

REVIEW ARTICLE

GLOBAL HEALTH

Disease Eradication

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N Engl J Med 2013;368:54-63.

DOI: 10.1056/NEJMra1200391

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SINCE THE LAST CASE OF NATURALLY OCCURRING SMALLPOX, IN 1977, there have been three major international conferences devoted to the concept of disease eradication.¹⁻³ Several other diseases have been considered as potential candidates for eradication,⁴ but the World Health Organization (WHO) has targeted only two other diseases for global eradication after smallpox. In 1986, WHO's policymaking body, the World Health Assembly, adopted the elimination of dracunculiasis (guinea worm disease) as a global goal,⁵ and it declared the eradication of poliomyelitis a global goal in 1988.⁶ Although both diseases now appear to be close to eradication, the fact that neither goal has been achieved after more than two decades, and several years beyond the initial target dates for their eradication, underscores the daunting challenge of such efforts, as does the failure of previous attempts to eradicate malaria, hookworm, yaws, and other diseases.¹

The word "eradicate" is defined as "to pull or tear up by the roots" and "to remove entirely, extirpate, get rid of."⁷ Definitions of eradication and elimination have also been suggested by various international bodies (and are used herein), and the International Task Force for Disease Eradication uses certain scientific and social criteria when evaluating candidate diseases (see box).^{1,2,4} Eradication of a disease means worldwide interruption of transmission, whereas elimination means interruption of transmission in a limited geographic area. The term "elimination" is often used imprecisely.⁸ For example, the World Health Assembly resolutions in 1986 and 1989 referred to the "elimination" of dracunculiasis but changed the term to "eradication" for the same global goal in a 1991 resolution.

A brief review of five diseases selected for eradication or elimination will illustrate the potential benefits of such efforts and some of the challenges they pose (see the interactive graphic, available with the full text of this article at NEJM.org). Although dracunculiasis and poliomyelitis are now the only officially sanctioned targets of eradication campaigns, the WHO has designated the campaign against lymphatic filariasis as the Global Program to Eliminate Lymphatic Filariasis. These three programs represent different levels of international commitment to disease eradication. The program to eliminate onchocerciasis (river blindness) from the Americas is an example of a highly successful regional initiative, whereas the effort to eliminate malaria and lymphatic filariasis from Hispaniola is an example of a compelling, binational initiative that might suggest the feasibility of a global eradication effort.

Several key principles are inherent in an eradication or elimination campaign: the need to intervene everywhere the disease occurs, no matter how remotely located or difficult to access occurrences of disease are or how minor the perceived problem is in an individual country or area; the importance of monitoring the target disease and the extent of interventions closely; the need for flexibility and urgency in response to ongoing monitoring and operational research; and the need

for an intense focus on the goal of stopping transmission of the targeted disease, even when the costs per case rise sharply as the number of cases declines. Common difficulties faced by such campaigns include sporadic or widespread political insecurity in areas where the disease is endemic, inadequate or delayed funding, and the challenges of motivating officials, health workers, and affected populations.

DRACUNCULIASIS

The global campaign to eradicate dracunculiasis began in 1980 at the Centers for Disease Control and Prevention (CDC)⁹ and since 1986 has been led by the Carter Center in close cooperation with the WHO, the CDC, and the United Nations Children's Fund (UNICEF).¹⁰ The life cycle of the parasite *Dracunculus medinensis* is shown in Figure 1A. When exposed to water, the adult worms discharge thousands of larvae, which are ingested by tiny crustaceans (cyclops). About a year after a person has drunk water from ponds or open wells contaminated with these crustaceans, adult worms measuring about 1 m in length slowly begin to emerge through the infected person's skin.

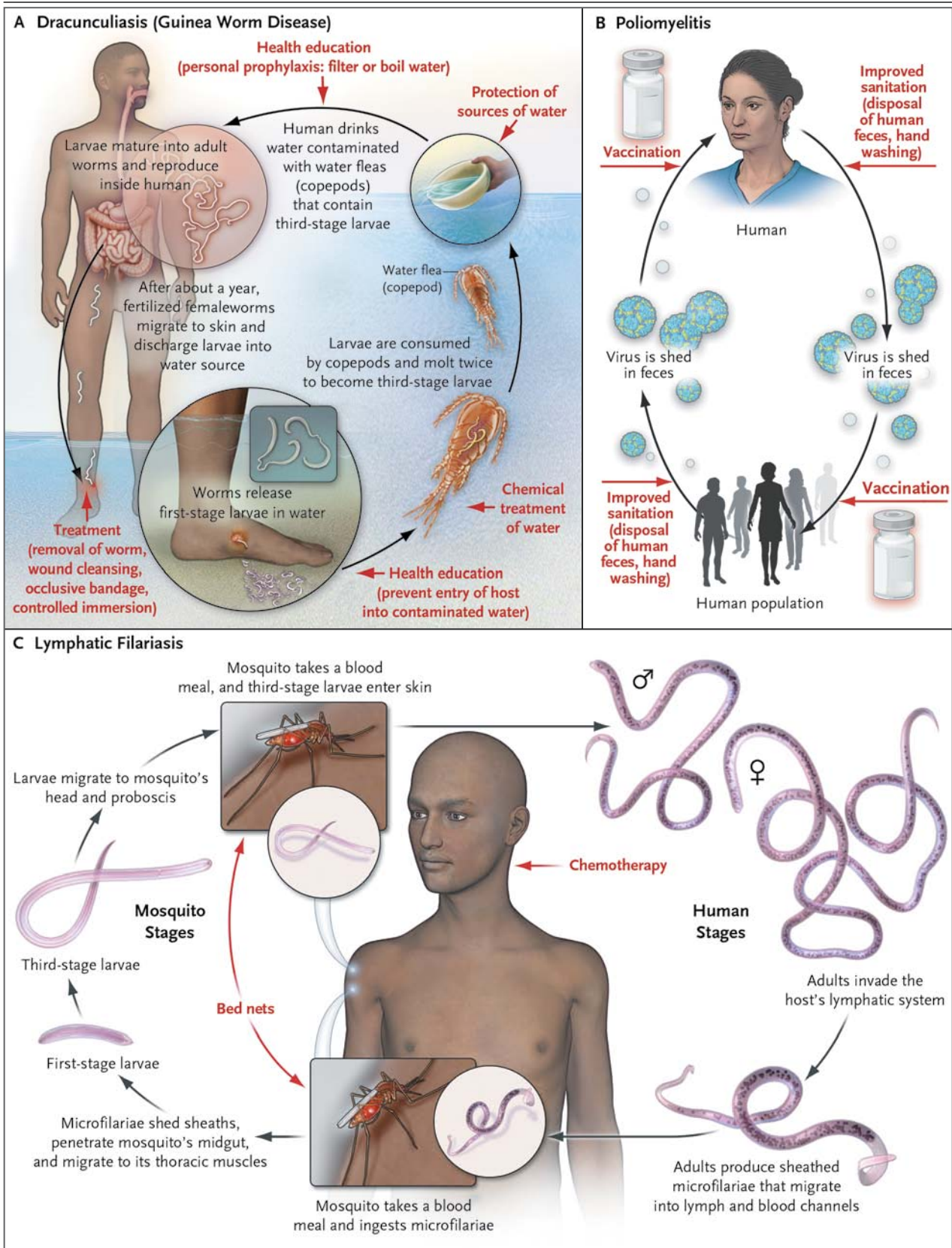
Dracunculiasis met the scientific criteria for eradication (see box), although the campaign was handicapped by the 1-year incubation period of the parasite and the lack of a vaccine or curative treatment. The true extent and burden of the disease among neglected populations were unknown because cases of dracunculiasis were greatly underreported. The adverse effects of this disease on health, agriculture, and school attendance were easy to imagine, however, since the pain and secondary infections associated with the emergence of the worms incapacitated many affected persons for several weeks during the agricultural season. The main interventions included health education focused on teaching villagers how to filter their drinking water and avoid contaminating the water, application of a mild larvicide to water sources, voluntary isolation of patients (case containment), and provision of safe water sources when possible.¹¹ Synergistic benefits of this campaign have included the development of village-based active case surveillance and health education and improved supplies of drinking water.

Definitions
<p>Eradication</p> <p>Zero disease globally as a result of deliberate efforts</p> <p>Control measures no longer needed</p> <p>Elimination</p> <p>Zero disease in a defined geographic area as a result of deliberate efforts</p> <p>Control measures needed to prevent reestablishment of transmission</p>
Criteria for Assessing the Eradicability of a Disease
<p>Scientific feasibility</p> <p>Epidemiologic susceptibility (e.g., no nonhuman reservoir, ease of spread, naturally induced immunity, ease of diagnosis)</p> <p>Effective, practical intervention available (e.g., vaccine, curative treatment)</p> <p>Demonstrated feasibility of elimination (e.g., documented elimination from island or other geographic unit)</p> <p>Political will and popular support</p> <p>Perceived burden of the disease (e.g., extent, deaths, other effects; relevance to rich and poor countries)</p> <p>Expected cost of eradication</p> <p>Synergy of eradication efforts with other interventions (e.g., potential for added benefits or savings)</p> <p>Need for eradication rather than control</p>

Down from an estimated 3.5 million cases in 20 African and Asian countries in 1986,¹² the number of cases reported in 2011 was only 1058, most of which were in the new Republic of South Sudan, with a few in Mali (12 cases) and Ethiopia (8 cases), as well as Chad (10 cases), in which a new outbreak was discovered in 2010 (Fig. 2).^{13,14} The eradication strategy evolved from an emphasis on the provision of safe water supplies to a focus on health education and the use of cloth filters and, later, to case containment. The active leadership of former U.S. President Jimmy Carter, the focus on village-based reporting and interventions, and major funding provided by the Bill and Melinda Gates Foundation all facilitated this program's achievements. Political instability in some affected areas of South Sudan and Mali are the main challenges to eradicating dracunculiasis. The estimated cost for this program (1986–2015) and for certification of eradication, not including provision of a water supply, is approximately \$350 million.



An interactive graphic with information on dracunculiasis is available at NEJM.org



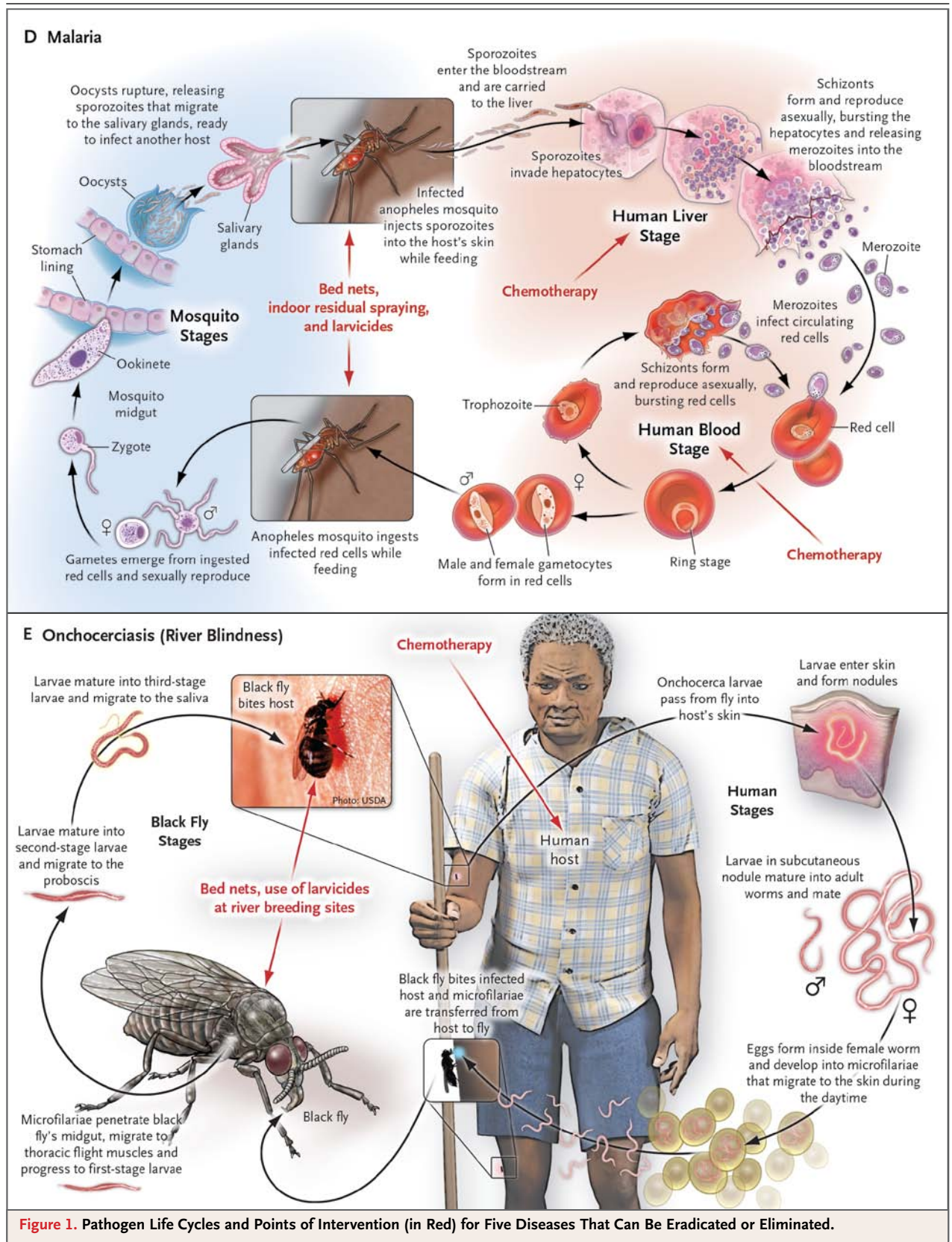
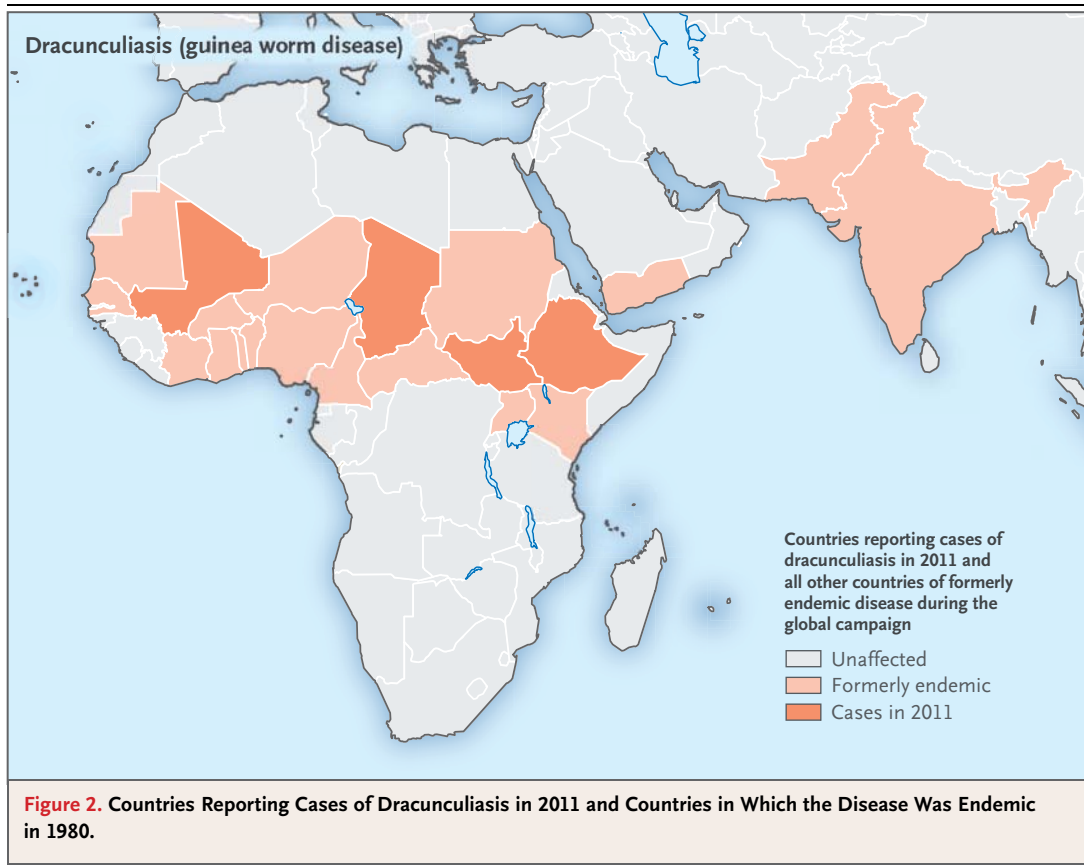


Figure 1. Pathogen Life Cycles and Points of Intervention (in Red) for Five Diseases That Can Be Eradicated or Eliminated.



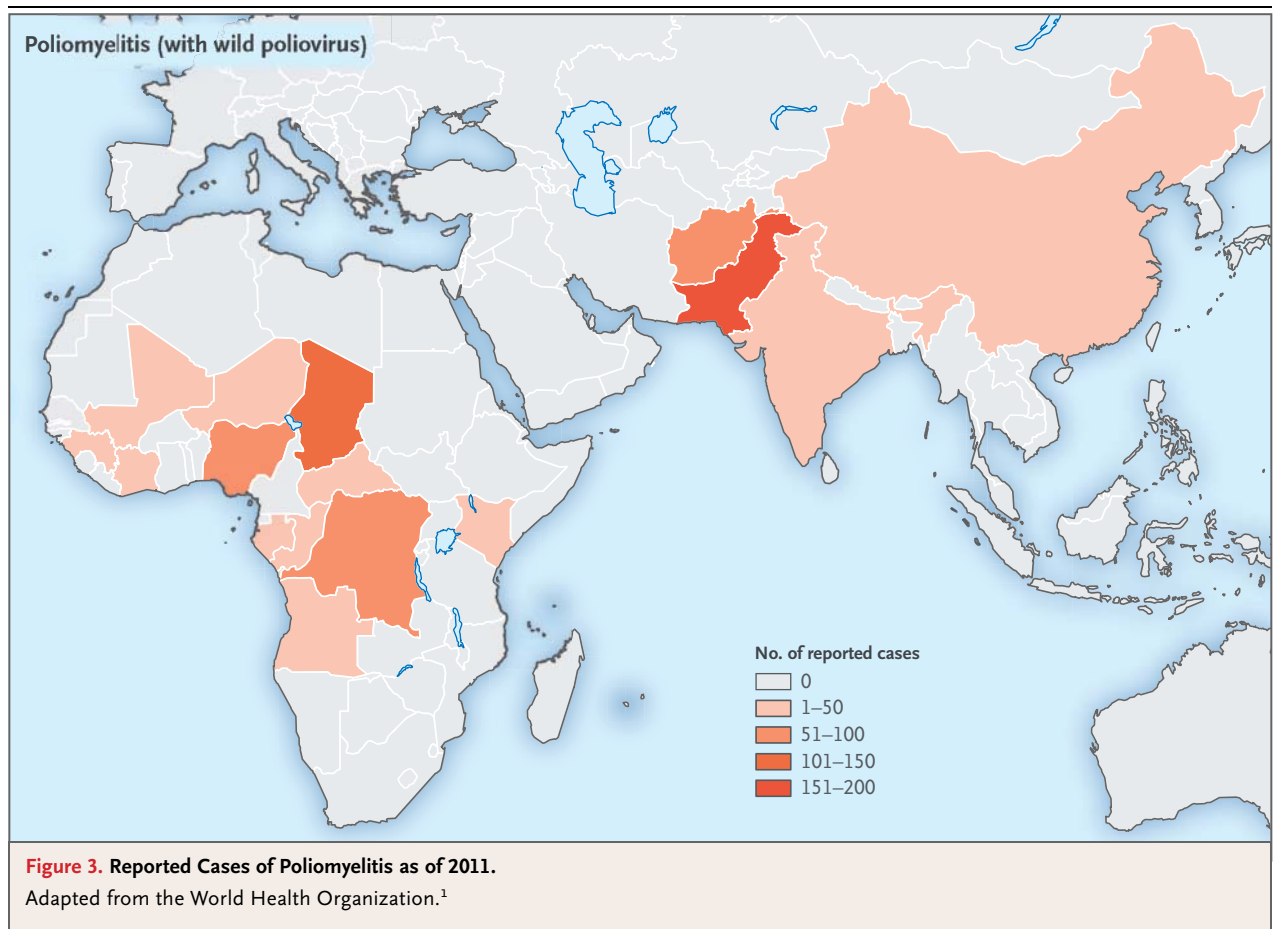
POLIOMYELITIS

The Global Polio Eradication Initiative, which began in 1988,¹⁵ was inspired by the successful elimination of this disease in the Americas. An enteroviral infection characterized by influenza-like symptoms, poliomyelitis causes muscle paralysis in one or more limbs or the chest, or both, in less than 1% of infected persons. People are infected by ingesting virus shed in feces or by inhaling viral particles exhaled by those already infected (Fig 1B). Patients may exhale virus for a week and shed virus in feces for a month, beginning just before symptoms develop, 7 to 14 days after they are infected. Persons who recover are then immune to the viral type that infected them (poliovirus 1, 2, or 3). Vaccination to prevent infection requires three or more doses of live attenuated virus administered orally or of killed virus administered by injection. Before polio vaccination was introduced, in the 1950s, the disease killed or paralyzed an estimated 600,000 persons each year worldwide.¹⁶

The Global Polio Eradication Initiative engendered massive global immunization and surveillance efforts with the support of the WHO, UNICEF, the CDC, Rotary International, the Bill and Melinda Gates Foundation, and others. These efforts have helped strengthen routine immunization in some instances (e.g., measles immunization in the Americas) and the delivery of vitamin A supplements in others. Surveillance for polioviruses, which is performed in health facilities and laboratories, involves the use of sophisticated methods for characterizing polioviruses detected in specimens from sewage or from patients with suspected infection.¹⁷ Type 2 wild poliovirus was eradicated worldwide by 1999.¹⁸ By 2006, transmission of indigenous wild virus had been halted in all but four countries. In India, suboptimal seroconversion due to poor sanitation and high population density required immunization with many more doses than expected; parts of Afghanistan and Pakistan became inaccessible after 2002, owing to political conflict; and rumors of side effects from vaccination



An interactive graphic with information on poliomyelitis is available at NEJM.org



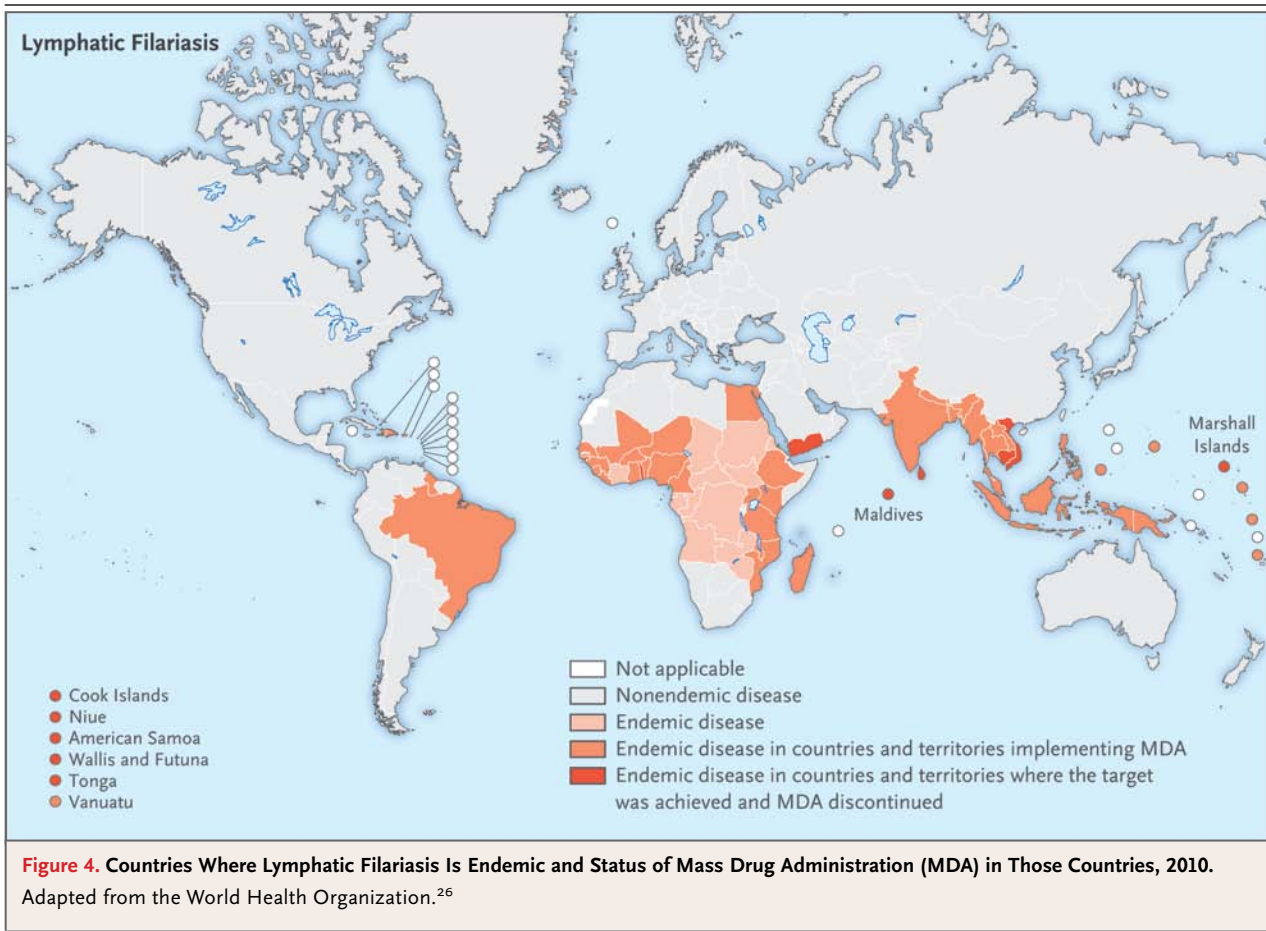
compromised the acceptance of immunization in Nigeria. Additional problems included the discoveries that immunosuppressed persons could excrete virus indefinitely and that the virus in the live-virus vaccine could, in rare cases, regain virulence and spread to others, just as the virus in the attenuated vaccine did, although spread of the attenuated virus was beneficial, augmenting herd immunity.¹⁸

By 2011, after setbacks that resulted in cases being exported to other countries, 650 confirmed cases of poliomyelitis were reported provisionally from 16 polio-affected countries: 4 countries where the disease was endemic and 12 countries with reestablished transmission (lasting ≥ 12 months) or outbreaks (lasting < 12 months) after importations (Fig. 3).^{15,17,19} Global coverage of infants with three doses of oral trivalent vaccine was about 85% in 2010 but is uneven at the national and subnational levels.¹⁵ In January 2012, India celebrated a full year with no cases of poliomyelitis, leaving Nigeria, Afghanistan, and Paki-

stan as countries with endemic disease where eradication was problematic because of political instability or fear of immunization.²⁰⁻²² Among countries with reestablished transmission, Chad and the Democratic Republic of Congo reported the most cases (132 and 93, respectively) in 2011.¹⁹ The goal is to interrupt transmission of poliovirus types 1 and 3 by December 2012. The main challenges to poliomyelitis eradication are donor fatigue; political instability in parts of Afghanistan, Pakistan, and some other affected countries; public fatigue with repeated immunizations against poliomyelitis alone; and weak routine immunization systems. This program is estimated to cost \$9.5 billion for the period from 1988 through 2013.²³

LYMPHATIC FILARIASIS

In 1997, after the International Task Force for Disease Eradication had first suggested the potential eradicability of lymphatic filariasis, the



World Health Assembly formally targeted the disease for global elimination.²⁴ Characterized by painful adenolymphangitis, damage to kidneys and other organs, and grotesque swelling of limbs and genital organs, lymphatic filariasis is caused by the filarial parasites *Wuchereria bancrofti*, *Brugia malayi*, and *B. timori* and is transmitted to humans by repeated bites of mosquitoes that previously ingested microfilariae from the blood of an infected person (Fig. 1C). In Africa, lymphatic filariasis is transmitted by the same anopheles species of mosquitoes that transmit malaria (Fig. 1D). Annual oral mass drug administration with ivermectin and albendazole or with diethylcarbamazine and albendazole suppresses microfilaremia and interrupts transmission. About 6 years of treatment are required before the adult worms die. Mass drug administration with ivermectin is contraindicated in African areas where the parasite *Loa loa* occurs (because treatment of persons with heavy *L. loa* infections

may have fatal side effects), but bed nets to thwart nocturnal, indoor-biting mosquitoes such as anopheles also prevent the transmission of lymphatic filariasis.²⁵ In 2010, about 120 million people were infected and almost 1.4 billion were at risk for lymphatic filariasis in 72 countries of Asia, Africa, and Latin America (Fig. 4).²⁶

In 2000, generous donations of drugs helped launch the Global Program to Eliminate Lymphatic Filariasis, which aims to eliminate lymphatic filariasis “as a public health problem” by 2020. In 2010, a total of 466 million (34%) of the persons at risk for lymphatic filariasis received treatment, and mapping was complete in 59 countries.²⁶ India, Indonesia, and Nigeria have the most cases. Scaling up mass drug administration for lymphatic filariasis has been slowest in Africa, where the expanding use of long-lasting impregnated nets provides synergy between efforts to eliminate lymphatic filariasis and efforts to control malaria. Mass drug administra-



An interactive graphic with information on lymphatic filariasis is available at NEJM.org

Table 1. Ocular Morbidity and Transmission Status of Onchocerciasis in the Americas.

Focus	Population at Risk no. (%)	Blindness Eliminated	Ocular Morbidity Disappeared	Transmission Status*
Santa Rosa, Guatemala	12,208 (2)	Yes	Yes	Eliminated
Lopez de Micay, Colombia	1,366 (0.2)	Yes	Yes	Eliminated
Escuintla, Guatemala	62,590 (11)	Yes	Yes	Eliminated
North Chiapas, Mexico	7,125 (1)	Yes	Yes	Eliminated
Huehuetenango, Guatemala	30,239 (5.5)	Yes	Yes	Interrupted in 2008
Oaxaca, Mexico	44,919 (8)	Yes	Yes	Interrupted in 2008
Esmeraldas, Ecuador	25,863 (4.7)	Yes	Yes	Interrupted in 2009
North-central Venezuela	14,385 (2.6)	Yes	Yes	Interrupted in 2010
South Chiapas, Mexico	114,024 (21)	Yes	Yes	Interrupted in 2011
Central Guatemala	124,498 (22)	Yes	Yes	Interrupted in 2011
Northeastern Venezuela	93,239 (17)	Yes	No	Suppressed
Amazonas, Brazil	12,521 (2)	Yes	No	Ongoing
Southern Venezuela	9,168 (1.7)	Yes	No	Ongoing

* Eliminated means that there has been no recrudescence of infection during a period of 3 or more years since mass drug administration was halted, with ongoing post-treatment surveillance. Interrupted means that there has been no transmission during a period of fewer than 3 years since mass drug administration was halted, with ongoing post-treatment surveillance. Suppressed means that transmission indexes are negative; mass drug administration has not yet been halted. Data are adapted from the WHO.^{35,36}

tion for lymphatic filariasis also treats onchocerciasis and several soil-transmitted helminths.²⁷ There is evidence that mass drug administration has interrupted the transmission of lymphatic filariasis in some parts of Nigeria where the disease is heavily endemic,²⁸ in Egypt²⁹ and in Togo³⁰ and has reduced microfilariae levels to less than 1% in 12 Asian and Pacific Island countries.²⁶ There is also evidence from Nigeria that widespread use of long-lasting impregnated nets can halt transmission of the disease (Richards F: personal communication). The main challenges to a full-scale campaign for lymphatic filariasis eradication are inadequate political and financial support for scaling up mass drug administration, constraints on such treatment because of the presence of *L. loa* in certain areas (although the use of impregnated nets may eliminate this constraint), and political insecurity in certain countries. The overall costs of this program have not been estimated, although limited studies have suggested that interventions against lymphatic filariasis are very beneficial in relation to their cost.^{31,32}

ONCHOCERCIASIS IN THE AMERICAS

The Americas was the first WHO region to eliminate smallpox, poliomyelitis, and measles. Since 1992, the region has pursued a program to eliminate onchocerciasis from 13 foci in six countries of Central and South America with the use of mass administration of ivermectin twice a year.^{33,34} The parasite *Onchocerca volvulus* is spread to humans by the bites of tiny black flies, after which the adult worms cluster in nodules and release millions of microfilariae that migrate to the skin, causing intense itching, and to the eyes, where they may impair sight and, after many years, cause blindness (Fig. 1E). By the end of 2011, onchocerciasis transmission had been halted or suppressed in all but 2 of the 13 foci and in four of the six affected countries (Table 1).^{35,36} Accessing indigenous populations in remote adjacent areas of Venezuela and Brazil is still a challenge. Progress in the effort to eliminate onchocerciasis in the Americas has inspired a reappraisal of ongoing programs to control the disease in Africa, where most cases occur.^{37,38}



An interactive graphic with information on onchocerciasis is available at NEJM.org

Over the past two decades, the Onchocerciasis Elimination Program for the Americas has cost approximately \$124 million, with \$46 million of that amount paid for by the countries themselves, \$51 million paid by Merck in the form of donated drugs, and most of the remainder raised by the Carter Center.

MALARIA AND LYMPHATIC
FILARIASIS IN HISPANIOLA

A special opportunity also exists in the Americas to apply the principles of disease elimination in Hispaniola, comprising the Dominican Republic and Haiti. These two countries are the only remaining foci of endemic malaria among the Caribbean islands and account for more than 90% of all cases of lymphatic filariasis in the Western Hemisphere. The International Task Force for Disease Eradication highlighted this compelling opportunity in 2006, concluding that eliminating both diseases from Hispaniola “is technically feasible, [is] medically desirable and [would be] economically beneficial.”³⁹ The Dominican Republic has almost eliminated lymphatic filariasis already. Despite the earthquake in 2010, Haiti extended mass drug administration for lymphatic filariasis to all affected districts for the first time in 2011 and estimates that \$49 million will be needed to eliminate the disease by 2020. In 2009, the two countries also announced a binational plan to eliminate malaria by 2020 by combining active case detection and treatment with vector control at an estimated cost of \$194 million over the decade.⁴⁰ An outbreak of malaria in 2004 cost the Dominican Republic an estimated \$200 million in lost revenue from tourism alone.³⁹



An interactive graphic with information on malaria is available at NEJM.org

SOME LESSONS AND CONCLUSIONS

Past and current experience confirms that disease eradication is difficult and risky and will probably require more effort, time, and money than initially expected, even when it is successful. It is advisable to start early in the most heavily affected areas, since they will present the most difficult challenges and require the longest effort and because the specific challenges cannot be anticipated on the basis of work in areas that are less heavily affected. The inherent risks of failure to achieve eradication are offset by the benefits that accrue indefinitely from a successful eradication campaign. The unique power of eradica-

tion campaigns derives from their supreme clarity of purpose, their unparalleled ability to inspire dedication and sacrifice among health workers, and their attractiveness to donors, all of which are needed to overcome the barriers to successful eradication. Evidence that disease incidence and intervention coverage are being monitored closely and that progress is being made toward eradication can help secure the resources needed for these demanding campaigns.

Political instability and insecurity, which are usually outside the realm of public health professionals and can be avoided in a program designed to control disease, are inescapable challenges in an eradication program. Smallpox eradication succeeded despite civil wars in Nigeria, Pakistan, and Sudan, and the programs to eradicate dracunculiasis and poliomyelitis face similar challenges. Unlike the dracunculiasis eradication program, the programs to eradicate smallpox and poliomyelitis must address the risk of waning immunity levels, should the virus be reintroduced by bioterrorists after eradication, when routine immunizations have ceased.

In the medical realm, each eradication or elimination program is different and will require its own strategies and tactics. No program will have all the answers from the outset, so ongoing innovation and research are important. The smallpox eradication program switched from mass vaccination to the successful surveillance-containment strategy after it was under way, and the guinea worm and poliomyelitis eradication programs also developed new strategies after they had begun.⁴¹ All eradication programs, however, require an intensive focus. Opportunities for integrating interventions of eradication programs with those of control programs will be scarce, but such opportunities should be seized when it makes sense to do so. Measles immunization was combined with smallpox eradication efforts in West Africa, despite the additional logistic and financial burdens imposed by the need to refrigerate the measles vaccine (but not the smallpox vaccine), because the African governments requested it.⁴² Meeting this request added public health value and political virtue to the campaign. Similar opportunities for mutually beneficial, combined interventions against lymphatic filariasis, onchocerciasis, malaria, and soil-transmitted helminths in Africa are also evident.²⁷

The successful eradication of dracunculiasis with interventions other than a vaccine will soon

validate and expand the concept of disease eradication as we have known it, such as in the use of vaccination to eradicate smallpox (and in the impending eradication of poliomyelitis). That imminent success, generous drug donations for combating lymphatic filariasis, and ongoing elimination efforts in the Americas and elsewhere against other diseases augur well for the future, although the eradication of lymphatic filariasis is not yet an official goal of the WHO. However, the fact that neither dracunculiasis nor poliomyeli-

tis was eradicated by December 2012, as planned, underscores the inherent difficulties of disease eradication. I believe this powerful public health tool will be used to eradicate other carefully selected diseases in the future, provided that inflated promises and failure to deliver on them do not tarnish the concept. In the meantime, lessons from eradication programs could be adapted to improve control of many other diseases.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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