF) and (b) dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).

The four dengue serotypes, known as dengue 1, 2, 3, and 4, constitute a complex of the flaviviridae transmitted by *Aedes* mosquitoes, particularly *Ae. aegypti*. Infection by any of the four serotypes induces lifelong immunity against reinfection by the same serotype, but only partial and transient protection against the others. Sequential infection by different serotypes seems to be the main trigger for DHF/DSS.

Disease Manifestations

The incubation period is four to six days. Infants and young children usually develop fever, sometimes accompanied by a rash. Older children and adults may develop either a mild febrile syndrome or classic DF with fever, headache, myalgias, arthralgia, nausea, vomiting, and rash. Skin bleeding, petechiae, or ecchymosis are observed in some patients. Bleeding from the nose, gums, and gastrointestinal tract; hematuria; or hypermenorrhea can accompany the clinical

picture. Leukopenia is common and thrombocytopenia is sometimes observed. DF can be incapacitating, but the prognosis is favorable and the case-fatality rate is low.

By contrast, DHF/DSS can be life threatening. It is characterized by high fever, bleeding, thrombocytopenia, and hemoconcentration (Nimmanitya 1993; PAHO 1994). Plasma leakage differentiates DHF/DSS from classic DF. Severity is classified as mild (grades I and II) or severe (grades III and IV), with the main difference being shock in the latter. In some epidemics, hepatomegaly has been prominent. As with DF, DHF generally begins with a sudden temperature rise accompanied by facial flush and other nonspecific manifestations, such as anorexia, vomiting, headache, and muscle or joint pains. The most common hemorrhagic manifestation is a positive tourniquet test, although petechiae, ecchymosis, epistaxis, and gingival or gastrointestinal bleeding may also be observed. After three or four days, when the temperature returns to normal or below, the patient's condition can suddenly deteriorate with signs of circulatory disturbance. The patient may sweat, be restless, have cool extremities, and show changes in pulse rate and blood pressure. Many recover spontaneously or after brief fluid therapy, but some proceed to shock with typical signs of circulatory failure. Initially patients may be lethargic but become restless and rapidly enter a critical stage of shock. Some patients evolve to severe circulatory failure (DSS), presenting a rapid and weak pulse, a narrow pulse pressure or hypotension, cold and clammy skin, and an altered mental state. DSS is fatal in 5 to 10 percent of cases if fluid management is inadequate or delayed.

Transmission and Epidemiological Trends

The dengue virus is transmitted from humans to humans by *Aedes* mosquitoes, of which the most important is *Ae. aegypti* (Bennett and others 2002; Gubler 1979; Tardieux and others 1990). Female mosquitoes ingest the virus while feeding on viremic individuals, and after an 8- to 12-day incubation period they can transmit the virus to other humans during blood feeding (Watts and others 1987). Thereafter, the female mosquito remains infective for life. Transmission of the virus from infected females to their progeny has been documented, but its epidemiological significance is not well understood (Hull and others 1984; Rosen and others 1983).

Although believed to be of African origin, *Ae. aegypti* is now established throughout the tropics and subtropics, exploiting almost any water-filled container as larval habitat. *Ae. aegypti* is also the urban vector of yellow fever. *Ae. albopictus* also transmits dengue and is an important secondary vector in parts of Southeast Asia and the Pacific. This species is of Asian origin but has spread to parts of Africa, the Americas, and Europe by depositing egg masses in used car tires, which are traded around the world.

Major epidemics of denguelike illness were documented in the 18th and 19th centuries in Africa, the Americas, and Asia, and clinical descriptions of illness compatible with dengue in China date from about 265. During 1900–50, dengue epidemics occurred in Australia, China, Greece, India, Japan, Malaysia, Thailand, and Vietnam and in the Caribbean (Gubler and Kuno 1997). DHF was first recognized in the 1950s, although a similar hemorrhagic fever was reported in Philadelphia in 1780, in Australia in 1897, and in Greece in 1928. Dengue is now endemic in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific. According to WHO, it occurs in more than 100 countries and an estimated 2.5 billion people are at risk.

The increase in dengue epidemics can be attributed to rising levels of urbanization, which promote contact between humans and *Ae. aegypti*; inadequate domestic water supplies; and increasing international travel, migration, and trade, which help disseminate vectors and the

virus. Epidemiological changes in the Americas since the 1970s illustrate this process. During the 1940s through the 1960s, the *Ae. aegypti* control program was successful in most of the region, with several countries declaring complete eradication. However, after some years, reinfestation with *Ae. aegypti* was apparent, and by 1995 it had returned to most of the previously infested countries. Reinvasion by the vector was followed by increased circulation of the virus, and the region evolved from nonendemic to hypoendemic (sporadic epidemics caused by a single serotype) to hyperendemic (simultaneous circulation of multiple serotypes resulting in frequent epidemics). DHF became a major public health problem. Before 1981, 5 countries in the region reported only a few cases of DHF, but by 2002, 21 countries reported more than 14,000 cases and 250 deaths (Gubler 2002; Guzmán and Kouri 2002; Guzmán and Kouri 2003; Guzmán and others 2002).

Leishmaniasis

Leishmaniasis (or the leishmaniasis) refers to infections caused by protozoan parasites of the genus *Leishmania* transmitted by female sandflies (*Phlebotominae*). More than 20 *Leishmania* species are pathogenic to humans, and more than 30 species of sandflies are proven vectors. The disease tends to be focal in distribution. In anthroponotic foci, sandflies transmit parasites from human to human, and in zoonotic foci, sandflies transmit the parasites between mammal hosts and from them to humans.

Disease Manifestations

The different species of *Leishmania* cause illness of differing severity. Visceral leishmaniasis (VL), caused by species of the *L. donovani* complex, is usually fatal if untreated. Mucocutaneous leishmaniasis, caused by the *L. braziliensis* complex, is highly disfiguring and mutilating, and it can be fatal because of secondary complications. Cutaneous leishmaniasis (CL), caused by the *L. major*, *L. donovani*, and *L. braziliensis* complexes, may be a simple, self-limiting skin ulcer, but it can be disabling when numerous lesions occur. Diffuse cutaneous leishmaniasis, caused by the *L. mexicana* and *L. aethiopica* complexes, is longer lasting because of deficient immune responses.

Epidemiological Trends

Leishmaniasis is found in 88 countries worldwide. VL occurs in 62 of those countries, with most of the estimated 500,000 annual cases occurring in poorer rural and suburban areas of Bangladesh, Brazil, India, Nepal, and Sudan. Mucocutaneous leishmaniasis is mainly limited to South and Central America, whereas most of the estimated 1 million to 1.5 million annual CL cases occur in the Middle East (Afghanistan, Algeria, the Islamic Republic of Iran, Saudi Arabia, and the Syrian Arab Republic) and in Brazil and Peru (Desjeux 1996). Reliable data on incidence and prevalence are scarce because only 33 endemic countries provide official notification of infection.

Leishmaniasis transmission is increasing in several areas. For example, the number of cases of CL in Kabul, Afghanistan, increased from 14,200 in 1994 to 65,000 in 2002, and the number of cases of VL in northeastern Brazil increased from 1,840 in 1998 to 6,000 in 2002. Such increases reflect the following environmental, land-use, and behavioral changes that increase exposure to the sandflies:

- Rural-urban migration seems to have contributed to urbanizing VL in Brazil, whereas in East Africa, VL seems to be more closely associated with migrations of seasonal workers and refugees. Transborder migrations between Bangladesh, India, and Nepal are also a risk factor for VL.
- New settlements in high-risk endemic areas, such as those established by people migrating from high plateaus to tropical plains in some Andean countries, increase their exposure to vectors.
- Development in areas of zoonotic transmission, such as road building, mining, oil prospecting, forestry, and eco-tourism, and military activity increase risks for those involved (Desjeux 2001).
- Deteriorating social and economic conditions in the poorer suburbs of some cities may contribute to increasing transmission, especially of VL.

Leishmaniasis can be an opportunistic infection in people with HIV/AIDS, and coinfections have been reported in 34 countries (Desjeux and Alvar 2003). Malnutrition or HIV/AIDS coinfection can also increase disease severity by impairing the immune response.

African Trypanosomiasis

African trypanosomiasis is caused by parasites transmitted by tsetse flies (*Glossinidae*). The most important are forms of *Trypanosoma brucei* that infect humans and livestock, and *T. congolense* and *T. vivax* that infect only livestock. Human infection causes severe disease known as sleeping sickness, which is acute in the case of infection with *T. brucei rhodesiense* but more chronic with *T.b. gambiense*. Both forms lead to central nervous involvement and are fatal without appropriate treatment.

Disease Manifestations

Parasites are transmitted by the bite of infected tsetse flies. They multiply locally in extracellular spaces, producing a characteristic lesion or chancre. The parasites circulate in blood and lymph, resulting in waves of parasitemia with episodes of fever, often accompanied by chills, rigor, malaise, prostration, and weight loss. These symptoms may occur within days of development of the chancre and constitute the hemolymphatic early stage. Febrile episodes become less severe as the disease progresses, and after a variable period the parasites invade the central nervous system and cerebrospinal fluid, leading to the late stage, with meningoencephalitis typically accompanied by severe and protracted headache, apathy, sleep disorders, irritability, and antisocial behavior.

The clinical features of late-stage sleeping sickness can resemble AIDS. With *T.b. rhodesiense*, meningoencephalitis typically occurs within weeks of initial infection, whereas with *T.b. gambiense*, this syndrome occurs later, sometimes after several years. Untreated disease causes relentless deterioration in cerebral function, with patients becoming increasingly difficult to rouse and passing into coma and death. Infection does not seem to confer immunity, so reinfection can occur after treatment.

Transmission and Vectors

Male and female tsetse flies are obligate bloodsuckers and can transmit trypanosomes, which undergo cyclical development in the infected flies. With *T.b. gambiense*, the main reservoir host is people, so tsetse flies mainly transmit from person to person, although

increasing evidence suggests that pigs and some other animals are also important reservoirs. With *T.b. rhodesiense*, the main reservoir hosts are cattle and related animals, so transmission occurs mainly from animals to humans, although transmission from human to human also occurs (Okoth 1986). Mechanical (Frézil 1983), sexual (Rochas and others 2004), and transplacental (De Raadt 1985; Libala, Wery, and Ruppel 1978; Traub and others 1978) transmission have been described but are believed to be insignificant.

Thirty-one species and subspecies of *Glossina* are recognized. All probably can transmit trypanosomes, but only eight are known vectors for human infection. Animal trypanosomiasis can be found wherever wild tsetse flies occur, but human trypanosomiasis is usually associated with historic foci with strong epidemic potential. Most *T.b. gambiense* transmission is attributed to *G. palpalis* species occupying riverine and forest habitats in West and Central Africa, whereas *T.b. rhodesiense* transmission is mainly attributed to *G. morsitans* species in East African savannas. *G. fusca* species, although important vectors of animal trypanosomiasis, are considered insignificant for human forms.

Tsetse flies have an unusual life cycle. An inseminated female nurtures the egg and larva in her uterus, depositing the mature larva on the ground, where it burrows and pupates. Thus, each female produces only one offspring at a time. She produces up to 12 during her two- to three-month adult life span. The intrinsic population growth rate is low. Even small increases in average daily mortality rates can cause population decline, even to extinction.

Epidemiological Trends

Tsetse flies occur in parts of 37 countries in Sub-Saharan Africa. Animal trypanosomiasis is widespread throughout this region, but human disease is focused in areas of 20 countries. Over the entire tsetse-fly belt, WHO estimates that 60 million people are at risk of infection, with a standing prevalence of about 300,000 infections. Of these, probably fewer than 15 percent are diagnosed and treated (Cattand, Jannin, and Lucas 2001). For *T.b. rhodesiense*, epidemiological work in Uganda estimated that for every individual correctly diagnosed and treated, a further 12 cases are undiagnosed and unreported (Odiit 2003). The incidence of sleeping sickness has been increasing steadily since the 1970s, with epidemics in several areas, particularly the Democratic Republic of Congo (DRC) and northern Angola. In 1998–99, some 45,000 new cases were reported each year, representing a 10-fold increase since the 1960s. Most current epidemics are due to *T.b. gambiense*, although major epidemics of *T.b. rhodesiense* occurred in Uganda in 1978, 1980, and 1988.

The apparent increase is largely attributable to a decline in tsetse and trypanosomiasis control operations, which are influenced both by changing political priorities and by civil unrest and war. In the DRC, some 10,000 cases were diagnosed annually during the 1980s, but after four years with little or no control, the number of reported cases rose to 30,000 per year. In Angola, cases rose sixfold following the interruption of control operations because of war. Transmission is also occurring in new locations. In 1999, urban and periurban transmission was reported in Kinshasa, DRC, and in Luanda, Angola, and a new focus was reported in Soroti, Uganda, where an epidemic of *T.b. rhodesiense* disease followed the introduction of infected cattle (Fèvre and others 2001).

Disease Burden

All three diseases affect substantial populations. Globally, WHO estimates that 500,000 cases of DHF occur annually. Assuming that DHF cases constitute 6 percent of all clinical

dengue cases (that is, all other cases are classical DF) implies a total of almost 8 million new infections per year. For leishmaniasis, current estimates suggest an overall prevalence of 12 million people infected in an at-risk population of 350 million, suggesting more than 2 million new infections each year. The prevalence of sleeping sickness is estimated at 300,000 people, with 60 million people considered to be at risk. Uncertainty about the true number of cases makes all these estimates approximate, particularly because incidence is increasing. In terms of disability-adjusted life years (DALYs) lost to these diseases (Table 1), a dengue or trypanosomiasis death accounts for 27 to 28 DALYs lost. Leishmaniasis kills less often than trypanosomiasis, but each death is responsible for a loss of 34 DALYs.

Table 1: Number of Deaths and DALYs Caused by Dengue, Leishmaniasis, and African Trypanosomiasis, by World Bank Region, 2001 (thousands)

Region	Dengue		Leishmaniasis		African trypanosomiasis		Total	
	Deaths	DALYs	Deaths	DALYs	Deaths	DALYs	Deaths	DALYs
East Asia and the Pacific	8	217	2	48	0	0	10	265
Europe and Central Asia	0	0	0	6	0	0	0	6
Latin America and the Caribbean	2	59	0	37	0	0	2	96
Middle East and North Africa	0	8	1	48	1	22	2	78
South Asia	9	240	40	1,306	0	0	49	1,546
Sub-Saharan Africa	0	4	8	312	48	1,310	56	1,626
Total	19	528	51	1,757	49	1,332	119	3,617

Source: Disease Control Priorities in Developing Countries. 2nd edition. Jamison DT, Breman JG, Measham AR, et al., editors. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006.

Dengue

In hyperendemic areas of Southeast Asia, where multiple virus serotypes are circulating, DF and DHF are mainly childhood diseases and in some countries are leading causes of pediatric hospitalization and death, particularly in Cambodia, Myanmar, and Vietnam. Worldwide, 80 to 90 percent of deaths occur before age 15. In recent years in the Americas, DHF in adults in endemic form has been reported frequently (Diaz and others 1988; Guzmán and others 1999; Harris and others 2000; Zagne and others 1994). In some countries, the disease is more frequent among females, and in Cuba, significantly more severe cases occur among Caucasians than among those of African descent (Kouri, Guzmán, and Bravo 1987). Dengue causes relatively few deaths, estimated at 19,000 in 2001, corresponding to a case-fatality rate of 3.8 percent for DHF. Nonetheless, it can cause a substantial burden: in Puerto Rico during 1984–94, the DALY loss per million population was similar to that for the entire Latin America and Caribbean region from malaria, tuberculosis, intestinal helminths, and the childhood disease cluster (Meltzer and others 1998).

Economic Impact

Studies in Thailand estimated the economic impact of dengue as equivalent to US\$12.6 million in 1994, of which patients and their families incurred 45 percent (Okanurak, Sornmani, and Indaratna 1997). Kouri and others (1989) estimate the cost of the 1981 DHF epidemic in

Cuba at US\$103 million, constituting US\$41 million in medical care, US\$5 million in social security disability payments, US\$14 million in lost production, and US\$43 million for vector control. For Southeast Asia, Shepard and others (2004) estimate individual treatment costs of US\$139 for DHF and US\$4.29 for DF (including health clinic visits, hospitalization, medications, travel expenses, and parents' time seeking treatment for their children). This estimate implies annual costs in the region of US\$105 million—US\$69.5 million for DHF and US\$35.5 million for DF. Extrapolating from current trends (on the basis of cases reported to WHO since 1960), this figure will increase to an average of US\$118 million each year through the first decade of the 21st century. Using the Thailand study to add the value of productive work lost doubles this figure to US\$236 million. Thus, during the next decade, Southeast Asian economies could lose a total of US\$2.36 billion because of DF and DHF. Additional economic losses are expected because of the impact of dengue outbreaks on tourism.

Social Impact

During the transmission season, parents familiar with DHF are anxious about their children's survival and the financial consequences of emergency medical care. In Cambodia, even relatively modest out-of-pocket health expenditures can lead to debt and poverty (Van Damme and others 2004). The psychological burden is poorly understood and warrants further study.

Even though dengue affects all strata of society, it may selectively affect the poorest. Most larval habitats in dengue-endemic communities are artificial: water storage containers, flower vases, discarded food containers, used tires, and habitats created by poor design of roof gutters and drains. Local vector ecology is largely determined by community social and cultural practices and infrastructure, and increasing urbanization typically attracts the poor to periurban settlements with deficient water supplies. Studies in the República Bolivariana de Venezuela (Barrera, Avila, and Gonzalez-Teller 1993; Barrera and others 1995) and in Thailand (Nagao and others 2003) have shown higher *Ae. aegypti* infestations where water distribution systems are deficient or unreliable. Along the border between Mexico and the United States, Reiter and others (2003) attribute the low dengue seroprevalence reported in Laredo, Texas, to factors such as air conditioning that limited human-vector contact, whereas in contiguous Nuevo Laredo on the Mexican side, where per capita income was one-seventh of that in Laredo, seroprevalence was much higher despite lower vector densities.

In countries with weak or unprepared health services, epidemics of dengue can be extremely disruptive and health services can be rapidly overwhelmed. Frequently, governments declare states of emergency to mobilize additional resources against dengue outbreaks, sometimes deploying the army to eliminate or apply larvicides to larval habitats. These responses are often launched at or after the peak of the epidemic, and the decline in transmission is unjustifiably attributed to the intervention rather than to the natural epidemic decline.

Leishmaniasis

In 2001, leishmaniasis killed an estimated 51,000 people, including 40,000 in South Asia and 8,000 in Sub-Saharan Africa, representing 0.3 percent and less than 0.1 percent, respectively, of all deaths (Table 1). Nearly all deaths occurred at ages 5 to 29. Males were more affected than females, especially in Sub-Saharan Africa, where the ratio was three to one.

Economic Impact

Treatment for leishmaniasis is expensive, especially for VL. For many countries, the cost of treating all leishmaniasis patients would far exceed their total health budgets. For a WHO-recommended course of pentavalent antimonials, current drug costs per patient are US\$150 for sodium stibogluconate, US\$120 for meglumine antimoniate, and US\$30 for generic sodium stibogluconate. Cases not responding to antimonials may require second-line, more toxic drugs, such as amphotericin B at a cost of US\$60 or pentamidine at a cost of US\$70. Less toxic amphotericin in liposomes is effective, but costs US\$1,500 per patient. The first oral drug for VL, miltefosine, currently costs US\$120 per patient.

In addition to drug costs, the additional costs of drug delivery can be high, especially for patients in remote areas. Patients often live far from a treatment center, and the expense of hospitalization may lead to interrupted treatment, facilitating resistance and requiring additional therapy. Without treatment, severe leishmaniasis can become chronic and debilitating, incapacitating patients and making them unable to work and vulnerable to poverty, malnutrition, and secondary infections.

Social Impact

Even self-limiting CL can leave disfiguring scars, which have associated stigma and may affect marriage prospects. CL can be disabling when lesions are numerous, and the most severe form, recidivans leishmaniasis, is difficult to treat, long-lasting, and disfiguring. In individuals with a defective cell-mediated immune response, the disseminated lesions of diffuse cutaneous leishmaniasis resemble those of leprosy. They do not heal spontaneously and frequently recur after treatment. Diffuse cutaneous leishmaniasis is recognized as a special public health problem, both clinically and because of its severe emotional consequences.

The lesions of mucocutaneous leishmaniasis can cause extensive destruction and distortion of oronasal and pharyngeal cavities, leading to mutilation of the face. Patients may be shunned and, in severe cases, even incarcerated. Although mainly associated with *L. braziliensis* and *L. guyanensis* in the Americas, mucocutaneous leishmaniasis has been reported in Africa, Asia, and Europe as a complication of *L. donovani* and *L. major* infections and, in immunosuppressed patients, of *L. infantum*.

Untreated VL is usually fatal. Even after recovery, patients may develop a chronic form of CL that usually requires prolonged and expensive therapy.

African Trypanosomiasis

WHO estimates the number of deaths caused by sleeping sickness as 48,000 in 2001 (Table 1), although current estimates are in the range of 50,000 to 100,000 per year. Men are affected at nearly twice the rate of women. In relation to mortality, of all parasitic diseases in Sub-Saharan Africa, trypanosomiasis ranks behind only malaria. As concerns DALYs, the health burden is similar to that of schistosomiasis. In Sudan, 33 DALYs on average are lost because of each premature death from sleeping sickness (McFarland 2003). In Uganda, 23 DALYs were lost per death, but only 0.21 DALYs per successfully treated individual (Odiit and others 2004). Underreporting makes deriving estimates for the whole continent difficult: 100,000 deaths per year would imply more than 2 million DALYs lost, compared with the WHO estimate of 1.31 million (830,000 for males and 480,000 for females) (Table 1).

Economic Impact

Information on age at death indicates that sleeping sickness mainly affects economically active adults. Data from Uganda show nearly 25 percent of cases occurring in those age 20 to 29 and more than 60 percent in those age 10 to 39 (Odiit 2003). Thus, when people become ill, their families not only become burdened with the care of seriously ill individuals but also often lose their breadwinners. Poor diagnostic support in many areas means that families often invest in a number of treatments that have no effect on the disease. In a *T.b. rhodesiense* area of Uganda, Odiit and others (2004) find that some patients made up to seven visits to health facilities before being correctly diagnosed, with just under three-quarters initially being diagnosed with malaria. For the 11 of 12 who were never diagnosed or were told that they had a different fatal disease, the costs to and burdens on their families can only be imagined.

In addition to the economic losses caused by interruption of their work, sleeping sickness patients face direct financial costs. Even though WHO now provides specific first-line drugs at no cost in excess of delivery and administration, hospitalization and treatment are expensive. In the DRC, Gouteux and others (1987) estimate that total costs are -equivalent to at least 25 percent of a year's income from agriculture.

Social Impact

The importance of sleeping sickness lies not only in the number of new cases reported, but also in its potential for epidemic outbreaks causing thousands of deaths: during recent epidemics in the DRC, in some villages up to 70 percent of the population became infected. Because of the severity of the disease, one case can affect all family members, placing a burden on the whole community, reducing the labor force, interrupting agricultural activities, and jeopardizing food security. Although untreated trypanosomiasis is lethal, treated patients often remain incapacitated, perpetuating the cycle of poverty, malnutrition, and disease. DALYs do not take into account the psychosocial impact and the "minor" disabilities. In adults, loss of memory and ability to concentrate is common. Such disabilities are often accompanied by reading and writing difficulties and occasionally by extreme incoherence. These disabilities greatly affect everyday life, particularly for those school-age children who, even after successful treatment, do not recover fully and cannot pursue their studies (Frézil 1983).

Burden of Animal Trypanosomiasis

Animal trypanosomiasis constrains agricultural production—in particular, the use of draft power. Cattle infected with *T.b. brucei*, *T. vivax*, or *T. congolense* quickly succumb to a wasting form of anemia. In many areas with a high tsetse challenge, such as Central Africa, cattle are few or not present at all. Elsewhere, countries invest an estimated total of US\$30 million to US\$50 million per year in some 35 million doses of veterinary trypanocides to prevent the disease in livestock (Geerts and Holmes 1998). About 60 percent of the cattle at risk are not treated, and the disease is thought to kill about 1 million a year. Current drugs are more than 40 years old, and drug resistance is increasing, as are problems of drug availability and accessibility, counterfeit drugs, and drug mismanagement (Geerts and Holmes 1998). Constraints on draft power mean that farmers can till only small plots, making subsistence farmers extremely vulnerable to food shortages. Milk yields are lower in infected cows, and animal trypanosomiasis lowers fertility and increases mortality, thereby constraining the overall growth rate of the number of livestock (Swallow 2000). Kristjanson and others (1999) estimate annual direct losses of US\$1.3 billion

per year as a result of lowered production of milk and meat, with aggregate agricultural losses attributable to trypanosomiasis estimated at US\$4.5 billion per year.

Management and Control Strategies

Dengue

Patient Management and Treatment

Classic dengue fever is generally self-limiting. No specific treatment is available, but supportive treatment must be given, including fluid replacement when necessary. Early recognition of DHF cases—indicated by intense, continuous abdominal pain; persistent vomiting; and restlessness or lethargy—and early supportive treatment are of utmost importance to reduce case-fatality rates (Martinez 1992). For differential diagnosis, a wide spectrum of viral and bacterial infections should be considered, especially leptospirosis, malaria, yellow fever, chikungunya virus, rubella, and influenza.

Vector Control

Although good patient management can be effective for individual cases, currently no alternative to vector control is available for the prevention of dengue. Most endemic countries have a vector control component in their programs; however, the application of vector control measures is frequently insufficient, ineffective, or both and is currently failing to reduce the public health burden to an acceptable level.

Most *Aedes* control programs rely on the application of larvicides and adulticidal insecticide space sprays (Zaim and Jambulingham 2004). Because *Ae. aegypti* characteristically breeds in water that does not contain high levels of organic pollutants, control measures typically must be applied to water stored for household purposes, including drinking water. WHO currently approves five insecticides for application to potable water (FAO 1999; WHO 1991). Since the early 1970s, the organophosphate temephos has been the most widely used, but increasing levels of resistance to this insecticide are reducing the duration of effectiveness of treatments in some countries (Brengues and others 2003; Lima and others 2003; Rodriguez and others 2001). An additional challenge is the growing objection among householders, particularly in Latin America, to the application of chemicals to drinking water.

Biological control agents, including larvivorous fish and copepods, have had a demonstrable role in integrated control of *Ae. aegypti*, but operational difficulties—particularly a lack of facilities and of expertise in mass rearing and the need for repeated introduction of these agents into some container habitats—have largely precluded their widespread use. One encouraging exception is Vietnam, where indigenous species of predatory copepods are increasingly used to control semipermanent larval habitats of *Ae. aegypti* (Kay and others 2002; Nam and others 2000). However, some communities have strong cultural objections to the introduction of live animals into household water storage containers—for example, in Thailand, where bathing with water that contains small fish or other creatures is widely regarded as unacceptable.

Environmental management is generally considered the core component of dengue prevention and control, including cleanup campaigns, regular emptying and cleaning of containers, installation of water supply systems, solid waste management, and urban planning. However, huge investments in infrastructure are needed to increase access to safe and reliable water supplies, to provide solid waste management services, and to dispose of liquid waste. In addition to overall health gains, such provision would have a major effect on vector ecology, although the relationship is not invariably an inverse one. Cost-recovery mechanisms, such as the

introduction of metered water, may encourage household collection and storage of roof catchment rainwater that can be harvested at no cost. Although unproven, the installation of community water services in rural townships and villages may be contributing to the rural spread of dengue in Southeast Asia and elsewhere.

At the household and community levels, where most vector control efforts are centered, increasing attention is given to such activities as covering or frequently cleaning water storage vessels, removing discarded food and beverage containers, and storing or disposing of used tires in such a way that they do not collect rainwater. Such tasks would seem to be simple and well suited to engagement by communities, but with a few exceptions, achievements to date have been unspectacular. Nevertheless, such community-based interventions are widely seen as the most promising way of achieving sustainable control through behavior change (Parks and Lloyd 2004).

Leishmaniasis

Leishmaniasis control is based primarily on finding and treating cases, combined where feasible with vector control and, in some zoonotic foci, control of animal reservoirs.

Diagnosis and Treatment

For VL, serological diagnosis is usually based on the enzyme-linked immunosorbent assay (ELISA), indirect fluorescent antibody tests, and direct agglutination tests, including a new direct agglutination test kit using lyophilized antigen, which avoids the need for refrigeration (Schallig and others 2001). A dipstick test based on a highly specific recombinant antigen is also available, together with a latex agglutination test that can be used to detect antigens in urine (Attar and others 2001; Sundar and others 1998). Parasitological diagnosis relies on microscopy of aspirates of the spleen, bone marrow, and lymph nodes.

Specific treatment includes the first-line drugs, which are pentavalent antimonials (sodium stibogluconate and meglumine antimoniate), and the second-line drugs, which are amphotericin B and AmBisome (amphotericin B in liposomes). Miltefosine for VL was registered in India in 2002, and aminosidine (paromomycin) has just completed phase 3 clinical trials and follow-up. For CL, parasitological diagnosis is made from skin smears followed by treatment with pentavalent antimonials. Treatment is given locally if lesions are few and relatively small, or systemically if lesions are more numerous. For mucocutaneous leishmaniasis, diagnosis relies on serology because patients generally develop a strong humoral response.

Vector and Reservoir Control

In foci of peridomestic or intradomestic transmission, vector control can be carried out by indoor residual spraying using pyrethroid insecticides. Individual protection using pyrethroid-impregnated bednets is also used in some areas. In zoonotic foci of VL, control has also included culling stray dogs—and pet dogs if found to be infected—although this practice is often poorly accepted by communities and is probably of limited effectiveness. Trials with insecticide-treated dog collars are showing some promise as an alternative way to reduce the peridomestic reservoir of infection (Mazlouni Gavgani and others 2002). For zoonotic CL, rodent reservoirs can be controlled using poisoned bait and environmental management, including physical destruction of rodents' burrows.

African Trypanosomiasis

For human trypanosomiasis, control consists primarily of active and passive case finding and treatment, occasionally associated with vector control operations. Dissemination of sleeping sickness can be prevented by regular surveillance of the population at risk, including diagnosis and treatment; control of the tsetse-fly population can affect the transmission of sleeping sickness as well as of animal trypanosomiasis. In *T.b. rhodesiense* foci, where cattle are reservoirs of the disease, treating cattle with trypanocides is being investigated as an additional approach to controlling outbreaks.

Case Finding and Treatment

No single clinical sign is regarded as pathognomonic for sleeping sickness. Tests have been developed to detect antibodies, circulating antigens, or trypanosomal DNA, but all require parasitological confirmation. For mass screening, infection can be confirmed by the card agglutination trypanosomiasis test, which is easy to perform and relatively inexpensive. Parasitological confirmation is by microscopy of lymph node aspirates and of thin or thick blood films. Concentration methods increase sensitivity. The most sensitive is the miniature anion exchange centrifugation technique. The capillary tube centrifugation technique is less sensitive but is commonly used in the field because of its ease and rapidity of use and its low cost.

Determining the stage of disease is essential, because early- and late-stage infections require different treatments. The criteria for late-stage infection are based on cerebrospinal fluid analysis.

Sleeping sickness is fatal if untreated. No vaccination exists. Specific drugs are currently available free through WHO. Pentamidine is used to treat early-stage *T.b. gambiense* infection, and suramine is used for early-stage *T.b. rhodesiense*. The organoarsenical compound melarsoprol (Arsobal) is used for the late stages of both. Eflornithine has been introduced to treat late-stage *T.b. gambiense* but is difficult to administer. Nifurtimox, although not yet registered for the treatment of sleeping sickness, has been used on compassionate grounds to treat patients unresponsive to melarsoprol.

Vector Control

A wide range of techniques for tsetse control is available (Maudlin, Holmes, and Miles 2004). Most current approaches exploit the acute susceptibility of tsetse flies to biodegradable pyrethroid insecticides. Spraying can be applied from the ground to known fly resting sites or at ultra-low volume from the air. Spraying is carried out sequentially to kill all flies initially present and thereafter to kill each generation of newly emerging flies. The sequential aerosol technique uses extremely low levels of insecticide and has been effective in Botswana, Somalia, South Africa, and Zambia. It is also useful against epidemic outbreaks of sleeping sickness, where a rapid cessation in contact between humans and tsetse flies is needed.

Tsetse flies can also be controlled using traps and targets. Targets are combinations of cloth and netting baited with an odor attractant and impregnated with a pyrethroid insecticide. Traps work on the same principle, but the fly is encouraged to enter a net or plastic chamber where it remains trapped. Live bait techniques are also used. Cattle are treated with a veterinary formulation of pyrethroid insecticides applied as sprays or pour-ons, which kill both tsetse flies and ticks. This technique has been successfully used in Burkina Faso, Ethiopia, Kenya, Tanzania, Zambia, and Zimbabwe (Kuzoe and Schofield 2005).

The sterile insect technique involves mass release of sterilized male tsetse flies, which compete with local males to mate with females. Because female tsetse flies generally mate only

once, the result is infertile offspring and a decline of the wild tsetse population. This technique is expensive, because it requires large-scale rearing of flies, and it is only recommended for use once the wild tsetse population has been suppressed to low levels using other techniques. A combination of insecticide spraying and trap deployment followed by the sterile insect technique has been successfully used to eliminate *G. austeni* from Zanzibar (Vreysen and others 2000).

Degrees of resistance to trypanosome infection are found in the N'dama, Dwarf, and Savannah Shorthorn breeds in West Africa and, to a lesser extent, in some Orma Boran breeds in East Africa. However, even though these cattle show tolerance, can control parasitemia, and resist development of anemia, they can ultimately succumb to the disease.

Costs and Cost-Effectiveness of Interventions

Dengue

Few studies are available on the cost-effectiveness of vector control for reducing dengue transmission. One of the difficulties is that the level of vector population control needed to reduce transmission is influenced by the human population's past exposure to the circulating virus serotype. A direct relationship is apparent between seroprevalence rates and levels of vector abundance needed for epidemic transmission. Thus, the paradox is that, as herd immunity declines over time in response to effective vector control, progressively lower vector densities can maintain the same level of transmission.

Modeling of the dynamics of dengue transmission is helping to improve understanding of the interrelationships between virus, vector, and host (Ferguson, Donnelly, and Anderson 1999; Focks and others 1995; Newton and Reiter 1992; Shepard 2001), but the absence of epidemiologically defined target levels for vector control has hindered calculations of cost-effectiveness. According to Shepard and others (2004), average annual costs for dengue vector control per 1,000 population were US\$15 in 1998 in Indonesia, US\$81 in 1994 and US\$188 in 1998 in Thailand, US\$240 in 2002 in Malaysia, and US\$2,400 in 2000 in Singapore. In 1997, spending on dengue control in 14 Latin American countries ranged from US\$20 to US\$3,560 per 1,000 population, with a median of US\$260. For 17 Caribbean islands in 1990, the corresponding expenditures ranged from US\$140 to US\$8,490, with a median of US\$1,340 (Nathan 1993). By contrast, McConnell and Gubler's (2003) study in Puerto Rico concludes that larval control programs that achieve a 50 percent reduction in dengue transmission and cost less than US\$2.50 per person would be cost-effective in that setting. From research based on analytical models (Shepard 2001) and primary data from Singapore, we estimate the cost of using environmental management for control at US\$3,139 per DALY averted and the cost of using insecticides at US\$1,992 per DALY averted.

Dengue case management depends on the severity of the illness. Despite the lack of information about cost-effective interventions to treat dengue cases, Shepard (2001) estimates an average cost of US\$587 per DALY averted by appropriate case management. Were a dengue vaccine to become available, the Shepard model estimates that immunization would cost US\$3,040 per DALY averted.

Leishmaniasis

Case Finding and Treatment

For leishmaniasis, diagnosis represents a small proportion of the cost of case finding and treatment, with diagnostic tests becoming available at approximately US\$1.50 for the dipstick, US\$3.00 for the direct agglutination test using freeze-dried antigen, and US\$1.50 for the urine

latex agglutination test. These tests can be used in the field. A study in Nepal (Pokhrel 1999) comparing outreach case detection using serology (the dipstick) with parasitological diagnosis at health centers (bone marrow aspirate) concluded that the median cost per VL case detected was US\$25 in the outreach program, compared with US\$145 at health centers (of which more than 50 percent was due to absence from work). Treatment costs increased these figures to US\$131 and US\$200 per patient, respectively.

In India, an examination of the costs of drugs and hospitalization and of the evolution of the disease under treatment (cure, relapse, failure, intolerance) indicated that the final cost of successful treatment depends largely on the basic drug cost, which averaged US\$86 per patient successfully treated with miltefosine (using reduced pricing because of the large number of patients), US\$467 for treatment with amphotericin B, and US\$1,613 for treatment with AmBisome. Given current estimates of about 100,000 cases of VL each year in the state of Bihar, India, the estimated total cost of treatment using miltefosine as a first-line drug and amphotericin B as a second-line drug would be about US\$11 million, or approximately US\$110 per patient (personal communication with P. Oliaro and S. Sundar on treatment options for kalaazar [visceral leishmaniasis], 2003). By contrast, analysis of humanitarian relief interventions by Médecins sans Frontières–Holland that combined case finding with treatment after a VL epidemic in southern Sudan indicated total costs of US\$394 per patient, or an average cost of US\$595 per life saved (Griekspoor, Sondorp, and Vos 1999). Thus, the average cost per DALY averted was US\$18.40.

Vector Control

Vector control is rarely carried out as a specific approach to leishmaniasis control, and cost-effectiveness estimates are not available. In general, domestic and peridomestic sandfly vectors are more susceptible to indoor residual spraying than are other domestic vectors, such as anopheline mosquitoes or triatomine bugs, so that transient suppression of sandfly populations is seen as an additional benefit of malaria or Chagas disease vector control in areas where these vectors coincide. However, insecticide-treated bednets, which are becoming widely deployed against malaria transmission, may also become cost-effective for reducing leishmaniasis in areas of domestic transmission. In Yenice, Turkey, the use of impregnated bednets reduced the incidence of CL from 1.90 percent to 0.04 percent between 2000 and 2001 (Alten and others 2003).

African Trypanosomiasis

Case Finding and Treatment

WHO (1986, 1998) has analyzed the costs of *T.b. gambiense* control by means of case finding and treatment based on practice in Côte d'Ivoire and Uganda. This work and other studies indicate that, at current prices, the cost of active detection using the card agglutination trypanosomiasis test with parasitological confirmation varies around US\$1 per person screened or slightly more for mobile teams. However, mobile teams are more effective in screening a high proportion of the population and are also more successful in ensuring that a high proportion of patients receive treatment. Unit costs are currently US\$0.33 per person for the card agglutination trypanosomiasis test and US\$2.20 for the miniature anion exchange centrifugation technique. Less sensitive parasitological techniques, such as examination of lymph node aspirate or blood smears, cost only a few cents but may miss a third to half of patients.

By contrast, treatment is expensive despite the availability of free drugs. Treatment of early-stage disease incurs costs of more than US\$100 per person, rising to more than US\$250 for late-stage treatment with melarsoprol and about US\$700 with eflornithine (WHO 1998). The long hospitalization period is a major component of costs during the second stage, although work undertaken by Burri and others (2000) on a shorter melarsoprol regimen offers opportunities for reducing these costs.

Despite the costs and the risk of complications, treating sleeping sickness patients in the second stage of the disease is cost-effective. In Uganda, costs were less than US\$10 per DALY averted for melarsoprol treatment and less than US\$20 per person for eflornithine (Politi and others 1995). Similarly, in southern Sudan, the cost per DALY averted ranged from US\$4 to US\$22 (Trowbridge and others 2001). Shaw and Cattand (2001) considered the costs of case finding and treatment for *T.b. gambiense* infection for three delivery options and a wide range of prevalences. Given the limited information available on DALYs gained or on the effect on transmission of reducing the size of the human reservoir, they estimate that under different scenarios the costs per DALY averted tend to converge. For most assumptions, the cost per DALY averted fell below a US\$25 threshold at prevalences of 0.5 to 1.0 percent but rose sharply at low prevalences, which explains the reluctance of control programs to invest in screening operations when prevalence is less than 0.2 percent. With better quantitative understanding of the effects of screening and removing patients from the reservoir in preventing future epidemics, investigators could demonstrate that even at low prevalences screening for sleeping sickness is highly cost-effective.

Vector Control

Several countries have undertaken community-based programs to trap tsetse flies, notably Côte d'Ivoire, where costs came to US\$2.30 per person protected per year (Laveissière and others 1994), and Uganda, which achieved a cost of US\$0.50 per person protected per year (Lancien and Obayi 1993). Vector control costs have been studied in more detail in the context of livestock disease (Maudlin, Holmes, and Miles 2004). These costs vary according to the technique used and the environmental context, often ignoring overheads for organizing and planning. With that caveat in mind, the figures per square kilometer cited for local tsetse-fly eradication range from about US\$250 to US\$550 at current prices for aerial spraying (based on experience in Somalia, South Africa, Zambia, and Zimbabwe); US\$250 to US\$400 per square kilometer for ground spraying; and US\$200 to US\$400 per square kilometer for targets. However, the cost of traps and targets falls to US\$25 to US\$60 per square kilometer for control or suppression operations alone. Projects treating cattle with insecticides have been implemented at costs of US\$50 to US\$60 per square kilometer. Use of the sterile insect technique is much more expensive because it relies on prior suppression of fly populations using another technique. The overall costs of the experimental eradication of *G. austeni* from Zanzibar using the sterile insect and other techniques were about US\$3,000 per square kilometer, although the International Atomic Energy Agency (IAEA) envisages that the cost of the sterile insect technique component could be reduced to less than US\$800 per square kilometer as the technology is developed and applied on a sufficiently large scale, (Dr. Udo Feldmann, IAEA, Vienna, personal communication).

Problems and Challenges for Disease Control

Dengue

Potential for Vaccine Development

The occurrence of DHF in children and adults with previous dengue antibodies, acquired passively or actively, has been the most important challenge for the development of a dengue vaccine. Lack of a suitable animal model, insufficient knowledge of disease pathogenesis, and limited research funding have also had a negative influence. Researchers generally agree that a dengue vaccine must confer long-lasting protection against the four dengue serotypes. Currently, they are following different strategies in the development of several vaccine candidates. Some vaccines are currently undergoing human clinical trials—for example, live attenuated dengue and yellow fever chimeric vaccines. The conventional live attenuated vaccines are entering phase 3 trials, while the chimeric vaccines are presently in phase 1 and phase 2 trials. Others are in the preclinical phase of development. To accelerate the development of a dengue vaccine, a new initiative—the pediatric dengue vaccine initiative—has been launched, with the major objective of mobilizing resources to accelerate the development of a safe and effective pediatric dengue vaccine (Almond and others 2002; Halstead and Deen 2002; Pang 2003).

Vector Control

Without a vaccine, vector control remains the only available strategy against dengue. Selective, integrated vector control with community and intersectoral participation, active disease surveillance based on a strong health information system, emergency preparedness, capacity building and training, and vector control research constitute the major elements of WHO's global strategy for dengue prevention and control. Since the eradication era, few examples of successful dengue prevention and control on a national scale are available. Exceptions include Cuba and Singapore, both island states. Cuba, with approximately 11 million inhabitants, has been able to interrupt dengue transmission. Despite being in an endemic area, the country has maintained low vector densities and has successfully controlled epidemics in recent years (Arias 2002). Critical factors contributing to this achievement are the strong dengue surveillance system, which integrates environmental, entomological, epidemiological, clinical, and virological surveillance in conjunction with the public health infrastructure, and a strong vector control program, along with good intersectoral coordination, active community involvement, and strong political commitment.

A limited array of tools is available for vector control interventions, any one of which can control at least part of the vector population or provide personal protection. However, approaches are converging, at least at the policy level, toward application of vector control tools through social or community mobilization. Consensus is growing that community-based approaches are desirable and necessary, and many believe that only through such approaches can a degree of sustainability be accomplished in relation to dengue vector control. Even though few such interventions have expanded beyond the pilot stage, the decentralization of budgetary and operational responsibilities for program delivery appears to offer opportunities for strengthening and expanding this integrated vector management approach.

Increasing levels of resistance of *Ae. aegypti* to temephos imply shorter intervals between treatments. This situation is already a reality in some countries, including Brazil and several Caribbean islands (Carvalho and da Silva 1999; Rawlins 1998). Resistance of adult mosquitoes to malathion and to pyrethroids has been reported in the Americas and in Asia (WHO 1992) and is likely to reduce the efficacy of space spraying. Given the peridomestic ecology of *Ae. aegypti* in most regions and the widespread use of pyrethroids for public health purposes and in household insecticide products, the rate of development of pyrethroid resistance is likely to

accelerate. At the same time, few new insecticide products are becoming available in the public health market because of the costs involved in development and registration compared with the returns on investment from the relatively small commercial market. The high cost of re-registration of existing products is also contributing to the withdrawal of some insecticides from the market.

New Risk Factors

Environmental changes, particularly those related to climate, directly affect the incidence and prevalence of vectorborne diseases. However, social factors, such as lifestyles and population density, particularly in the case of dengue, are also important. Using an empirical model of the effect of population and climate change on the global distribution of dengue fever, Hales and others (2002) conclude that predicted changes in humidity will increase the areas with a climate suitable for dengue transmission.

The world is also becoming increasingly urbanized: during 2000–25, Asia's urban population is expected to double, and that of Latin America and the Caribbean is expected to increase by almost 50 percent. The resulting high human population densities, coupled with lifestyles that increasingly contribute to the proliferation of larval habitats and infrastructural deficiencies in relation to water supply and sanitation, are such that effective delivery of vector control on the scale needed is beyond the reach of many governments. The increasing global trend in international travel also facilitates the dissemination of virus serotypes and strains between vulnerable populations.

Genetic variability is another element to be considered. The genetic diversity of the viruses is increasing, with some genotypes associated with severe disease (Cologna and Rico-Hesse 2003; Leitmeyer and others 1999; Rico-Hesse and others 1997). Recombination has been demonstrated in all four serotypes, but the implications in terms of pathogenesis are unknown. In addition to recombination, mutations, gene flow, and other factors could further influence the genetic diversity and selection of virulent strains (Holmes and Burch 2000). At the same time, in addition to initial observations of the higher risk of DHF in Caucasian than in those of African descent, a few reports associate some human leukocyte antigen alleles with disease severity (Bravo, Guzmán, and Kouri 1987; LaFleur and others 2002; Loke and others 2001; Paradoa, Trujillo, and Basanta 1987; Stephens and others 2002). The sequence of infecting viruses and, more recently, the longer interval between primary and secondary infection as a risk factor for DHF, add a new perspective to the problem (Guzmán and others 2002; Nisalak and others 2003).

Leishmaniasis

Because the primary control strategy against leishmaniasis is based on case finding and treatment, the priority for control is developing and implementing improved diagnostic methods and better treatments that are more amenable to field use. A parallel requirement is for the development of more cost-effective drug delivery systems, especially ones that take advantage of new oral drugs, such as miltefosine, and the planned registration and local production of aminosidine in India.

Improved Diagnostics and Treatment

Even though the new serological tests, such as the dipstick, lyophilized direct agglutination test kit, and latex agglutination urine test, represent major improvements, they are not yet widely used in endemic countries. Moreover, they are indirect tests that cannot provide direct

parasitological confirmation of infection or of cure immediately following treatment. Current parasitological tests tend to be highly invasive and can be costly to perform; therefore, simple molecular-based tests would be an advantage.

For leishmaniasis treatment, development of the oral VL drug, miltefosine, represents a substantial improvement, but it remains expensive and with a long treatment regimen and cannot be administered to pregnant women because of the risk of teratogenicity. Further clinical evaluation is required to establish the possibility of shorter treatment regimes and the potential of combination therapy to inhibit the development and spread of drug resistance. Another oral drug, sitamaquine, is currently under development and will require similar clinical and implementation studies. Clinical trials of aminosidine (paromomycin) are proceeding, and use of this drug against VL may become widespread. An improved understanding of disease pathogenesis would be helpful in refining the criteria for cure and in improving patients' prognosis.

Vaccine Development

The leishmaniasis offer substantial opportunities for vaccine development, and a crude vaccine against CL has been widely used in parts of the Middle East. Trials of a second-generation vaccine that includes three *Leishmania* antigens are currently in progress.

Vector Control

Control of domestic and peridomestic sand-fly vectors will probably continue as an additional benefit accruing to programs against other insect vectors using indoor residual spraying or insecticide-treated bednets. However, in areas where dogs are among the main reservoir hosts, increased use of insecticide-treated dog collars would merit further appraisal. Such collars not only would reduce the likelihood of new infections in dogs, but also could reduce the risk of transmission from dogs to humans.

African Trypanosomiasis

Improved Diagnostics

Serological diagnosis is reliable for verifying infection; however, most district hospitals or peripheral health units have neither the facilities nor the necessary expertise to perform and read serological tests. In the past, serological diagnosis, based on indirect fluorescent antibody tests and ELISA, was restricted to central-level facilities or specialized mobile teams. The card agglutination trypanosomiasis test has substantially simplified the use of serology but requires specifically equipped health units with a cold chain. Parasitological diagnosis, such as the miniature anion exchange centrifugation test, is more expensive and complicated to use in field surveys despite the development of a simplified sterile kit version. Molecular diagnostics are not yet developed to a level appropriate for widespread field use.

Treatment

Despite the availability of drugs free of charge from WHO, treatment is hampered by the length of hospitalization required and by the toxicity of currently available drugs. In addition, inability to use the same drug in the early and late stages of the disease complicates the treatment protocol. The existing late-stage drug, melarsoprol, is unsafe, its secondary reactions are numerous, and the occurrence of a lethal encephalopathic syndrome in 5 to 10 percent of treated cases means that patients on melarsoprol must be hospitalized. A new oral drug for the early stage, soon to be registered, must be introduced in the field, which will take several years.

Drug resistance is well established in animal trypanosomes. For *T. congolense*, *T. vivax*, and *T. evansi*, resistance to all available drugs has been reported, along with trypanosome populations with multiple drug resistance (Geerts and Holmes 1998). Much less information is available on human pathogenic trypanosomes. The resurgence of human African trypanosomiasis in recent years has been accompanied by increasing reports of treatment failure using melarsoprol. As early as 1960, *T.b. rhodesiense* patients in Uganda were reported to have relapsed after two or more courses of melarsoprol, and in 1977, a 40 percent melarsoprol relapse rate was reported in the DRC.

Relapses after treatment with early-stage drugs remain rare. Whether relapses after melarsoprol treatment reflect parasite drug resistance or host factors is unknown. Furthermore, even though increasing rates of melarsoprol failure have been observed in several countries, the magnitude and geographic distribution of the problem have not been determined. Analyses of existing data are complicated by the lack of a standard treatment regimen and the range of clinical and laboratory criteria used to define a relapse.

Vector Control

Even though available techniques to control tsetse flies can be highly effective (Maudlin, Holmes, and Miles 2004), all are constrained by the difficulties of applying them on a large enough scale for long enough to achieve sustainable results. Insecticide spraying is efficient but is difficult to sustain because of logistical constraints and high costs. Targets and traps are effective, but their deployment is difficult to sustain for long periods, and implementation through community participation requires constant motivation and supervision to remain effective. To address these problems, the African Union has launched the Pan African Initiative (PATTEC), which focuses on identifying regions where elimination of the tsetse fly may be feasible using currently available techniques. This initiative is designed as part of a poverty reduction strategy that aims at eliminating the problem of tsetseborne animal trypanosomiasis, but in several areas it will also reduce the risk of human infections.

Summary

For dengue, leishmaniasis, and African trypanosomiasis, the longstanding problem is the lack of adequate specific treatment. For dengue, no specific treatment is available. For the leishmaniasis and African trypanosomiasis, specific treatment has long depended on antiquated drugs that would be considered far too toxic for introduction under modern registration systems. Even though progress is being made, especially in relation to the development of new oral drugs for leishmaniasis, in purely pragmatic terms what is currently available will probably represent almost the entire therapeutic arsenal for the coming decades. Even without toxicological problems, the development and registration of a new candidate drug will, given current requirements, take at least a decade.

Although basic research will continue (Table 2), the current challenge is to make better use of what is already available. Dengue can be prevented with available vector control tools and strategies designed to reduce the risk of transmission. This method requires a sustainable surveillance system capable of providing early warning and predictions based on experience of factors predisposing to new epidemic outbreaks. To a large extent, it becomes a management exercise that accepts that some dengue transmission will occur but aims at preempting epidemic outbreaks rather than instigating emergency measures after an outbreak is in full crudescence.

Moreover, because preemptive measures and emergency responses are competing strategies, analyses of their relative cost-effectiveness would be appropriate.

Case finding and treatment for the leishmaniasis and African trypanosomiasis depend on the effectiveness of the diagnostic and treatment packages. Such packages are available, and research is required into the most cost-effective means for large-scale implementation. Again, the management exercise is to accept that some transmission will occur but to be aware that cases can be found and treated with minimal losses to healthy life. As with dengue, predictive surveillance will help focus attention on those areas where outbreaks seem most likely, and rapid, accurate diagnostics are crucial both to avoid the waste and danger of mistreatment and to minimize delays in administering the specific treatment required. But should such approaches rely on health centers, on mobile teams, or on some combination of the two? To what degree can the specialist diagnosis and treatment teams be integrated into more general approaches to health care? And, most crucially, how is the epidemiological surveillance to be organized: disease and vector notification, geographic information system mapping, analysis, and prediction?

Table 2: Control Strategies, Major Challenges, and Research Needs of Each Disease

Disease	Principal control strategy	Major problems and challenges	Major research needs
Dengue	Interruption of transmission through vector control Patient management and supportive treatment	Lifestyles that provide abundant artificial larval habitats Urban water infrastructure and management Sustainable vector control Early diagnosis and treatment Vaccine development	Vector control thresholds to interrupt transmission Behavioral changes conducive to dengue prevention Pathogenesis and disease prognosis Vaccine development
Leishmaniasis	Case detection and treatment	Rapid field diagnosis Deployment of oral drugs for treatment Vaccine development	Molecular-based field diagnostic kits Effective, safe, oral drug treatments, including combination therapy Diagnosis and treatment strategies
African trypanosomiasis	Case detection and treatment Interruption of transmission through vector control	Rapid field diagnosis, including determination of stage of infection Safer drug treatment regimens Sustainable large-scale vector control	Molecular-based field diagnostic kits Effective, safe, oral drug treatments Vector population genetics to determine areas amenable to vector population elimination

For the leishmaniasis, vector control seems unlikely to become a major component of disease control except where sandfly distribution overlaps with that of other vectors or where use of personal protection measures can be more widely encouraged. For dengue, vector control is a major component, but unless *Aedes* eradication appears again on the agenda, predicting the levels of control required in specific situations will require much greater understanding of transmission dynamics. Significant resources have been wasted on emergency dengue vector control, which has subsequently been seen to have had little more than a palliative effect, whereas sustained suppression of vector populations may require changes in urban water management and in human behavior that exceed the usual remit of health specialists.

For African trypanosomiasis, however, the prospects for sustainable vector control are more promising. The vector's low reproductive rate, combined with its extreme sensitivity to ultra-low doses of biodegradable insecticides, put tsetse flies among the most promising candidates for large-scale elimination. Campaigns against tsetse flies during the past century were invariably successful until they were discontinued and the controlled areas became reinvaded. Thus, the operational issue is to design large-scale international programs that can successively eliminate tsetse populations and prevent reinvasion of controlled areas, as contemplated by the African Union's Pan African Initiative.

In essence, all three diseases face parallel needs involving some marginal improvements to existing control techniques, but, most important, they require a management exercise that acknowledges the long-term need for surveillance, adequate reporting, case finding, and treatment. The primary challenges seem to reside less in the domain of new tools and more in the deployment of what is already available.

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