11

ONCHOCERCIASIS

ADRIAN HOPKINS AND BOAKYE A. BOATIN

11.1 INTRODUCTION

Onchocerciasis (or river blindness) is a parasitic disease cause by the filarial worm, *Onchocerca volvulus*. Man is the only known animal reservoir. The vector is a small black fly of the *Simulium* species. The black fly breeds in well-oxygenated water and is therefore mostly associated with rivers where there is fast-flowing water, broken up by cataracts or vegetation. All populations are exposed if they live near the breeding sites and the clinical signs of the disease are related to the amount of exposure and the length of time the population is exposed. In areas of high prevalence first signs are in the skin, with chronic itching leading to infection and chronic skin changes. Blindness begins slowly with increasingly impaired vision often leading to total loss of vision in young adults, in their early thirties, when they should be at their most productive and when, as a result, their children are forced to be permanently at their side to accompany them. Other effects include epilepsy and growth retardation and these are most evident again in communities with high prevalence.

The disease is found mostly in Africa but is also found in Latin America and in Yemen as shown in Table 11.1, which gives the global estimates of the population at risk, infected, and blind in 1995 (1).

In Africa more than 100 million people are at risk of getting the infection in 30 countries south of the Sahara. However, further mapping of the disease in non-Onchocerciasis Control Programme (OCP) areas has shown that more people are infected in these areas than was thought; the total number of people infected is now estimated as 37 million (2). The control measures are now having an impact; the risk of the infection is actually much reduced and elimination of transmission in some areas has been achieved. Differences in the vectors in different regions of Africa, and differences in the parasite between its savannah and forest forms led to different presentations of the disease in different areas.

It is probable that the disease in the Americas was brought across from Africa by infected people during the slave trade and found different *Simulium* flies, but ones still able to transmit the disease (3). Around 500,000 people were at risk in the Americas in 13 different foci, although the disease has recently been eliminated from some of these foci, and there is an ambitious target of eliminating the transmission of the disease in the Americas by 2012.

Host factors may also play a major role in the severe skin form of the disease called Sowda, which is found mostly in northern Sudan and in Yemen.

The disability-adjusted life years (DALYs) lost due to onchocerciasis is 1.49 million as of 2003 of which 60% is attributable to "troublesome itching." Although the disease is not normally associated with mortality, a few studies have shown that life expectancy of the blind due to onchocerciasis was greatly reduced and that mortality in blind adults on the average was three to four times greater than in the fully sighted population.

The unprecedented donation of Mectizan® (ivermectin) by Merck & Co Inc. to as many people as needed it, for as long as it was needed was a watershed in public health (4). This donation, which began in 1987, has not only revolutionized the strategies for control of onchocerciasis but has also led to other major donations by the pharmaceutical industry for the elimination of trachoma, lymphatic filariasis, and other neglected tropical diseases of poverty (5).

Water and Sanitation-Related Diseases and the Environment: Challenges, Interventions, and Preventive Measures, First Edition.
Edited by Janine M. H. Selendy.

TABLE 11.1 Global Estimates of the Population at Risk, Infected and Blind from Onchocercisis in 1995 (1)

Region	Population at Risk of Infection (Millions)	Population Infected	Number Blind as a Result of Onchocerciasis
Africa			
OCP area:			
Original area	17.6[a]	10,032	17,650
Extensions	6.0	2,230,000	31,700
Non-OCP area	94.5	15,246,800	217,850
African subtotal	118.1	17,486,832	267,200
Arabian peninsula	0.1	30,000	0
Americas	4.7	140,455	750
Total	122.9	17,657,287	267,950

[a] The population given is that which would have been at risk had the OCP not existed.

11.2 THE PARASITE, THE VECTOR, AND THE RELATED LIFE CYCLES

11.2.1 The Parasite

The adult forms of *O. volvulus* are found in the human host in fibrous nodules, or onchocercomata, many of which are found in the subcutaneous tissues especially over bony prominences, although others are found deeper in the tissues. Female worms, which are considerably larger than the male (30–80 cm and 3–5 cm long, respectively), are found entwined around each other in the nodules and each nodule may contain from one to two male worms and two to three female worms, although larger nodules may exceptionally contain up to 50 worms. Whereas the females remain in the nodules, the males are more mobile and may go between nodules. Females release 700–1,500 larvae or microfilariae (MF) each day. The vast majority of these MF are found in the skin. Some find their way to the eye and probably other tissues of the body. If they are not ingested by the vector, they live in the host from 6 to 24 months.

In order to develop further the MF must be ingested by the vector, a small black fly of the *Simulium* species where, after penetrating the wall of the mid gut, they migrate to the thoracic muscles (6). Here initially they undergo a big increase in size into a sausage-shaped larva. After a few days these sausage-shaped larvae elongate and become much more mobile becoming the preinfective form and eventually migrating into the hemocoel and toward the head where they wait in the proboscis for the next time the *Simulium* requires a blood meal. This part of the life cycle in the fly takes around 10 days (6–12 days). When the *Simulium* bites again the infective larvae (L3 stage) migrate actively into the wound made by the bite and live in the tissues for a few days before going through a further larval stage (L4). After about a week they develop into juvenile worms (L5). It takes a further 7–15 months before these juvenile becomes mature and moves toward the nodules where mating takes place and the cycle begins again. The adult worms live for 10–14 years. The life cycle of the parasite and its relationship to the human host and vector are shown in Fig. 11.1.

The pathogenicity of *O. volvulus* varies with different strains of the parasite. Savannah strains of the parasite provoke much more blindness than the forest strains (7–10). Both provoke skin changes. The different strains of *O. volvulus* are particularly well adapted to the vectors, forest strains being transmitted by the vectors adapted to the forest areas and similarly with savannah strains (11–14). The strains of *O. volvulus* in the Americas are also quite pathogenic to the eyes adding to the theory that the disease was introduced into the Americas with the slave trade.

11.2.2 The Vector

The most common vector is the very aptly named *Simulium damnosum*, "the damned black fly." This small fly, about the size of a mosquito, requires well-oxygenated water to lay its eggs, and where the larvae can develop. The female fly requires a blood meal to provide the necessary nutrition to produce each batch of eggs, and the time between blood meals varies from 6 to 12 days.

S. damnosum is actually a complex of sibling species. There are minor variations between the species but they show adaptations to local circumstances; the *S. damnosum* subcomplex contains species mostly responsible for transmission in savannah areas whereas the *S. sanctipauli* and *S. squamosum* subspecies are found in more forest areas. One intriguing group is the *S. neavei* complex. *S. neavei* larvae develop on the back of crabs, which are found in forest areas in eastern Africa. Another interesting species is *S. albivirgulatum*, which is found in the "Cuvette Central" of the River Congo. The larvae of this species are found on the underside of leaves floating down the River Congo and its many tributaries, thus, finding enough oxygen and nutrition for larval development. In the Americas the most common complexes are *S. ochraceum*, *S. metallicum*, and *S. exiguum*.

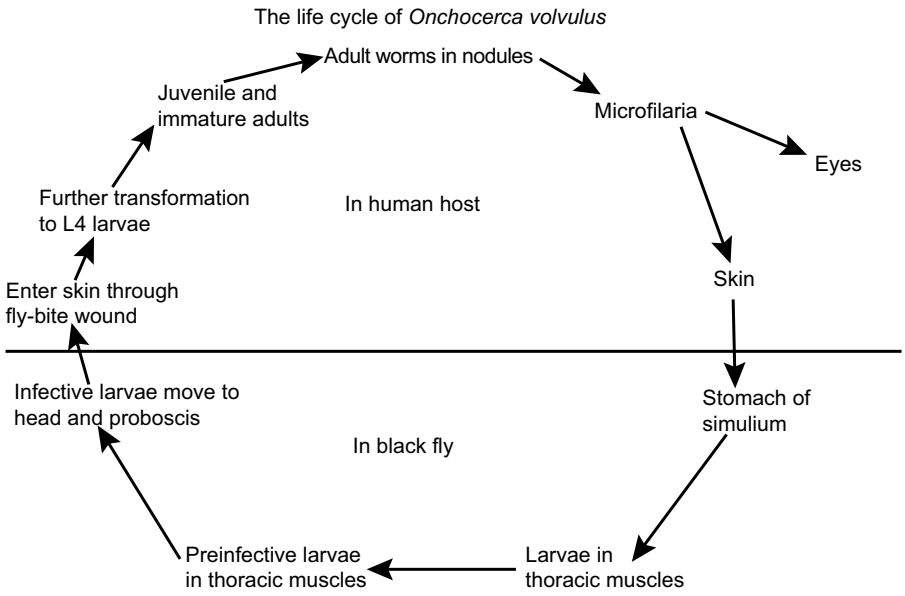

FIGURE 11.1 The life cycle of the parasite and its relationship to the human host and vector.

The importance of the different species relates to their capacity for transmission of the disease, and also the ease of control. Where vector control/elimination has been the main tool in the control of onchocerciasis, it has been important to understand the detailed biology of each species, to establish the best method of control. Some species of *Simulium* such as *S. neavei* do not fly far from breeding sites. *S. damnosum* however can fly long distances (400–500 km) by flying with the prevailing winds in West Africa. Generally, the *Simulium* try to feed as close to the breeding sites as possible. Populations living within 5 km of the breeding site are the most at risk although communities living up to 12–15 km may be affected. Communities living on the river's edge are more at risk than those a little further away. In fact, these communities very close to the breeding site to a certain extent "protect" the population living a little further away. This is one reason why blindness is relatively rare in towns, even if they are riverside communities.

The *Simulium* rarely enters houses to bite. Its preferred biting times are in the early morning and late afternoon. These are also times when populations who depend on the rivers for water, washing, and food are most likely to be at the river for these various activities. Those working in fields nearby or fishing in the river itself also tend to be less active during the midday heat.

11.3 RELATIONSHIPS BETWEEN PARASITE, VECTOR, AND THE HOST POPULATION

Onchocerciasis has had a significant impact on the populations in the savannah areas of West Africa. The close contact of man and the black fly poses not only medical problems for the communities that live near the river basin but also the bite of the flies causes intense irritation and a huge nuisance to the population. Communities are therefore compelled to abandon their villages and flee from the river basin for fear of acquiring the disease, notwithstanding the nuisance from the bite of the flies. Such movements have dire consequences on socioeconomic development. Moving to areas removed from the rivers has likewise led to poverty because the soil is much poorer away from the fertile valleys and water is more difficult to find so agriculture is gravely affected. Productivity is also affected negatively, leading to diminished earnings and adversely affecting the supply of labor. A high prevalence of blindness in young adults leads to further deterioration and deepens the cycle of poverty. These young adults are inflicted at the time when they should be their most productive and when they have young families to care for and educate. Often the children are forced to lead their blind parents around rather than go to school. Civil conflict and insecurity in Africa (particularly in Central Africa and the Sudan) has led to large population movements, often out of infected areas. However, when peace returns, populations may return to their traditional homelands and once again become exposed to the disease, although the chronic skin changes and blindness may take some time to develop.

The biting nuisance even where flies have been well controlled for a period has had a very positive effect on development, but the return of the flies after the control measures have been withdrawn lead to a lot of complaints from the population, even if the Simulium are not infected and not transmitting any disease (15). In the area of Inga on the Congo River during peak breeding times, the biting rate can reach to 13,000 bites per day and the population is often forced to wear protective clothing, long-sleeved shirts, even

gloves and hats, in spite of tropical weather just to reduce the irritation from these bites.

Migration of the fly can also be significant. Movements of the *Simulium* have been mentioned above. It is possible that infected flies can be carried by winds into areas where the disease has already been controlled. *S. neavei* is found in forest areas in central and eastern Africa. The Potamonautes crabs, on which the larva develop, like shady areas. With deforestation these crabs have disappeared in some areas and transmission of the disease has stopped as a result. However, unfortunately *S. damnosum*, which prefers more savannah areas, has invaded some of these sites and once again transmission of the disease could become a problem.

Because flies can travel long distances in Africa, care must be taken when development projects include the construction of dams. The fast runoff of water around a hydro turbine produces highly oxygenated water, ideal to establish new breeding sites for *Simulium*. This must be considered during all construction and maintenance of new dams.

11.4 THE DISEASE

11.4.1 Adult Worms

The onchocercomata produce little in the way of symptoms. Those that are found in subcutaneous tissues are easily palpable as a mobile mass in the subcutaneous tissues with a firm consistency at the center. With experience these masses can easily be differentiated from other subcutaneous masses, such as small lipomas, sebaceous cysts, lymph nodes, and even subcutaneous cysticerci. However, as the disease is more controlled and nodules become less numerous, the accuracy of diagnosis also declines.

One use of nodules has been in establishing a community diagnosis for decisions on mass treatment and this is used in rapid mapping strategies described later.

11.4.2 Microfilaria (MF)

The principal symptoms of the onchocerciasis are due to the MF. Each female can produce up to 1,500 MF per day. Live MF do not really create a major problem. However, the MF start to die after 6 months, if not ingested by a *Simulium*. When MF die, they produce an inflammatory reaction. Even if these reactions are small and localized, due to the large number of MF dying each day (particularly in the skin), they provoke widespread and chronic reactions. At first the reactions are reversible, but as the infection continues permanent changes occur. Recent evidence suggests *Wolbachia* endobacteria (symbionts of arthropods and filarial nematodes) may contribute to the inflammatory pathology associated with the disease (16–18).

11.5 CLINICAL SYMPTOMS

11.5.1 Skin

The first changes are due to itching and the lesions produced by energetic scratching. This is officially described as acute papular onchodermatitis (APOD), but the original description from West Africa of craw-craw somehow describes it more effectively (19). Sometimes patients use sticks or stones to scratch more vigorously. Figure 11.2 shows the typical

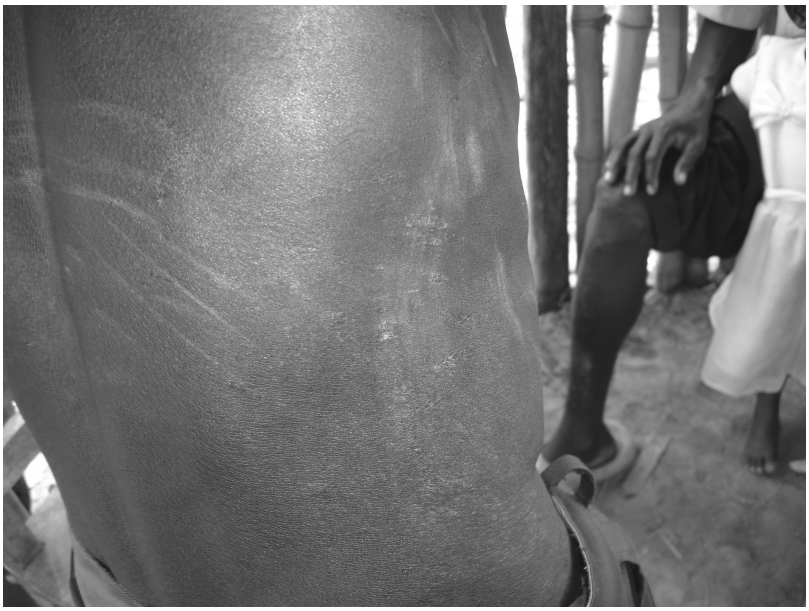

FIGURE 11.2 The typical changes of early onchocerciasis infection. (*See insert for color representation of this figure*.)

changes of early onchocerciasis infection. Trauma to the skin often leads to secondary infection, with localized edema and local lymphadenopathy. "Troublesome itching" has been shown to be one of the most important symptoms of onchocerciasis (20) and has recently been recognized as affecting more than 50% of the populations in some communities in the rain forest belt where blinding onchocerciasis is relatively rare.

Chronic onchocercal skin disease (OSD) leads to two skin changes. A scaly, often itchy thickening of the skin, called chronic papular onchodermatitis (CPOD) or lizard skin dermatitis is often seen over the back and buttocks. The more classic changes are changes in pigmentation of the skin, classically described on the lower limbs although sometimes seen elsewhere on the body. Patches of depigmentation give a classic appearance of "leopard skin" (depigmentation, DPM), as shown in Fig. 11.3.

FIGURE 11.3 Patches of depigmentation give a classic appearance of "leopard skin" (DPM).

A further change that happens to the skin is atrophy (ATR) manifested by loss of elasticity. The skin of someone in their thirties or forties already looks like that of an old person. Swollen lymph nodes are found just under the skin in the inguinal region and the weight of these nodes drags down on the skin, if it has lost its elasticity, creating the so-called "hanging groin."

In Yemen and the north of Sudan and in a small proportion of patients elsewhere there is a lichenified onchodermatitis (LOD), which typically affects young adults and is also called Sowda (21). The skin is itchy, thickened, and hyperpigmented. This gradually spreads and may cover large areas, particularly the lower limbs, but is often asymmetrical. Draining lymph nodes become inflamed, which usually results in lymphedema or thickening of the tissues.

11.5.2 Eyes

MF are found in all the tissues of the eye from the conjunctiva anteriorly, to the optic nerve posteriorly (22, 23). MF in the conjunctiva provoke itching.

Active MF can invade the cornea, where if they die, they provoke a punctuate keratitis, or fluffy, white inflammatory reaction, in the clear cornea. This is reversible initially, but severe chronic infections lead to permanent changes. The cornea gradually loses its transparency and becomes white and hard (sclerosing keratitis). This begins at the 3 o'clock and 9 o'clock positions and then gradually fills in from the bottom, creating a semilunar keratitis until the whole cornea is affected with so-called sclerosing keratitis, as shown in Fig. 11.4.

MF are also found in the anterior chamber of the eye. In this space between the back of the cornea and the pupil, MF can be seen with the slit lamp, swimming in the aqueous humor, sticking to the inner surface of the cornea, the endothelium, or in severe cases the microfilaria sink to the bottom of the anterior chamber and can be seen as a mass, a so-called pseudo-hypopyon.

MF also penetrates the iris and can cause inflammation (a chronic anterior uveitis). This chronic inflammation can also lead to blindness due to secondary glaucoma or secondary cataract. The pupil often becomes small and deformed and sticks to the lens (posterior synechiae) and therefore nonreactive. The patient from Sudan in Fig. 11.5 shows a typical chronic uveitis with secondary cataract in her right eye and sclerosing keratitis in her left eye.

In the posterior segment of the eye MF can be seen in the vitreous. The most serious aspects of posterior segment disease, however, are chronic chorioretinitis and optic nerve atrophy. The chronic chorioretinitis is an inflammation that often begins around the periphery of the retina and causes gradual loss of visual field starting in the periphery. The macula (for central vision) is often spared initially, but with

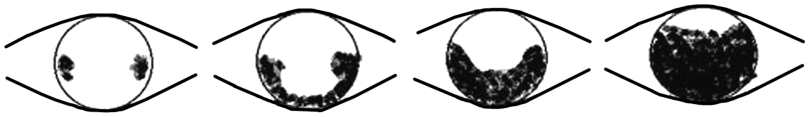

FIGURE 11.4 The evolution of sclerosing keratits.

FIGURE 11.5 A patient from Sudan showing typical chronic uveitis with secondary cataract in her right eye and sclerosing keratits in her left eye. (*See insert for color representation of this figure.*)

advancing disease central vision is also lost. Optic nerve atrophy also provokes loss of vision (24, 25).

11.5.3 Systemic Effects

Systemic effects such as low body weight, general debility, and diffuse musculoskeletal pain have been described as other features of onchocerciasis. Although bleeding and ulceration of skin, secondary infections, bone pain, headache, and fatigue have also been suggested, these are relatively minor. Evidence suggests that onchocerciasis is a risk factor for epilepsy (26, 27) and may be responsible for a type of dwarfism in certain areas (28). With a heavy microfilarial load there may be generalized lymphadenopathy and some dilatation of lymph vessels, leading to tissue swelling and mild elephantiasis, particularly in areas of Sowda.

11.5.4 Social Effects

Onchocercal skin disease (OSD) has been associated with a variety of psychosocial and economic effects. The disease also leads to stigmatization of affected persons and their families. Unsightly acute and chronic skin lesions and thickened and irritated skin limit the chances of young adolescent girls finding marriage partners. Likewise negative sociocultural aspects of the skin disease (people worried that skin disease would affect their ability to interact socially, fear of being ostracized, a feeling of low esteem, and children more likely to be distracted in school due to constant itching) have now been recognized.

At the community level, studies have shown a reduced productivity due to the incessant itching, leading to increased poverty, increased expenditure on health in spite of a reduced income, all adding to the vicious cycle of poverty that this disease creates; this is apart from the effects of blindness. Many young people leave the villages for the towns and areas free of *Simulium*, increasing the level of poverty and destitution among the older people left behind and further contributing to the shortened life span of the blind (29).

11.6 CONTROL MEASURES

11.6.1 Control of the Vector

The most effective way to control the vector is to attack the larval forms. They are easier to control because of their relatively easy-to-reach known habitats in fast flowing rivers, with a flow rate of 5 m/s. The fly has a wind-assisted flight range of about 400 km, making the adult fly more difficult to control directly (30).

Various methods have been used to control the vector, including attempts at environmental management. Environmental management involves clearing the vegetation and applying agents like Paris Green and Creosote to the breeding sites of the vector. This approach was tried in the Chiapas focus of Mexico without success. *S. neavei* was, however, successfully eradicated from the Raina focus—a rather small focus—in Kenya through simply clearing the riverine forest. Deforestation in some parts of Uganda has also seen the disappearance of *S. neavei*, although there is now the risk of invasion by *S. damnosum.* The application of dichlorodiphenyltrichloroethane (DDT) was instrumental in the eradication of *S. neavei* from the Kodera valley in Kenya (31).

The mainstay for vector control has been the use of insecticides with the aim to interrupt transmission of the parasite. In the Onchocerciasis Control Programme (OCP) of West Africa the objective was to continue larviciding for a sufficiently long period during which time the human reservoir of the parasite would die out.

For vector control to be effective larviciding needs to be carried out preferably weekly. The larval stages rarely take more than 7 days to about 12 days to change to the next stage. Ground and aerial larviciding are both used for control. Ground larviciding is best applied where this is feasible, such as in small foci, and where the type of vegetation allows it. Aerial larviciding on the other hand has been used more extensively to cover large tracts of river basins, which would otherwise be either impossible or very difficult to cover by ground larviciding.

The formulation of insecticides used for large-scale treatment of rivers must meet a range of requirements. They must be highly effective against the vectors, safe to the rest of the environment, including human and other life forms, with guaranteed supply for a long period and the cost should be low. They must be biodegradable but with a good carry downstream.

Various insecticides are available. Temephos (AgrEvo France) is a cheap and efficient organophosphorus with insignificant impact on the nontarget fauna. Its use, however, needs careful attention given that insecticide resistance emerges very quickly with its application. Other environmentally friendly larvicides that have been used are the organophosphates, carbamates, pyrethroids, and the biological *Bacillus thuringiensis* serotype H14-B.tH14. These are used in rotation in accordance with river flow rate, to help avoid the emergence of insecticide resistance in the vector; to minimize adverse impact on nontarget organisms, riverine flora and fauna; and to increase cost effectiveness (32). For the OCP an expert independent ecological advisory group was set up to help monitor the impact of insecticides on the nontarget organisms in the rivers under larviciding. The Ecological Group also advised on the best possible insecticides to use for the maximum impact on the vector, while still having the minimal impact on the environment.

11.6.2 Surgical Removal of Nodules

Nodulectomy can remove some of the adult worms and has been used in some circumstances to try to control symptoms of the disease. Because they are often multiple, and many are also impalpable in the deep tissues, it is impossible to eliminate all adult worms by nodulectomy. Nodules may be removed for cosmetic reasons or because of annoyance due to their position, for example, around the waist where a belt might irritate. The logistical exercise of removing all palpable nodules from all patients in an endemic area would also be overwhelming, so this is not a strategy used for control.

11.6.3 Control of the Disease with Medication

The ideal drug would be one that kills the adult worm causing no side effects and would be safe for mass distribution. Unfortunately Suramin, which does kill adults (a macrofilaricide), is also toxic and unsafe to give as a mass treatment. One drug is currently undergoing trials, Moxidectin, but it is unlikely to be cleared for mass usage before 2014 or 2015 even if it does prove to be effective. Doxycycline also has macrofilaricidal effects by killing *Wolbachia*, obligatory endosymbiotic bacteria in some species of filaria including onchocerciasis. If *Wolbachia* are killed, the female cannot reproduce and will eventually die. The problems with Doxycycline are that it has to be given for a prolonged period, at least a daily dose for 4 weeks, and it cannot be given to children under 12, which is a very significant proportion of the population in most endemic areas (33).

Ivermectin is an effective microfilaricide (killing microfilaria). It also has an effect on reproduction preventing the release of microfilaria by the adult female for approximately 4 months. When microfilariae are released the repopulation of the skin is very slow and after 12 months it reaches around 20% of the original level. There is also a macrofilaricidal effect. This effect was not thought to be particularly important but recent research shows that some of the early studies were not done in a closed system and some of the live adult worms found were possible worms from new infections rather than adult worms resistant to ivermectin. Ivermectin is contraindicated in children under 5 (less than 90 cm height or 20 kg weight), pregnancy and during the first week after delivery and also patients with chronic disease, or central nervous system diseases.

There is another microfilaricide, Diethylcarbamazine (DEC). DEC causes much greater inflammatory reactions, or Mazzoti reactions, due to the massive destruction of microfilaria, than is the case with ivermectin. This is especially important in the eye where the inflammation provoked can cause significant loss of vision and even blindness. This does not occur with ivermectin. DEC is therefore contraindicated for use in onchocerciasis. Flubendazole is a macrofilaricide but the complications of administering the drug have prevented its use (34).

11.6.4 The Role of Ivermectin in Disease Control and Elimination

Ivermectin has proved to be such a safe and effective drug that most onchocerciasis control programmes are now using mass drug administration (MDA) as the principal strategy for onchocerciasis control. MDA with ivermectin is done once or twice yearly. In well-defined endemic areas where treatment is given every 6 months, transmission of the disease can be virtually eliminated in 6–8 years provided there is a high enough coverage (around 80% of the

total population, or over 95% of those eligible to take the drug). In Africa the foci of the disease are not so small and well defined. In most areas ivermectin MDA is done annually, which is sufficient to control the main symptoms of disease but will require 16 or more years to achieve elimination depending on the initial prevalence and the coverage of treatments during the MDA.

11.7 ELIMINATION PROGRAMS

11.7.1 Onchocerciasis Control Programme in West Africa

Figure 11.6 (1) shows the geographical distribution of onchocerciasis in Africa and the Arabian Peninsula. The Onchocerciasis Control Programme (OCP) in West Africa was established as a regional program in the early 1970s. Its prime aim was to eliminate onchocerciasis as a disease of public health importance in West Africa and to place participating countries in a position to control any recrudescence of infection should it occur. The program was executed by the World Health Organization (WHO) on behalf of the Committee of Sponsoring Agencies (CSA) (Food and Agricultural Organization, United Nations Development Programme, the World Bank with a rich donor participation, and the WHO) and the 11 participating countries—Benin, Burkina Faso, Cote d'Ivoire, Ghana, Guinea Bissau, Guinea Conakry, Mali, Niger, Senegal, Sierra Leone, and Togo (35, 36).

The OCP started as a vertical control program with its vector operations in 1975. At the close of the program in 2002, the operations covered an area of 1,200,000 km^2 of which 764,000 km^2 benefited directly from vector control. Over 50,000 km of rivers was surveyed and appropriately larvicided. The objective of vector control was to interrupt transmission of the parasite for long enough periods to allow the human reservoir to die out. Initially planned to last 20 years, the period for larviciding was reduced to 14 years upon new evidence, which suggested a shorter reproductive life span (12 years) for the worm. This period of vector control was further reduced to 12 years when larviciding was combined with ivermectin treatment in light of additional information from model predictions. Vector control did not benefit the population already infected, or those who were already suffering the morbidity associated with the disease before larviciding started. However, as from 1987, when ivermectin treatment was added to larviciding in some areas, direct morbidity control became part of the program strategy.

The OCP is cited as one of the most successful large-scale control program ever undertaken in the developing world. Several reasons may be responsible for this success. First, there was a sense of common purpose by all concerned. There was a single objective that was developed by all, agreed upon, accepted, and was stuck to by the group concerned. It was as a "regional program" that the participating countries, which bore the brunt of the disease burden, wanted. It is clear that given the long range of the vector and the complex nature and heavy infrastructure involved in the operations only a regional approach was likely to succeed. All concerned devoted their attention in terms of time, funds, and in kind contribution to the OCP. Donor participation and funding was unflinching and the contribution through the free drug donation by Merck was remarkable. Furthermore, the program was driven by motivated and competent staff and by operational research whose findings underpinned the strategies that were used.

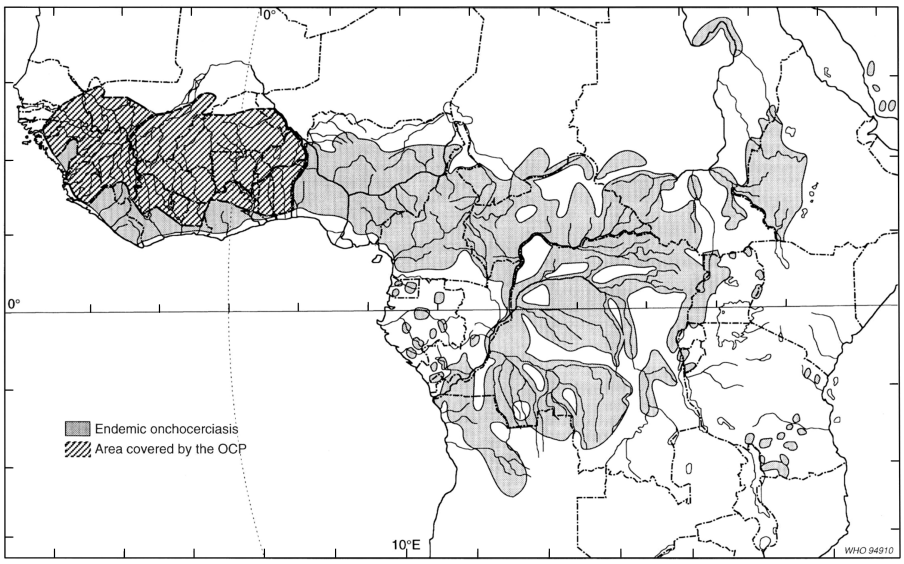

FIGURE 11.6 The geographical distribution of onchocerciasis in Africa and the Arabian Peninsula.

As the flies in the river basins were controlled, the communities returned to the previously abandoned villages. This, in several situations, was not done in a controlled fashion, creating a new challenge of intense pressure on the river basins and the land, although in some countries organizations were set up to coordinate this rehabilitation of abandoned land. Since the program has ended, flies have begun to reinvade the areas. Although these flies are no longer infected, and there is no risk of river blindness, the population in some areas is complaining of the "failure of the program," as they suffer once again from the biting nuisance.

11.7.2 African Programme for Onchocerciasis Control (APOC)

The African Programme for Onchocerciasis Control (APOC) was established at the end of 1995 to help control onchocerciasis in 19 countries that were thought to be endemic for onchocerciasis in Africa outside of the OCP area. The principal strategy was mass distribution of ivermectin and the chief objective of the program was to set up sustainable ivermectin distribution that would continue when the program finished. A secondary objective was to eliminate the vector completely in the few sites where the conditions existed to do so.

One of the first activities of APOC was to map out not only where the disease existed but where the prevalence of the disease was sufficiently high to warrant mass treatment (37). It was found that there is a fairly consistent relationship between the presence of nodules in the population and the overall prevalence of the disease, nodules being present in one third to one half of the population who are positive by skin snip (a small bloodless skin biopsy examined for skin microfilaria). Fifty people resident in a community for at least 10 years can be examined and an estimation of the prevalence can be made dividing populations into hyperendemic where mass treatment is urgent, mesoendemic where mass treatment is desirable, and hypoendemic where only individual cases with symptoms need treatment. Skin and eye disease is infrequent in hypoendemic communities. This assessment by village called Rapid Epidemiological Assessment (REA) was further adapted using knowledge of the terrain and the population into a broader based mapping system based on river valleys where a biased sample of villages were evaluated, according to strict criteria. Although this Rapid Epidemiological Mapping of Onchocerciasis (REMO) is not a detailed epidemiological study, it enables decisions to be made where mass treatment should be carried out (38). Although some refinement is still needed in difficult areas, most of the 19 countries have been mapped and red areas (needing mass treatment) and green areas (not needing mass treatment) have been defined. Three of the 19 countries—Kenya, Mozambique, and Rwanda—only have hypoendemic disease and are not therefore receiving MDA. The current REMO map can be seen on the APOC website (see Fig. 11.7).

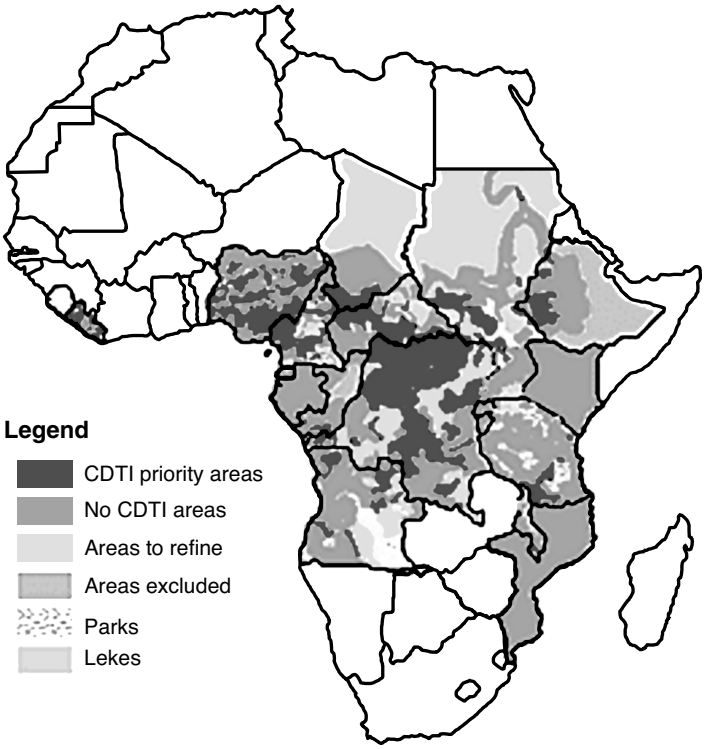

FIGURE 11.7 The current REMO map seen on the APOC website. http://www.who.int/blindness/partnerships/APOC/en/ (*See insert for color representation of this figure.*)

Because of this need for a sustainable method of MDA, a low-cost distribution system was needed. Early trials using mobile teams were not sustainable and community-based approaches were required. Research showed that if communities were empowered to make their own plans of actions once they had been fully sensitized and had been trained in the necessary technical details, they were able to organize their own MDA with minimal input from the health services, which are often nonexistent in remote communities. This led to a refinement of community-based approaches called Community-Directed Treatment with Ivermectin (CDTI) (39). Once communities are informed, they undertake the following tasks:

- Choose a distributor for training
- Do a census to calculate Mectizan requirements
- Organize the collection of Mectizan from a health center or other distribution point
- Organize a distribution method (house to house, fixed point in village, etc.)

FIGURE 11.8 Health education about onchocerciasis in a Burundi village.

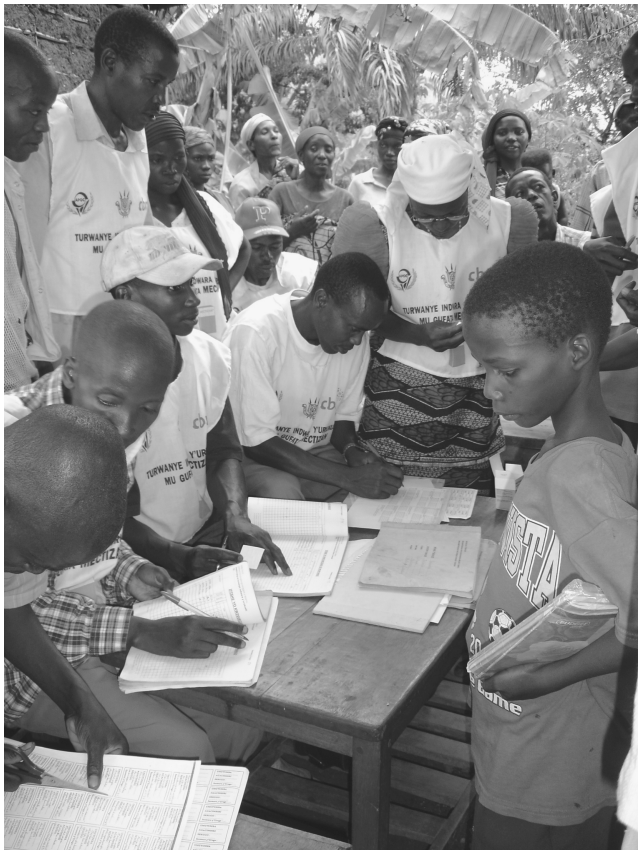

FIGURE 11.9 Registration of residents in a Burundi village.

- Help the distributor calculate the dose and distribute the Mectizan
- Organize transfer of patients with adverse events, if required
- Note the treatment statistics and report to the health authorities
- Participate in community supervision
- Arrange appropriate recognition at the community level of those who have given their time to work for the distribution.

The process of health education, registration of families, calculating the dose using a dose pole, and giving out tablets in a Burundi village are shown in Figs. 11.8–11.11.

After 5 years communities should be ready to continue treatment alone, with minimal help and supervision from the primary health care (PHC) services, so although it takes time and effort with each community to initiate CDTI, once the system is functional, it becomes more and more sustainable. The development of CDTI has been one of the major advances in PHC over the last decade and has been the foundation for other community activities (40).

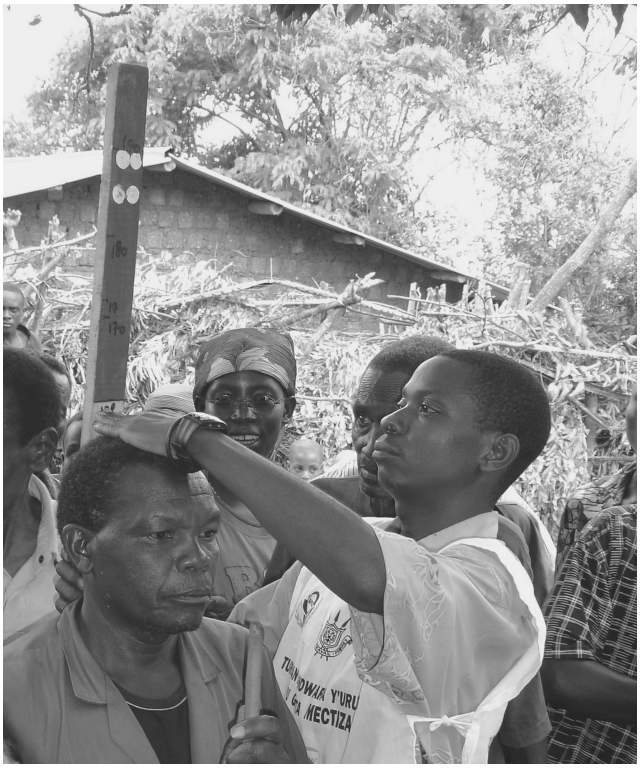

FIGURE 11.10 Dose pole used to estimate the dose of ivermectin based on height.

11.7.3 Ivermectin: The Stimulation of a New Public Health Approach—Community-Directed Intervention (CDI)

The strategy for onchocerciasis control until 1987 was entirely by controlling the vector. The community was hardly involved apart for the employment of some local people as fly catchers and participation in parasitological and epidemiological studies. With the introduction of ivermectin and mass drug administration (MDA), different strategies were needed. Many onchocerciasis MDA programs in Africa were begun initially by nongovernmental development organizations (NGDOs) working in eye care; these MDA were often a part of an integrated eye care program, and vitamin A distribution was added on to the MDA. In some areas MDA with Praziquantel for Schistosomiasis (Bilharzia), and/or MDA including Albendazole for Lymphatic Filariasis elimination were added on as well. Repeated MDA requires much more community participation and research has shown that if communities are empowered to organize their own treatment, they are fully able to do so, not just with ivermectin but also with other MDA. This co-implementation has now been fully tested and found to achieve better results than traditional methods using the health services in an approach called community-directed intervention (CDI). It has also been extended to other non-MDA interventions such as distribution of bed nets, and home treatment of malaria (41).

FIGURE 11.11 Giving out tablets.

11.7.4 A Paradigm Shift in Africa

APOC was conceived as a control program with two main objectives. First, the main objective was to set up sustainable program for MDA, with the eventual aim of eliminating onchocerciasis as a "public health problem." Second, another less important objective was to eliminate the vector of the disease where possible, which included a few small foci in non-OPC areas in Uganda, Tanzania, and the Island of Bioko (Equatorial Guinea) in the Gulf of Guinea. It was considered that onchocerciasis could not be eliminated in Africa using current tools (42).

Studies in Senegal and Mali have now showed that ivermectin could be stopped after 16 years, at least in some areas of savannah onchocerciasis (43). In some areas of Uganda, where there has been a combined vector and ivermectin approach treatment is on the point being discontinued (44). Skin snip research in other foci of infection have indicated similar results after 14–18 years, but further studies are required to confirm the interruption of transmission. Results have not been uniform and are probably related to the intensity of the original infection as well as levels of treatment coverage.

These studies have stimulated a major change in thinking, that onchocerciasis could be eliminated at least from some areas of Africa using ivermectin distribution. It is now conceivable to think of eliminating the transmission of onchocerciasis in western and eastern Africa, even though the central African region will remain a problem due to the problems caused by conflict and the presence of another filarial infection Loa-Loa (45).

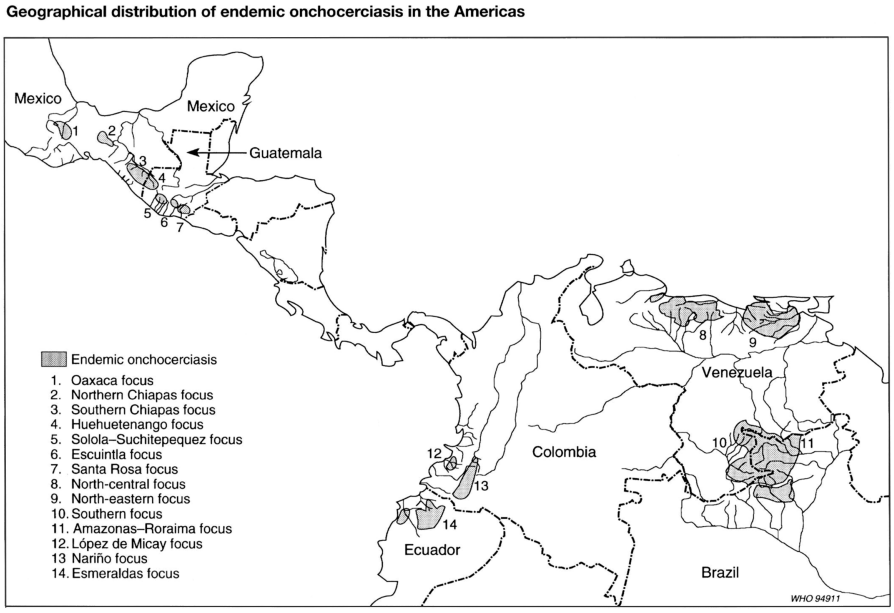

FIGURE 11.12 Onchocerciasis elimination program in the Americas is limited to small foci in six countries: Mexico, Guatemala, Columbia, Ecuador, Venezuela, and Brazil.

11.7.5 The Onchocerciasis Elimination Program for the Americas (OEPA)

Onchocerciasis in the Americas is limited to small foci in six countries—Mexico, Guatemala, Columbia, Ecuador, Venezuela, and Brazil (see Fig. 11.12) (1). The total number of people infected was half a million. In 1995 the program changed the policy of treatment to twice a year and from 2000 began a process of pushing for maximum coverage. Unlike APOC there is an attempt to treat everyone infected, even in hypoendemic areas. Because these foci are small and well localized, it has been possible to create closed systems and with the twice yearly treatments for 7 years the program has already managed to stop treatment in some areas where transmission has been interrupted (46). The program has been so successful that it is hoped that treatment can be stopped everywhere in 2012, although the focus on the Venezuelan–Brazil border with the Yanomami Indians deep in the Amazon forest remains a challenge. Intensive treatment is ongoing in the remaining foci with treatment cycles every 3 months and intensive epidemiological and entomological surveys both to follow progress and also for surveillance in areas where treatment has stopped. Figure 11.13 shows the treatment with ivermectin since the beginning of the program in the Americas and the projections into 2015 (47).

11.7.6 Yemen

The disease in Yemen was probably imported from Africa and is found in the river valleys (Wadis) draining into the Red Sea. The strategy has been based on individual treatment of symptomatic cases of Sowda, although this has also been extended to family members in some cases. Yemen has now planned an elimination campaign. This will have two parts. The first, which is vector control, should be reasonably easy because some of the Wadis dry up in the dry season. However, some breeding sites will be difficult to locate due to the difficult terrain. The second strategy is mass treatment with ivermectin in all the areas affected. This will be for approximately 300,000 people and will be four times a year. Individual patients already on treatment will be followed up regularly. Once the plan is fully implemented, it is hoped that the program will take around 7 years to complete.

11.8 CRITERIA FOR ELIMINATION OF TRANSMISSION OF ONCHOCERCIASIS

The World Health Organization has produced criteria for certifying elimination of the transmission of the disease. These are not applicable in all circumstances and will have to be adapted to different epidemiological situations.

Figure 11.14 shows a schematic representation of the phases in programs for elimination of onchocerciasis transmission, in relation to the theoretical fall-off of the adult worm population and annual transmission potential (ATP). Arrows mark major achievements, which indicate the transition between phases and changes in required interventions or surveillance activities as described. The four phases shown are critical periods in progress to elimination.

In Phase 1 transmission of the disease continues but the annual transmission potential is gradually reduced due to an

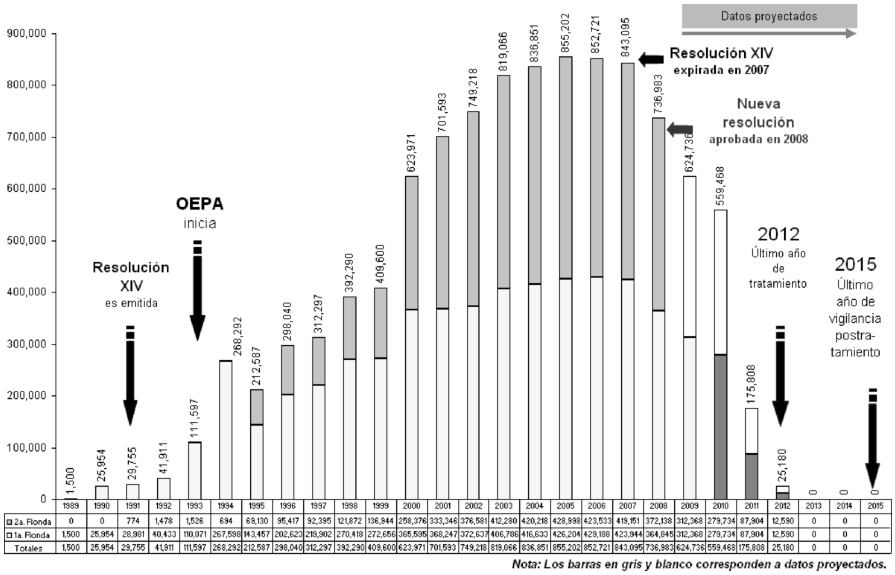

FIGURE 11.13 Graph of treatment with ivermectin since the beginning of the program in the Americas and the projections into 2015 (47).

appropriate intervention (ivermectin treatment, vector control, or both). The ATP is the number of infective larvae that could be transmitted to an individual if all the flies biting him during 1 year were able to transfer all the load of L3s. This figure varies with vector differences and the strains of *O. volvulus*. An ATP of less than 100 is considered to be safe to protect from eye manifestations of the disease but must be brought down much lower to eliminate transmission. This is considered the "break point" in modeling of the disease (48). As the treatment strategy continues, there will be no more transmission, either due to absence of flies using vector control or absence of infected bites if ivermectin treatment is used.

In Phase 2, transmission has ceased and the adult population will age and will die off. It should be noted, however, that while some adults are alive, there is always the possibility of transmission, if control activities are suspended. It is in fact vital during this phase that control efforts continue to the end of the phase, if not all that has been gained will be lost (49). OCP using vector control, used 14 years as the most appropriate length of Phase 2. A similar period is proposed for ivermectin, but if multiple treatments per year are used,

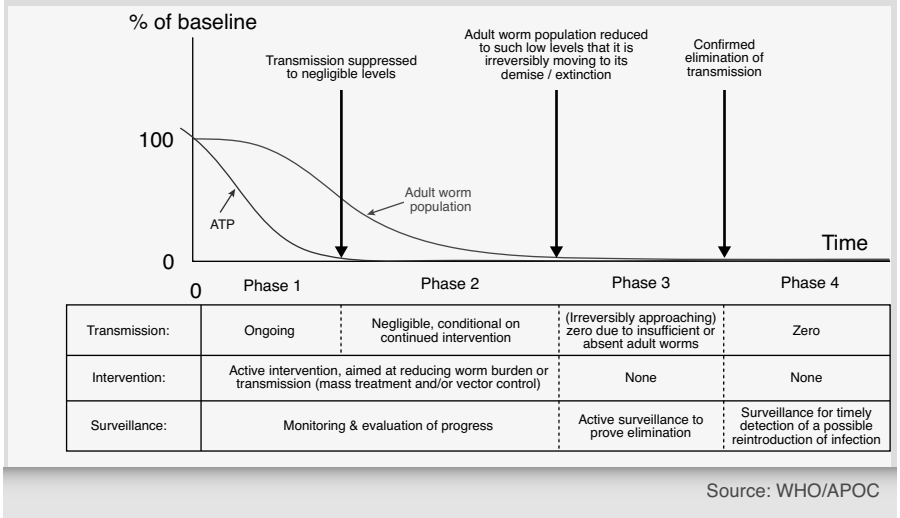

FIGURE 11.14 A schematic representation of the phases in programs for elimination of onchocerciasis transmission, in relation to the theoretical fall-off of the adult worm population and ATP. http://www.who.int/blindness/partnerships/APOC/en/ (*See insert for color representation of this figure.*)

the adult worms will age and die much more quickly and this period could be shortened to 6 or 7 years. It should be noted that Phase 2 only begins when transmission has been suppressed because until that is achieved, there is always the possibility of introducing new filaria into the system. Annual treatments with ivermectin, especially when coverage has not been adequate, will not suppress transmission and so will delay the beginning of Phase 2.

In Phase 3, treatment is stopped. The disease will die out under normal circumstances, even if all the parameters are not right down to zero, but regular surveillance is carried out to confirm that there is no recrudescence. It should be noted that during this phase there are surveillance activities that need to be continually funded!

Phase 4 covers a period of time when reinvasion could occur from another focus of infection, or alternatively due to massive movements of populations, for example, in a war situation, infected patients in sufficient numbers move to a new area where there are flies, so that transmission could recommence.

11.9 GUIDELINES FOR ELIMINATION

The World Health Organization has produced guidelines to certify elimination (50).

Elimination of Morbidity:
Prevalence of microfilariae (MF) in the cornea or anterior eye chamber $<1\%$.

Elimination of Transmission:
L3 in flies $<0.05\%$ (0.1% in parous flies).

ATP lower than 5–20 L3 per season.

Absence of detectable infection in school children and antibody prevalence of $<0.1\%$.

To certify elimination by WHO, this has to be country wide, for all foci of infection. Some modifications of these criteria are needed to adapt to different situations, for example, where flies have been eliminated by vector control methods.

11.10 CHALLENGES

There is a mixture of programmatic challenges as well as technical issues to be resolved (51) for the ongoing control or elimination of onchocerciasis.

11.10.1 Co-infection with Loa-Loa

In areas of tropical rain forest in Africa there is a common infection of patients with another filarial parasite, Loa-Loa. Although the mobile adult worm is found in the tissues, often not far under the skin, the MF are present in the blood. When patients with high levels of MF in the blood are treated with ivermectin, they can provoke serious adverse events. Although the pathology of these events is still poorly understood, the most significant event is an "encephalopathy." The patient develops neurological symptoms such as drowsiness, slurring of speech, walking difficulties, and eventually coma may occur. If properly managed, patients with coma will normally recover after a few days, although some sequelae may remain. Unfortunately many of these patients live in remote areas where access to suitable health services is non-existent, also in some cultures, patients with coma are treated with local remedies, initially delaying transfer to suitable health facilities. Often when patients eventually arrive at these health facilities, there are already major complications due to pressure sores and other infections, putting the lives of these patients further at risk. Special precautions must be put in place to manage these patients quickly and effectively where treatment is required for onchocerciasis.

11.10.2 Transmission Zones

This is an important issue for the APOC elimination program. Mass treatment is ongoing in mesoendemic and hyperendemic regions only. These are areas where skin disease and eye complications are present. In hypoendemic areas only patients with symptoms are treated. Transmission is certainly taking place in some of these hypoendemic zones, although it may not be important in some areas where the mesoendemic and hyperendemic foci have been well controlled. These areas need to be fully investigated to see where transmission is occurring and what would be an appropriate treatment strategy. In many of the foci in APOC countries there is co-infection with lymphatic filariasis, another filarial disease that uses ivermectin together with albendazole for an elimination program. Distribution of ivermectin may already be ongoing in some of these hypoendemic areas and programs must be coordinated.

11.10.3 Frequency of Treatment with Ivermectin

A single dose of ivermectin will reduce MF in the skin to negligible levels in a day or so. The adult females start to reproduce after 3–4 months and microfilaria can appear once again in the skin. However, as already mentioned, even after a year the worm load is around 20% of the pre-treatment levels. This has been the basis for suggesting annual treatment as a control measure. After a few rounds of annual treatment, levels of MF in the skin are so low as to already have an effect on transmission. If the objective is to change to the elimination of transmission, this may or may not be sufficient. Annual treatment has certainly proved effective in some circumstances and has eliminated the disease in some foci

in West Africa. To move from Phase 1 to Phase 2 of elimination twice yearly treatment would be quicker. However, in programs already well established with annual treatment and already moving toward elimination, the logistical complications of changing strategy is probably not warranted. This needs further investigation.

11.10.4 Conflict Areas

Civil conflict has unfortunately been a reality for several African countries, particularly in the central African region. Conflict not only causes significant population movements but also destroys infrastructure and leads to a significant brain drain when competent health workers look for jobs elsewhere where their skills can be better utilized. Annual treatment coverage in many areas in central Africa remains far too low to have any impact on transmission of the disease and efforts at scaling up are also difficult for the reasons mentioned above (52, 53).

11.10.5 Diagnostics

Skin snipping and fly dissection have been the mainstay of control diagnostics. Fly dissection is tedious, since many flies need to be dissected. However, for the flies, pool screening using polymerase chain reaction (PCR) is proving very effective and is very practical. Skin snipping becomes increasingly less sensitive as numbers of MF diminish. Also skin snipping is a painful procedure; to confirm the absence of the disease, it is recommended to check 3,000 children in the area. Two methods are useful, but both have drawbacks. First, the DEC patch test is noninvasive, but the patch must remain on the skin until read the following day and health staff must be available to read the result. Serological tests such as the OV16 test are very useful but require laboratories some distance from the field to analyze the results. If OV16 could be developed into a simple card test carried out in the field and read in the field, it could become an ideal test.

11.10.6 Sustainability

Whatever strategy is used for ivermectin distribution, it is clear that distribution is an ongoing activity and must be maintained at high levels of coverage if transmission is to be interrupted. It is difficult to maintain both donor interest and patient interest once the initial impact of the treatment is no longer evident. Programs must be fully integrated into the primary health care system and become part of the normal package of activities at this level in order to be maintained.

11.10.7 Integration with MDA for Other Health Activities

Several of the so-called neglected tropical diseases (NTDs) also use MDA as their primary strategy for control or elimination (54). It is logical to integrate MDA where it is safe to do so and where there is an obvious fit (55). For some of the diseases such as soil-transmitted helminths (intestinal worms) or schistosomiasis (bilharzia), the target population is school children, and treatment strategies involve school-based distribution. Other programs use child and maternal health weeks. For onchocerciasis and lymphatic filariasis the total population (except those excluded from treatment for medical reasons) are treated and some sort of CDTI is necessary. Programs should be integrated where it is a natural fit and safe to do so, but should not be forced at the risk of losing coverage or the losing the specificity related to any one of the diseases targeted in a control or elimination program.

11.11 CONCLUSION

Various public health measures and different programs for over 30 years have led to onchocerciasis, once the scourge of many areas of Africa and the Americas, gradually becoming controlled and even eliminated. This has been effective through different methods but all with effective partnership. Onchocerciasis is now being controlled with mass drug administration, which would not have happened without the donation of Mectizan (ivermectin) by Merck in 1987. This donation has been the inspiration for donations for the control of other neglected tropical diseases. The objective of eliminating onchocerciasis, however, should not be forgotten. If disease control efforts should falter during the next few years, there is a grave risk or recrudescence and populations once freed of the disease will once again be exposed. All that has been gained must not be lost through short-sighted policies or lack of funding for the last few years, needed to complete the elimination of this debilitating disease.

REFERENCES

1. WHO. Onchocerciasis and its Control. Report of a WHO Expert Committee on Onchocerciasis Control. WHO Technical Report, Series 852. WHO, Geneva, 1995.
2. Noma M, Nwoke BEB, Nutall I, Tambala PA, Enyong P, Namsenmo A, Remme J, Amazigou UV, Kale OO, Seketeli A. Rapid epidemiological mapping of onchocerciasis (REMO) its application by the African Programme for Onchocerciasis Control. *Ann Tropical Med Parasitol* 2002;96(Suppl 1):29–39.
3. Zimmerman PA, Katholi CR, Wooten MC, Lang-Unnasch N, Unnasch TR. Recent evolutionary history of American *Onchocerca volvulus,* based on analysis of a tandemly repeated DNA sequence family. *Mol Biol Evol* 1994;11(3):384–392.
4. Colatrella B. The Mectizan donation program: 20 years of successful collaboration. *Ann Trop Med Parasitol* 2008; 102(Suppl 1):S7–S11.

5. Gustavsen KM, Bradley MH, Wright AL. GlaxoSmithKline and Merck: private-sector collaboration for the elimination of lymphatic filariasis. *Ann Trop Med Parasitol* 2009;103 (Suppl 1):S11–S15.
6. Blacklock DB. The development of *Onchocerca volvulus* in *Simulium damnosum*. *Ann Trop Med Parasitol* 1926;20: 1–48.
7. Duke BOL, Anderson J. A comparison of the lesions produced in the cornea of the rabbit eye by microfilaria of the forest and Sudan-Savannah strains of *Onchocerca volvulus* from Cameroon. *Tropenmed Parasitol* 1972;23:354–368.
8. Duke BOL, Garner A. Fundus lesions in the rabbit eye following inoculation of *Onchocerca volvulus* in the posterior segment. *Tropenmed Parasitol* 1976;27:3–17.
9. Dadzie KY, Remme J, Rolland A, Thyelfors B. Ocular onchocerciasis and intensity of infection in the community II West African Savannah. *Ann Trop Med Parasitol* 1989;40: 348–354.
10. Remme J, Dadzie KY, Rolland A, Thyelfors B. Ocular onchocerciasis and intensity of infection in the community I West African Savannah. *Ann Trop Med Parasitol* 1989;40: 340–347.
11. Duke BOL. The population dynamics of *Onchocerca volvulus* in the human host. *Trop Med Parasitol* 1993;44:61–68.
12. Duke BOL, Lewis DJ, Moore PJ. *Onchocerca: Simulium* complexes I. Transmission of forest and Sudan-savannah strains of *Onchocerca volvulus* from Cameroon, by *Simulium damnosum* from various West Africa bioclimatic zones. *Ann Trop Med Parasitol* 1996;60:318–336.
13. Lewis DJ, Duke BOL. *Onchocerca: Simulium* complexes II. Variation in West African *Simulium damnosum*. *Ann Trop Med Parasitol* 1996;60:318–326.
14. Anderson J, Fuglsang H, Hamilton PJS, Marshall TFdeC. Studies on onchocerciasis in the United Cameroon Republic II. Comparison of onchocerciasis in rain forest and Sudan Savannah. *Tran R Soc Trop Med Hyg* 1974;68:209–222.
15. Hougard J-M, Sékétéli A 1998. Combatting onchocerciasis in Africa after 2002: the place of vector control. *Ann Trop Med Parasitol, Suppl*; 92;165–166.
16. Taylor MJ, Hoerauf A. *Wolbachia* bacteria of filarial nematodes. *Parasitol Today* 1999;15:437–442.
17. Hise AG, Gillette-Ferguson I, Pearlman E. Immunopathogenesis of *Onchocerca volvulus keratitis* (river blindness): a novel role for TLR4 and endosymbiotic *Wolbachia* bacteria. *J Endotoxin Res* 2003;9(6):390–394.
18. Saint André A, Blackwell NM, Hall LR, Hoerauf A, Brattig NW, Volkmann L, Taylor MJ, Ford L, Hise AG, Lass JH, Diaconu E, Pearlman P. The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. *Science* 2002;295(5561):1809–1811.
19. O'Neil J. On the presence of a filaria in "craw-craw." *Lancet* 1875;105(2686):265–266.
20. Murdoch ME, Hay RJ, Mackenzie CD, et al. A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol* 1993;129:260–269.
21. Anderson J, Fuglsang H, al-Zubaidy A. Onchocerciasis in Yemen with special reference to Sowda. *Trans R Soc Trop Med Hyg* 1973;67(1):30–31.
22. Hissette J. Mémoire on *Onchocerca volvulus* and ocular manifestations in the Belgian Congo. *Ann Soc Belge Méd Trop* 1932;12:433–529.
23. Ridley H. Ocular onchocerciasis, including an investigation in the Gold Coast. *Br J Ophthalmol* 1945;10(Suppl):1–58.
24. Abiose A, Jones BR, Murdoch I, et al. Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet* 1993;341:130–134.
25. Cousens SN, Yahaya H, Murdoch I, Samaila E, Evans J, Babalola OE, et al. Risk factors for optic nerve disease in communities mesoendemic for savannah onchocerciasis, Kaduna State, Nigeria. *Trop Med Int Health* 1997;2(1):89–98.
26. Druet-Cabanac M, Preux PM, Bouteille B, Bernet-Bernady P, Dunand J, Hopkins AD, et al. Onchocerciasis and epilepsy: a matched case-control study in the Central African Republic. *Am J Epidemiol* 1999;149(6):565–570.
27. Pion SDS, Kaiser C, Boutros-Toni F, Cournil A, Taylor MM, et al. Epilepsy in onchocerciasis endemic areas: systematic review and meta-analysis of population-based surveys. *PLoS Negl Trop Dis* 2009;3(6):e461.
28. Kipp W, Burnham G, Bamuhiiga J, Leichsenring M. The Nakalanga Syndrome in Kabarole District, Western Uganda. *Am J Trop Med Hyg* 1996;54(1):80–83.
29. Prost A, Vaugelade J. La surmortalite des avegles en zone de savanne ouest-africaine. *Bull World Health Org* 1981;59: 773–776.
30. Thompson BH. Studies on the flight rage and dispersal of *Simulium damnsosum* (Diptera Simuliidae) in the rain forest of Cameroon. *Ann Trop Med Parasitol* 1976;70: 343–354.
31. Roberts JMD, Neumann E, Guckel CW, Highton RB. Onchocerciasis in Kenya, 9, 11, and 18 years after elimination of the vector. *Bull World Health Org* 1986;64:667–681.
32. Hougard J-M, Poudiougo P, Guillet P, Back C, Akpoboua L, Quioevere D. Criteria for the selsction of larvicides by the onchocerciasis control programme in West Africa. *Ann Trop Med Parasitol* 1993;85:435–442.
33. Wanji S, Tendongfor N, Nji T, Esum ME, Ngwa JC, Nkwescheu A, et al. Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. *Parasit Vectors* 2009;2:39.
34. Dominguez-Vazquez A, Taylor HR, Greene BM, Ruvalcaba-Macias AM, Rivas-Alcala AR, Murphy RP, Beltran-Hernandez F. Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis. *Lancet* 1983; 1(8317):139–143.
35. Samba EM. The Onchocerciasis Control Programme in West Africa. An Example of Effective Public Health Management. Geneva: World Health Organization, 1994.
36. Boatin B. The Onchocerciasis Control Programme in West Africa (OCP). *Ann Trop Med Parasitol* 2008;102(Suppl 1): 13–17.

37. Taylor HR, Duke BOL, Munoz B. The selection of communities for treatment of onchocerciasis with ivermectin. *Trop Med Parasitol* 1992;43:267–270.
38. Ngoumou P, Wash JF. A manual for rapid epidemiological mapping of onchocerciasis. Doc No TDR/TDE/ONCHO/93. 4 World Health Organisation Geneva, 1993.
39. Amazigo U. The African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* 2008;102(Suppl 1): S19–S22.
40. WHO/APOC. Community-directed treatment with ivermectin (CDTI). 2009. Available at www.who.int/apoc/cdti/en.
41. WHO/TDR. Community-directed interventions for major health problems in Africa—a multi-country study: final report 2008. Available at www.who.int/tdr/publications WHO/APOC 2009. Informal consultation on elimination of onchocerciasis transmission using current tools in Africa "Shrinking the Map," WHO/APOC/2009.
42. Dadzie KY, Neira M, Hopkins D. Final report on the conference on the eradicability of onchocerciasis. *Filaria J* 2003;2:2.
43. Diawara L, Traoré MO, Badji A, Bissan Y, Doumbia K, et al. Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. *PLoS Negl Trop Dis* 2009;3(7):e497.
44. Ndyomugyenyi R, Lakwo T, Habomugisha P, Male B. Progress towards the elimination of onchocerciasis as a public-health problem in Uganda: opportunities, challenges and the way forward. *Ann Trop Med Parasitol* 2007;101(4): 323–333.
45. WHO/TDR. Press release. http://apps.who.int/tdr/svc/news-events/news/phase3-trial-moxidectin 2009.
46. Sauerbrey M. The Onchocerciasis Elimination Program for the Americas. *Ann Trop Med Parasitol* 2008;102(Suppl 1): S25–S29.
47. PAHO. Pan American Health Organisation 48th Directing Council (CD48-10-e), 2008. Available at www.paho.org/English/GOV/CD/cd48-10-e.pdf.
48. Plaisier AP, van Oortmarssen GJ, Habbema JD, Remme J, Alley ES. ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis. *Comput Methods Programs Biomed* 1990;31(1):43–56.
49. Hopkins AD. Onchocerciasis control: impressive achievements not to be wasted. *Can J Ophthalmol* 2007;42:13–15.
50. WHO. Certification of elimination of human onchocerciasis criteria and procedures, 2001. Available at WHO/CDS/CPE/CEE/2001.18a Accessed at http://whqlibdoc.who.int/hq/2001/WHO_CDS_CPE_CEE_2001.18b.pdf.
51. Hopkins AD. Ivermectin and onchocerciasis: is it all solved? *Eye* 2005;19:1057–1066.
52. Hopkins AD. Distribution d'ivermectine dans les pays en conflit. *Cahiers Santé* 1998;8(1):72–74.
53. Homeida MM, Goepp I, Ali M, et al. Medical achievements under civil war conditions. *Lancet* 1999;354:601.
54. Molyneux DH, Hotez PJ, Fenwick A. "Rapid impact interventions" how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. *PLoS Med* 2005;2(11):e336. Doi;10.1371/journal.pmed.002033.
55. Hopkins AD. Challenges for the integration of mass drug administration against multiple "neglected tropical diseases." *Ann Trop Med Parasitol* 2009;103(Suppl 1):S23–S31.