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ONCHOCERCIASIS AND ITS CONTROL

Report of a
WHO Expert Committee
on Onchocerciasis Control

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Geneva, 29 November–6 December 1993

Members

Professor A. O. Abiose, Medical Director, National Eye Centre, Kaduna, Nigeria (*Rapporteur*)

Dr K. Awadzi, Director, Onchocerciasis Chemotherapy Research Centre, Hohoe Hospital, Hohoe, Ghana (*Vice-Chairman*)

Professor E. W. Cupp, Professor of Medical/Veterinary Entomology, University of Arizona, Tucson, AZ, USA

Dr B. O. L. Duke, Medical Director, River Blindness Foundation, Lancaster, England (*Chairman*)

Dr E. I. I. Gemade, Mectizan Project Manager, Zone C, National Onchocerciasis Control Programme, Kaduna, Nigeria

Dr E. A. Ottesen, Head, Clinical Parasitology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA (*Rapporteur*)

Dr I. Petralanda, Director, Amazon Centre for Investigation and Control of Tropical Diseases, Puerto Ayacucho, Amazonas Federal Territory, Venezuela

Dr J.-B. Roungou, Director, Preventive Medicine and Control of Major Endemic Diseases, Bangui, Central African Republic

Dr H. Schulz-Key, Professor, Institute for Tropical Medicine, University of Tübingen, Tübingen, Germany

Dr N. Weiss, Head, Department of Medical Parasitology, Swiss Tropical Institute, Basel, Switzerland

Secretariat

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Dr K. Y. Dadzie, Programme for the Prevention of Blindness, WHO, Geneva, Switzerland

Dr C. P. Ramachandran, Chief, Filariasis Control, Division of Control of Tropical Diseases, WHO, Geneva, Switzerland (*Secretary*)

Dr J. H. F. Remme, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland

Abbreviations

The following abbreviations are used in this report:

FAO	Food and Agriculture Organization of the United Nations
L_3	infective larvae of *Onchocerca volvulus*
L_4	fourth-stage larvae of *Onchocerca volvulus* that have developed from L_3 larvae
NGO	nongovernmental organization
OCP	Onchocerciasis Control Programme in West Africa
OEPA	Onchocerciasis Elimination Program in the Americas
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
WHO	World Health Organization

1. Introduction

A WHO Expert Committee on Onchocerciasis Control met in Geneva from 29 November to 6 December 1993. Opening the meeting on behalf of the Director-General, Dr P. de Raadt, Director, Division of Control of Tropical Diseases, said that the Committee's discussions would be of particular importance in view of the need to draw attention to and evaluate new concepts and approaches to the effective and sustainable control of onchocerciasis throughout the endemic zones.

Despite the continued success of the WHO-executed Onchocerciasis Control Programme in West Africa (OCP), the increased attention given to onchocerciasis by WHO and by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases was an indication of the gravity of this disease, and the need for the measures that were being taken, both in the laboratory and in the field, to combat it.

Since the third meeting of the WHO Expert Committee on Onchocerciasis in 1986 (1), there have been some highly significant developments in onchocerciasis control which bode well for the future. In 1986, most of the appreciable advances in onchocerciasis control were being made by the OCP on the basis of a sound strategy of interruption of transmission through the continuous suppression of the blackfly vectors. At the same time, there was excitement about ivermectin, a new microfilaricidal drug which, in clinical trials, did not have the side-effects observed with other drugs of this type. Subsequent large-scale trials with ivermectin in the field confirmed that it was a safe and effective drug that could be used to attack onchocerciasis throughout the endemic zones, and that it was also a temporary inhibitor of microfilarial production by adult worms.

Ivermectin was registered in France in 1987 for large-scale use in onchocerciasis control, thanks largely to the late Dr Mohamed Aziz of Merck and Co., Inc., who was instrumental in guiding it through the necessary clinical trials. Once this had been accomplished, ivermectin was immediately made available by the manufacturer, Merck and Co., Inc., free of charge to all governments and organizations concerned with onchocerciasis control.[1] WHO and all other bodies concerned owe an immense debt of gratitude to the Mectizan Donation Program.

Sincere appreciation must also be extended to the community of non-governmental organizations (NGOs), which has responded so positively and continues to assist and support the distribution of ivermectin, especially in countries not covered by the OCP. The efforts made by

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[1] Mectizan (a trade mark of Merck and Co., Inc.) is the formulation of ivermectin for human use approved in France and by all onchocerciasis-endemic countries; the manufacturer stipulates that veterinary or agricultural preparations should not be used in humans.

NGOs in mobilizing resources in Africa, the Arabian peninsula and Latin America, and in collaborating in the development of distribution strategies and methodologies, have provided a new and important tool for onchocerciasis control in the form of large-scale ivermectin distribution. Furthermore, strong, new collaborative links have been forged between the recently established NGO Coordination Group for Ivermectin Distribution, the related WHO programmes, other United Nations bodies, such as the World Bank, UNDP and UNICEF, governments and the Mectizan Expert Committee. All of this augurs well for an acceleration of control activities and increased coverage of the communities at risk. It is also in accordance with the new health partnership called for by WHO, which will involve governments and communities, as well as the public and private sectors, with the aim of encouraging the sharing of responsibility for the protection and promotion of health, and for the prevention of disease.

The last few years have also been marked by the intensification of research on onchocerciasis and its diagnosis, surveillance and control; DNA-probe technology for accurate parasite identification, immuno-diagnosis for the detection of recrudescence, epidemiological mapping and rapid assessment of onchocerciasis endemicity levels, simplified methods of estimating individual doses of ivermectin, and the development of macrofilaricides are some of the most obvious areas in which notable and welcome advances have been made. It is also worthy of note that important studies on the sociological aspects of onchocercal disease, and on community acceptance of ivermectin, are now under way.

Although these achievements must be a source of satisfaction, there are no grounds for complacency: new developments can sometimes have unpredictable consequences and create new and complex problems. The possibility that parasite resistance to ivermectin may develop should be kept in mind as an ever-present, potential threat both to current control activities and to future plans and aspirations for more intensive campaigns against onchocerciasis. The search for a macrofilaricidal drug suitable for large-scale distribution is being actively pursued, but when such a drug is likely to reach the onchocerciasis sufferers who most need it remains uncertain.

Ideally, all control activities should be fully integrated into primary health care, but how best to achieve this, and how to ensure that they will be sustained by national health authorities and have acceptable cost-benefit ratios, are problems still to be faced. Increasingly, onchocerciasis-free zones are becoming available for settlement and development, and every effort must be made to provide guidance to governments and international development agencies to ensure that their development programmes are both compatible with national priorities for environmental protection and economically sustainable. These are by no means easy and straightforward tasks.

2. The parasite

Onchocerca volvulus is a thin nematode worm found as a parasite in human beings. Transmitted by blackflies of the genus *Simulium,* it constitutes a serious global microbial threat, causing itching and disfiguring skin disease, serious eye lesions and blindness in parts of tropical Africa, Latin America and the Arabian peninsula. The adult worms (females 30-80 cm, males 3-5 cm) live in fibrous nodules, some of which are subcutaneous and palpable while others lie deep in the connective and muscular tissues. They have a life span of some 9-14 years. The females produce abundant microfilariae (250-300 μm in length), which migrate from the nodules to invade the skin, eyes and some other organs. They cause most of the disease manifestations of onchocerciasis and have a life span of about 6-24 months. Those ingested from the skin by blood-feeding *Simulium* vectors develop over 6-12 days, without multiplication, to form infective larvae (L_3) which can be inoculated into a new host when the fly feeds subsequently. In the human host they moult twice, again without multiplying, to reach the adult stage; the first microfilariae produced by adult females may appear in the skin some 10-15 months after infection.

There are a number of different forms or "strains" of the parasite, one of which, the West African savanna form, is especially associated with severe blinding lesions in the anterior segment of the eye.

Fundamental studies on the biology both of the adult parasite and of the microfilaria are essential if new and improved methods of control are to be developed. This applies, in particular, to the reproductive biology of the worms in relation to certain drug targets, the mechanism of the immune response from the point of view of vaccine development, and the impact of chemotherapy on microfilariae and hence on transmission.

2.1 Habitat of adult worms

Infective larvae of *O. volvulus* probably moult to the L_4 stage within 3-7 days of arriving in the human host; the moult from L_4 to the juvenile adult stage probably occurs 4-6 weeks later. Although the route followed by immature worms is unknown, they appear to be attracted to existing nodules and may settle on their surface to form satellite or composite nodules. The proportion of infective larvae inoculated that develop into adult worms is unknown. Young, old and calcified dead worms are often associated in the same nodule. Onchocercomata are found in distinct sites of predilection in the body. On average, 80% of the nodules contain one or two male and two or three female worms. Accumulations of more than 50 worms can occur, but this is the exception. In contrast to the sessile female worms, male *O. volvulus* regularly leave the nodules; in excised onchocercomata, a striking predominance of female worms is often observed as a result of this migration in the host of a proportion of the male worms. Since a sex ratio of about 1:1 is found in the nodules of

persons harbouring an aging worm population, e.g. in areas where transmission has been interrupted over a long period, it is assumed that the migratory instincts and possibly the reproductive activity of male worms decrease with age. Inactive old male worms are often clearly separated from non-gravid female worms, although they remain in the same nodule.

2.2 Mating, insemination and fertilization

Nothing is known about the pheromones or other stimuli that attract males to the females in the nodules. Since sperm is scanty in female worms with empty uteri, shedding of oocytes into the uteri may be a prerequisite for the stimulation of males to mate. Conversely, in many females, oocytes are released from the narrow ovaries into the wide lumen of the uteri independently of the presence of male worms. If these females do not mate, large numbers of degenerating and shrinking oocytes may accumulate and subsequently be reabsorbed. Since nematode spermatozoa are short-lived, insemination normally continues during the early phase of embryogenesis. Only 10–15% of worms are found typically entangled in the mating position, and gravid females are regularly found deserted after insemination.

Spermatozoa transferred to the female worms show amoeboid movements which enable them to force their way through a stream of embryos or oocytes moving in the opposite direction until they reach the posterior parts of the uteri. The development of an oocyte into a mature microfilaria within the female has been variously estimated to take 3–12 weeks (*2, 3*).

2.3 Distribution of developmental stages in female worms

Female *O. volvulus* show a heterogeneous distribution of uterine stages. Primary oocytes are present, attached to the rachis of the posterior parts of the ovaries, in all mature female worms but, on average, fewer than two-thirds of the females actually contain embryonic stages and microfilariae. The remainder show only oocytes or empty uteri, and these are found even in large nodules where sufficient numbers of male worms are available. This distribution of different reproductive phases appears to be independent both of the age of the worms and of the intensity or endemicity of infection.

Oocytes and the early developmental stages of a new batch of embryos may be observed in female worms that still harbour degenerating microfilariae though not their precursors. The analysis of worm populations in different epidemiological circumstances and the examination of worms isolated from patients treated with drugs that interfere with intrauterine development have led some authors to conclude that the reproduction of *O. volvulus* occurs in asynchronous cycles lasting 2–4 months each (*2*). Such cyclic reproduction has been

observed for *O. ochengi, O. gibsoni,* and *Onchocerca* species in red deer and roan antelope, and may be typical for species with skin-dwelling microfilariae. However, other observers consider that female worms shed oocytes continually while awaiting insemination (*4*).

2.4 Microfilarial release from female worms

The reproductive capacity of female worms can be assessed by means of embryograms, which quantify the number of intrauterine stages actually present in a female worm, but this "snapshot" cannot indicate how many microfilariae are actually produced or released per day. Observations on worms maintained *in vitro* suggest that 700–1500 microfilariae per female are released into the host on average per day, i.e. only a small proportion of the microfilariae developed *in utero* actually leave the female worms. In contrast to other filarial species, microfilariae of *O. volvulus* are not expelled by the female worm but leave it actively one by one. It takes at least 5–10 seconds for a microfilaria to leave the female worm when it has arrived at the vulva. This is obviously a limiting factor. Microfilariae that stay in the uteri gradually degenerate and are then reabsorbed (*5*).

2.5 Duration of reproductive life span

The reproductive life span of *O. volvulus* has been estimated by longitudinal skin-snip surveys undertaken in villages under vector control and by the analysis of trends in community microfilarial load[1] using the mathematical model ONCHOSIM, as described in section 9.4. The mean duration of reproductive life has been estimated at 9–11 years, and 95% of adults do not reproduce for longer than 13–14 years (*6*).

2.6 Correlation between adult worm loads, microfilarial loads and exposure to infective larvae

Attempts have recently been made to relate the estimated numbers of adult worms in the body to the estimated total load of microfilariae (*5*) and also to the estimated exposure to infective larvae (*7*). These have shown that considerable numbers of female worms are hidden in deep-lying, impalpable nodules, and imply that a high proportion of infective larvae fail to develop into adult worms; furthermore, in many infected persons, tens or hundreds of thousands of microfilariae must die and be disposed of in the body each day.

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[1] The geometric mean number of microfilariae per skin snip among persons aged 20 years and over, including those with a zero count.

Suggestions for further study

- Further studies should be carried out on the reproductive biology of both male and female *O. volvulus* worms.
- Investigations are needed of the means whereby *O. volvulus* worms locate each other in the human host.
- Further studies are needed on the forms or strains of *O. volvulus* in geographical areas where these have not so far been investigated.

3. **The vectors**

The vectors of *O. volvulus* are members of the family Simuliidae in the genus *Simulium* (Table 1). The main vectors, *Simulium damnosum, S. neavei, S. ochraceum, S. metallicum* and *S. exiguum*, are complexes of sibling species which do not otherwise form a taxonomically close group of species.

In Africa and the southern Arabian peninsula, onchocerciasis is associated mainly with members of the *S. damnosum* complex, and to a lesser extent with the *S. neavei* group. The broad distribution of both of these groups has been well known for many years (*1, 8, 9*). *S. albivirgulatum,* the vector in the "Cuvette centrale" focus of Zaire, is the only vector species outside these two taxonomic groups.

The vectors of onchocerciasis in Central America and their geographical distributions are also well known. Recent findings indicate that *S. ochraceum* is also a species complex and that there are many cytospecies within the *S. metallicum* complex.

Knowledge of vectors and potential vectors, and their distributions in the Americas, has increased in the last decade, as has knowledge of the distribution of onchocerciasis itself (*10*). Unlike the situation in Africa and Central America, onchocerciasis in South America is probably still spreading and new foci are being discovered.

There is a marked difference between the situations in Africa and the Americas with regard to the distribution of *Simulium* spp. vectors and potential vectors, and that of the disease. In Africa, wherever anthropophilic members of the two vector complexes occur, the human population suffers from some degree of onchocerciasis. In contrast, in the Americas, potential vectors occur widely outside the areas in which onchocerciasis is endemic. In Central America, the primary and secondary vectors are much more widespread than endemic onchocerciasis. Despite large seasonal migrations to and from the coffee-growing districts, there has been no change in the foci in recent years. However, it is believed that the North Chiapas focus in Mexico was originally established as a result of agricultural workers from that area visiting the South Chiapas focus for

Table 1

Simulium vectors of Onchocerca volvulus and their geographical distribution

Taxon	Principal area	Habitat/epidemiological status
Africa and Arabian peninsula		
S. damnosum complex		
S. damnosum subcomplex		
S. damnosum s.s.	West Africa to southern Sudan, Uganda	Savanna
S. sirbanum	West Africa to Sudan	Dry savanna
S. rasyani	Yemen	Local vector
S. dieguerense	West Africa	Savanna
S. sanctipauli subcomplex		
S. sanctipauli s.s.	West Africa	Forest
S. soubrense	West Africa	Forest
S. leonense	West Africa, especially Guinea, Sierra Leone	Forest
S. konkourense	West Africa	Guinea highlands
S. squamosum subcomplex		
S. squamosum s.s.	West Africa	Forest and highlands
S. yahense	West Africa	Upland forest
S. mengense	Cameroon	Probable vector in forest habitat
S. kilibanum	Burundi, Malawi, Uganda, United Republic of Tanzania, Zaire	Local vector in montane habitat
S. neavei complex		
S. neavei s.s.	Uganda, eastern Zaire	Local vector
S. woodi	United Republic of Tanzania	Local vector
S. ethiopense	South-western Ethiopia	Local vector
S. albivirgulatum	"Cuvette centrale", Zaire	Local vector

Table 1 *(continued)*
***Simulium* vectors of *Onchocerca volvulus* and their geographical distribution**

Taxon	Principal area	Habitat/epidemiological status
Americas		
S. ochraceum s.l.	Mexico, Guatemala	Primary vector in highland foci
S. metallicum s.l.	Mexico, Guatemala, northern Venezuela	Vector; secondary vector in Central and South America
S. callidum	Mexico, Guatemala	Secondary vector
S. exiguum s.l.	Colombia, Ecuador, northern Venezuela	Vector; secondary vector in northern Venezuela
S. guianense	Brazil/Venezuela (Amazonia)	Primary vector in highlands, secondary in lowlands
S. incrustatum	Brazil/Venezuela (Amazonia)	Secondary vector in highlands
S. oyapockense s.l.	Brazil/Venezuela (Amazonia)	Vector in lowlands
S. quadrivittatum	Central America, Ecuador	Secondary vector
S. limbatum	Brazil/Venezuela (Amazonia)	Suspected vector in highlands

the coffee harvest. The development of other foci in this manner cannot be entirely ruled out. In South America, human-biting blackflies occur over vast areas in the absence of the disease; however, the missing element here is not only the parasite but also a significant human population. It is probable that current changes in settlement patterns, together with long-distance migrations of large numbers of people, such as gold-miners, will eventually lead to the establishment of new foci.

In Africa, the spread of onchocerciasis has resulted from human activity and consequent environmental changes such as deforestation, resulting in the conversion of forest habitats into savanna and the creation of artificial breeding sites. In West Africa, such changes have resulted in a shift of the distribution area of the savanna species into forest zones.

3.1 The *Simulium damnosum* complex

S. damnosum was originally considered to be a fairly uniform species, differing biologically in different bioclimatic zones. However, since the mid-1960s it has become apparent that it is a complex of morphologically similar (sibling) species which can be distinguished by the banding patterns of the larval chromosomes. At present, over 40 different cytological forms have been described, half of which have been given formal Latin names. Unfortunately, several have been named without adequate morphological and cytological study.

3.1.1 General situation

In West Africa, west of Nigeria, the *S. damnosum* complex has received detailed study (Table 1). All of these species are either known or suspected (*S. dieguerense*) vectors. In addition to the formally named species, numerous additional cytospecies have been described in West Africa and given vernacular names (*11*).

The situation in Central and East Africa is much more complex. In contrast to West Africa, the cytospecies of the *S. damnosum* complex have not been fully studied and described. Many have very restricted distributions, they are often zoophilic, and many are not known to be vectors of *O. volvulus*. However, it is clear that species of the *S. damnosum* complex are responsible for most of the transmission of onchocerciasis that occurs in Ethiopia, Malawi and the United Republic of Tanzania.

3.1.2 Cytotaxonomic differentiation of species

Various techniques have been employed to separate the members of the *S. damnosum* complex, but so far larval cytotaxonomy and adult morphometry have been the most successful. The former remains the most reliable method for the specific identification of the members of the *S. damnosum* complex. In West Africa, problems still exist in interpreting the chromosomal variation of different populations within the recognized species of the complex. In East Africa, recent cytotaxonomic studies on *S. damnosum* s.l. have addressed the taxonomic status of previously described forms in that region with the aim of providing reference chromosomal maps for species identification.

The species described in West Africa generally fall within three subcomplexes, namely the *S. damnosum, S. sanctipauli* and *S. squamosum* subcomplexes.

The *S. damnosum* subcomplex comprises the "savanna" species *S. damnosum* s.s., *S. sirbanum* and *S. dieguerense,* the second of which includes the dry savanna form previously designated as *S. sudanense*. In addition to the two forms of *S. sirbanum* that occur in West Africa, a third distinct form is found in the Abu Hamed focus of northern Sudan, where it is probably the vector of a non-blinding form of onchocerciasis. *S. sirbanum* and *S. damnosum* s.s. have also been recorded in the forest zone of Liberia and southern Sierra Leone.

The taxonomy of the *S. sanctipauli* subcomplex in Guinea, Liberia and Sierra Leone has been revised. Four sibling species have been described in the subcomplex for this area, namely *S. sanctipauli* s.s., *S. soubrense, S. konkourense* and *S. leonense. S. sanctipauli* s.s., which occurs mainly in Côte d'Ivoire, Ghana and Togo, is also found occasionally in Guinea, Liberia and Sierra Leone. *S. konkourense* consists of two geographical variants, the konkoure and menankaya forms, both identified principally

in Guinea. *S. soubrense* has been found in Guinea, Liberia and Sierra Leone. *S. leonense* is a newly defined species that was previously termed *S. soubrense* "B".

The *S. squamosum* subcomplex consists of *S. squamosum* s.s. and *S. yahense.* Chromosomal variation among populations of these species has been described mainly in unpublished reports, for example in populations of *S. yahense* in the Fouta Djallon area of Guinea, eastern Guinea, Côte d'Ivoire, southern Ghana, Nigeria and Equatorial Guinea, and in populations of *S. squamosum* s.s. from eastern Zaire (*S. squamosum kitetense*) and from the United Republic of Tanzania, where eight cytospecies have been described.

The only cytospecies of the *S. damnosum* complex identified in the Arabian peninsula has been designated *S. rasyani.* This species was previously considered to belong to the *S. squamosum* subcomplex, but a reappraisal of the chromosome maps and other supporting data indicate a closer affinity to the savanna species *S. sirbanum.*

3.1.3 Cytotaxonomy and insecticide resistance studies

Different populations of the same species can differ in their susceptibility to insecticides. Cytological evidence from the OCP indicates that limited introgression between members of the *S. damnosum* complex occurs and thus that the possibility exists for the transfer of genetic factors, such as insecticide resistance alleles, from one species to another.

3.1.4 Morphometric differentiation of species

Cytotaxonomic identifications of larvae are inadequate for such purposes as the determination of vector importance where two or more species are sympatric. Adult identification is then necessary. However, techniques such as cuticular hydrocarbon analysis, the use of DNA probes (see section 7.4), adult cytotaxonomy and isoenzyme analysis have either not yet been successful or have technical limitations under field conditions.

The usefulness of traditional morphotaxonomy is also restricted because interspecific morphological variation is limited. However, five morphological characters have been observed to be of taxonomic value, namely the colour of the abdominal setae, wingtuft colour, forecoxa colour, thorax length and the colour and length of the antenna. The measurement of adult morphological characters and the use of statistics to quantify the degree of overlap between species (morphometrics) increase the accuracy with which adult blackflies can be specifically identified. The use of multivariate statistical analysis is being evaluated by the Vector Control Unit of the OCP. A recent development is the integration of morphometrics and molecular biology techniques to separate the closely related savanna species *S. damnosum* s.s. and *S. sirbanum.*

3.2 The *Simulium neavei* group

Detailed cytological investigations of the *S. neavei* group are still awaited. The distribution outlined in the third report of the WHO Expert Committee on Onchocerciasis (*1*) remains valid. The only changes are likely to have been reductions in vector range following deforestation. Examples of deforestation resulting in a decrease in transmission by members of the *S. neavei* group are known from Malawi, Uganda and the United Republic of Tanzania. In Malawi and parts of Uganda, members of the *S. damnosum* complex have replaced *S. neavei* s.l.

3.3 Vector capacity and transmission in West Africa

3.3.1 *Transmission under natural conditions*

Under natural conditions, there are significant variations in transmission both between and within species, the differences observed being the result mainly of factors such as longevity, trophic preferences and the relative abundance of the various hosts. In the forest zone of southern Guinea and Sierra Leone, the mean number of infective larvae morphologically indistinguishable from *O. volvulus* and associated with species of the *S. sanctipauli* subcomplex is six. Cytological identification confirms that these areas are populated mainly by *S. leonense.* In most of the basins of the western zone of the OCP, the equivalent values are four L_3 larvae for *S. yahense* and five for the other forest species. In the savanna region, *O. volvulus* is associated with *S. sirbanum* and *S. damnosum* s.s., and the average number of L_3 larvae per infective fly is just over two.

3.3.2 *Experimental studies of vector competence*

Extensive experimental studies of vector competence show that all species of the *S. damnosum* complex in West Africa (with the exception of *S. dieguerense*, which has not been studied) are capable of transmitting *O. volvulus.* However, the compatibility of vectors and parasites may depend on their respective origins. Thus the vector competence of the main species of *S. damnosum* s.l. may differ for the two main strains of *O. volvulus* (savanna and forest). The highest parasite yields under normal conditions of transmission occur with species of the *S. sanctipauli* subcomplex and with *S. yahense*, which is consistently a more efficient vector than *S. squamosum.* The lowest parasite yields are found among savanna vectors (*S. sirbanum* and *S. damnosum* s.s.).

Considerable differences exist when vectors and parasite strains are of different geographical origins (cross-transmission). Under experimental conditions, forest parasite strains develop poorly or not at all in savanna vectors (*S. sirbanum* and *S. damnosum* s.s.). The parasite yields obtained from different species of the *S. sanctipauli* subcomplex are high, in general, irrespective of the geographical origin of the parasite strains concerned.

In view of recent epidemiological data on southern Sierra Leone (blinding onchocerciasis occurring in a forest region), the *O. volvulus* strains of that area have been the subject of a number of experimental transmission studies with *S. leonense* (the main vector in that region), *S. sirbanum, S. yahense* and *S. squamosum.* The vector capacity of *S. leonense* has also been evaluated for savanna strains of *O. volvulus* (obtained from western Mali). With the local parasite strain, high yields of infective-stage larvae were found in *S. leonense,* almost none in *S. sirbanum,* and very low levels in *S. squamosum. S. yahense* exhibited a strong vector capacity only when patients had very high parasite loads. The savanna parasite strains developed as well in *S. leonense* as did the local strain from the forest regions of southern Sierra Leone.

In order to quantify the relationship between the potential infectivity of *S. damnosum* s.s. and the intensity of *O. volvulus* infection of the human host, the OCP conducted an experiment in the savanna focus of Asubende, Ghana, in which blackflies were engorged on 40 volunteers with a wide range of microfilarial loads. A clear relationship was found between vector infectivity and skin microfilarial load: persons with a low intensity of infection contributed only little to transmission but the potential infectivity of the vector increased rapidly with the skin microfilarial load of the host. However, even with the most heavily infected patients, fewer than 50% of the flies became infected.

These results, while valid for *S. damnosum* s.s., cannot be extrapolated to other vector species because of differences in the relationship between vector infectivity and skin microfilarial loads. Such differences are of great importance for onchocerciasis control since they should determine the relative effectiveness of large-scale ivermectin treatment programmes in preventing *O. volvulus* transmission.

3.4 Vector species in the Americas

The vectors of onchocerciasis in Central America and their distribution are well known (*1*). *Simulium ochraceum,* a species complex of at least three cytospecies, is considered to be the primary vector in all five foci in Guatemala and Mexico, while *S. metallicum* s.l. and *S. callidum* play secondary roles. It is likely that the same cytospecies of *S. ochraceum* occurs in the Yepocapa and South Chiapas foci, but a different one in the Oaxaca focus. *S. metallicum,* which is also widespread in South America, is a species complex of at least 11 cytospecies, three of which occur in the Yepocapa focus and, together with a fourth, in the South Chiapas focus. Several other species are anthropophilic in parts of Central America.

In South America, the potential vectors of onchocerciasis have been studied in much less depth than in the other endemic areas. The situation is complicated by the presence of large numbers of human-biting forms in areas from which onchocerciasis is at present not reported. Most of

the vectors undoubtedly belong to species complexes. The known vectors are *S. exiguum* s.l., *S. guianense, S. incrustatum, S. metallicum* s.l. *S. oyapockense* s.l. and *S. quadrivittatum. S. limbatum* is strongly suspected of acting as a vector. Additional information on these species is given below.

3.5 Vector capacity and transmission in the Americas

3.5.1 *Simulium ochraceum*

The most extensive data collection available for the appraisal of the vector capacity of New World blackfly vectors exists for *S. ochraceum* in Guatemala. Extensive bionomic studies have shown it to be an aggressive, highly anthropophilic blackfly in the major onchocerciasis foci of Guatemala and Mexico, and indicate that other species (particularly *S. metallicum*), while somewhat zoophilic, may also be involved in transmission. However, in a controlled study of vector competence, *S. ochraceum* was shown to be a better vector than *S. metallicum*, even though a much higher skin microfilarial density was required to promote infection of the thoracic musculature of *S. ochraceum* because of the presence of a buccopharyngeal armature. The densities of host-seeking blackflies of this species were sufficiently high to ensure transmission in spite of the vector's relative inefficiency. Analysis of both seasonal and diurnal patterns of human-biting activity in an onchocerciasis endemic zone in Guatemala during a 13-month period indicated that *S. ochraceum* was the predominant species, accounting for 87% of all blackflies collected during that time. The annual biting rates of this species and other vectors in the Americas are usually higher than those of members of the *S. damnosum* complex; this aspect of vector biology is the hallmark of onchocerciasis transmission in the Americas.

Calculation of the length of time required for ovarian development at the temperatures occurring within endemic onchocerciasis foci and characterization of follicular relics in parous females of *S. ochraceum* have led to the derivation of accurate estimates of the length of the gonotrophic cycle in wild *S. ochraceum*, in concert with the development of *O. volvulus* to the infective stage in infected females. This information was used in interpreting a mark–release–recapture study of both blood-engorged and non-engorged females (*12*); the results indicated that both sets of flies dispersed generally within a range of 3.5 km and that blood-engorged flies tended to take both initial and subsequent blood-meals in the same general geographical area. This behavioural trait, which is associated with the ready availability of humans as blood sources and the presence of shaded, aquatic oviposition habitats, intensifies parasite transmission within discrete areas that are usually coffee and tea agro-ecosystems.

Estimates of vector survival and blood-feeding over the second and third gonotrophic cycles during the wet and dry season indicate that, during the

dry season, a higher proportion of parous flies reach an age at which they can transmit *O. volvulus* L$_3$ larvae. Transmission is assumed to occur at the time of the fourth blood-meal approximately 11–12 days after initial infection. Because vector survival is higher and parasite development more rapid during the dry season, *O. volvulus* transmission in Guatemala and Mexico is highly seasonal.

Because of the mechanical limitations on the infection of *S. ochraceum* resulting from the presence of the buccopharyngeal armature, another highly important factor contributing to variability in transmission is the size of the community microfilarial reservoir in relation to the annual biting rate; there is therefore a direct correlation between prevalence rates of infection in the community, daily biting rate and the frequency of *O. volvulus* L$_3$ larvae in the vector population. As a result, it has been suggested that the transmission of infection in Guatemala could be described more precisely by using two statistics previously employed in Africa – infective biting rate and transmission potential.

3.5.2 *Other species*

Data on other vectors in the Americas are restricted essentially to bio-systematics and distribution, together with a few limited observations on intrinsic vector competence and natural infection rates. It is therefore difficult to estimate vector capacity or other relevant transmission statistics for these species. Known vectors in South America include *S. exiguum, S. guianense, S. metallicum, S. oyapockense* and *S. quadrivittatum.*

S. exiguum s.l. is widely distributed and occurs in all South American onchocerciasis foci. In Ecuador, four cytospecies occur; the cayapa form is an efficient vector in the Santiago focus (Esmeraldas Province) and can become infected by feeding on the blood of people with low densities of skin microfilariae. There are probably other cytospecies of the complex in Brazil and Venezuela. *S. exiguum* s.l. is the only vector in Colombia; it is of secondary importance in Venezuela. Intrinsic vector competence for *O. volvulus* varies with location, perhaps reflecting differences at the population or cytospecies level. In areas where *S. exiguum* is anthropophilic, natural infection rates may be high. In the Santiago focus, this species is most abundant as a human-biter during the rainy season, exhibits a biting peak just before midday and also enters houses to obtain blood-meals.

S. guianense (close to or synonymous with *S. pintoi*) is also widely distributed from southern Venezuela to southern Brazil and in French Guiana, Guyana and Suriname. It is an important vector in the Brazil/Venezuela Amazonia onchocerciasis focus, human biting rates varying with location and season within that large area. Daily biting activity is continuous, with discrete peaks mainly in the morning between 08:00 and 12:30 and early in the evening (16:00–17:00). Unlike *S. exiguum*, this species apparently does not enter houses, instead preferring to feed out of doors on the lower extremities of human hosts.

S. oyapockense s.l. is one of the most common moderately anthropophilic species of lowland forest and savanna of the Amazon and Orinoco basins of Bolivia, Brazil, Colombia and Venezuela. It is also present in French Guiana, Guyana and Suriname. This species is polymorphic and includes taxa designated as *S. amazonicum, S. cuasisanguineum, S. minusculum, S. sanguineum* and *S. roraimense*. It is the only significant vector in lowland forested areas of the Amazonia focus. This species has a low vector competence for *O. volvulus* and, in nature, exhibits low infection rates. It is most abundant during the wet season.

S. metallicum s.l. is widely distributed from Central America and some Caribbean islands to the Andes as far south as Ecuador, and through northern Venezuela. As previously mentioned, it is now known to comprise at least 11 cytospecies. It is the primary onchocerciasis vector in the northern Venezuelan foci of Altamira and Caripe, where it feeds on both humans and large domestic animals, and a secondary vector in Guatemala and Mexico.

S. quadrivittatum is widely distributed from Central America, including certain Caribbean islands, to the lowland forest of Ecuador. It is strongly anthropophilic and plays a secondary role as a vector in Ecuador. *S. incrustatum* is a secondary vector in the highland zone of the Amazonia focus. *S. limbatum* (including yarzabali) is probably a secondary vector in the highland zone of the Amazonia focus.

3.6 Suggestions for further study

- There is a need to identify an institution or institutions to serve as reference centre(s) for *S. damnosum* s.l. cytotaxonomy in Africa to help to clarify or resolve taxonomic difficulties and train personnel.
- The multivariate approach to morphometry that has been so successfully applied in the OCP area needs to be extended to other parts of Africa.
- Studies on vector competence and on annual transmission potential should be conducted in South America, particularly in the Brazilian–Venezuelan foci of onchocerciasis.

4. The disease

4.1 Clinical signs and symptoms

4.1.1 General

The manifestations of onchocerciasis are predominantly dermal, lymphatic and ocular in character. Several other features of uncertain association, etiology or pathogenesis have also been described, including low body weight, general debility, diffuse musculoskeletal pain and, in Africa, epilepsy and hyposexual dwarfism.

The extent and distribution of skin and lymphatic lesions permit classification of the disease into generalized and local forms. Generalized onchocerciasis is the usual presentation, characterized by fairly symmetrical lesions which may be more marked in the lower, or less commonly, the upper part of the body. The local form is asymmetric and may be confined to one limb and the adjacent area or to a circumscribed part of the body. Acute manifestations of localized onchodermatitis occur in new residents and in people from outside the endemic areas; the chronic form of localized onchodermatitis is synonymous with hyperreactive onchodermatitis or *sowda* and is characterized by frequent acute exacerbations.

Many infected persons in endemic areas are asymptomatic and the disease is diagnosed only during surveys or other investigations, e.g. for eosinophilia. Although some present with acute symptoms related to the skin or eye, most patients have chronic established disease.

The principal manifestations of onchocerciasis are summarized in Table 2. Detailed descriptions of lesions, the clinical picture in different geographical areas and the pathological changes can be found in the third report of the WHO Expert Committee on Onchocerciasis (*1*). The more recent findings described below relate to the localization of the microfilariae in the skin and the parasitological, clinical and immunological changes following treatment with ivermectin.

4.1.2 *Localization of microfilariae in the skin*

The traditional teaching is that microfilariae can be found at all levels in the dermis but tend to be most numerous at the dermal–epidermal junction. Intact microfilariae excite little inflammatory reaction. However, in a recent histological study of skin lesions in people living in the West African "forest" and "savanna" (*13*), the microfilariae of *O. volvulus* were found predominantly in the lymphatic channels of the dermis surrounded by minor areas of inflammatory reaction. Reactions thought to represent successive stages of an inflammatory process were observed around extralymphatic microfilariae.

These findings need to be confirmed and extended. They may, however, provide some explanation for recent observations on the dynamics of microfilariae and some of the side-effects observed following treatment with ivermectin.

4.1.3 *Classification and grading of cutaneous changes*

Although some individuals with onchocerciasis may have clinically normal skin, others have intense pruritus and disfiguring skin lesions. At present, there is no widely used system for classifying the skin changes in onchocerciasis. Such a system is urgently required in order to facilitate the collection of standardized data on the global skin disease burden due

Table 2
Principal manifestations of onchocerciasis

Dermal generalized
Pruritus
Lesions
Papules, macules, urticaria, oedema
Excoriations, pustules, crusts, scaling ulceration, lichenification, pachydermia
Atrophy–focal, regional, general
Pigmentary change
Leopard skin
Other–*erisipela de la costa, mal morado,* leonine facies

Dermal localized
Acute–onchocerciasis in people from outside the endemic areas
Chronic–reactive onchodermatitis (sowda)

Nodules (onchocercomata)

Lymphatic
Lymphadenopathy–mild, generalized; marked in groin and femoral triangle
Lymphoedema
Hanging groin

Ocular
Anterior segment
Conjunctiva
Hyperaemia
Chemosis
Limbitis
Cornea
Live microfilariae
Dead microfilariae
Punctate keratitis
Sclerosing keratitis
Anterior chamber/anterior uveal tract
Live microfilariae
Iritis–synechiae, pear-shaped pupil
Secondary glaucoma
Lens
Cataract

Posterior segment
Retina
Pigment epithelial atrophy
Intraretinal deposits
Cotton wool spots
Haemorrhages
Choroid
Choriocapillary atrophy
Subretinal fibrosis
Pigment hyperplasia
Chorioretina
Chorioretinitis
Optic nerve
Optic neuritis
Optic atrophy

Table 2 *(continued)*
Principal manifestations of onchocerciasis

Visual function
   Night blindness
   Visual field loss
   Visual impairment
   Blindness

Systemic
   Localization of microfilariae other than in skin, eye or lymph glands
      Other tissues and organs–liver, spleen, pancreas
      Other body fluids–sputum, tears, joint and vaginal fluid
   Microfilaraemia
   Microfilaruria
   Signs and symptoms of uncertain association, pathogenesis or etiology
      Low body weight
      Musculoskeletal pain
      Epilepsy
      Hyposexual dwarfism

to onchocerciasis. It would also enable comparisons to be made between onchocercal skin lesions in different geographical areas and would allow the effect of larvicidal or ivermectin mass-treatment programmes on skin disease to be assessed. A scheme has, however, been developed recently (*14*) in which the main categories of onchocercal skin disease are defined as follows; acute papular onchodermatitis, chronic papular onchodermatitis, lichenified onchodermatitis, atrophy and depigmentation (see Annex 1). Two important points regarding this classification should be emphasized. First, it is based on clinical findings consistent with cutaneous onchocerciasis but not necessarily specific or diagnostic of the disease. Second, the categories are not mutually exclusive and one pattern may coexist with, or evolve into, another. The scheme also includes a method of grading for use in recording the clinical severity of lesions, the clinical activity in terms of pruritus and excoriation, and the extent of distribution over the body. Its practical usefulness is currently being evaluated.

4.2 Ocular signs and symptoms

The ocular signs of onchocerciasis are related to the presence of living or dead microfilariae; these can be seen with a slit lamp and have been demonstrated in all tissues of the eye. Detailed descriptions of the clinical picture of ocular onchocerciasis can be found in the third report of the WHO Expert Committee on Onchocerciasis (*1*). In the present report, findings in the optic nerve, blindness and visual field loss will alone be considered.

4.2.1 *Optic nerve*

It was commonly believed at one time that active optic neuritis was rare in patients suffering from onchocerciasis, but this lesion has been observed in a number of subjects in a community-based ivermectin study carried out in Nigeria (*15*). Clinical experience has shown that the active optic neuritis associated with onchocerciasis lasts from several weeks to one year or more. It appears as a congested suffused disc with or without swelling, while postneuritic optic atrophy is often associated with scarring and pigment disturbance at the disc margin. Associated dense vascular sheathing may extend along retinal vessels for a considerable distance beyond the optic nerve head. Primary optic atrophy may also occur, and may be partial or complete.

The reported prevalence of optic atrophy has varied between 1% and 4% in the hyperendemic rain forest and savanna communities of Cameroon to between 6% and 9% in the guinea savanna of northern Nigeria.

4.2.2 *Blindness and visual field loss*

Blindness is the most serious consequence of onchocerciasis, and can result from lesions that affect different parts of the eye. Blindness in the savanna was previously attributed mainly to sclerosing keratitis, but a recent study has shown that optic nerve disease plays a significant role in some localities (*15*). In the rain forest, blindness is said to be due mainly to posterior segment disease. By definition, an individual is blind when visual acuity is less than 3/60 in the better eye; there is thus a specified cut-off point. However, the overall visual consequences of onchocerciasis can be fully appreciated only when the importance of uniocular blindness and visual impairment is recognized, since blindness prevalence reflects only part of the problem (*16*).

Onchocerciasis can cause severe reduction in peripheral visual fields, leaving an individual with a small island of central vision, which is often preserved until late in the disease process. Assessment of overall visual disability and blindness from onchocerciasis should therefore take account of visual field loss. In a recent study, the prevalence of blindness defined as visual acuity less than 3/60 in the better eye was 2.7%, but the figure was 3.3% when those considered blind by visual field assessment (fields less than 10° in the better eye) were included. Almost 25% of those who were functionally blind would therefore have been missed without peripheral field assessment.

Currently available methods for visual field assessment are time-consuming and difficult to carry out systematically in the field. A promising tool for field use is the Wu-Jones Computerized Visual Function Test, which measures paracentral visual fields and acuity; the results are reproducible and are immediately entered into a laptop computer, thus making comparison at future follow-up visits possible.

4.3 Immune responses and pathogenesis

4.3.1 *Immune responses*

Studies of the systemic immune responses of patients with onchocercia-sis (reviewed in detail elsewhere (*17*)), have yielded several major conclusions. First, and most importantly, a cellular immune (lymphocyte) hyporesponsiveness to onchocercal antigen exists in patients with microfiladermia. Second, in contrast to this cellular hyporesponsiveness, specific antibody responses are vigorous in all patients, the highest antibody levels being found in those with localized (sowda-form) onchocercal dermatitis. Third, seemingly uninfected "endemic normal" individuals (who are considered to be immune) generally have higher cellular responses to onchocercal antigen than those with generalized microfiladermia, but definitely have lower specific antibody responses. In contrast to the above, few studies of local immune responses in the eye have been carried out (see section 4.3.2 below) and none at all in the skin.

Whether immune responses to non-parasite antigens or mitogens are altered by onchocercal infection is an important question to which the answer is not entirely clear (*17*). The most convincing studies on the evaluation of antibody responses to non-parasite vaccines have shown no impairment in patients with onchocerciasis. Whether cellular reactivity to non-parasite antigens is also normal remains uncertain, however. *In vitro* assessment of cellular responsiveness to such antigens has often shown a trend towards reduced responsiveness in infected patients, but this has rarely been of statistical significance. On the other hand, vaccination of infected and non-infected individuals to test for delayed-type hyper-sensitivity responses or assessment of skin reactivity to environmental "recall" antigens has clearly shown that infected patients are significantly less responsive. However, a major design problem in such studies is that the organ system used to assess cell-mediated immune responsiveness (i.e. the skin) is itself abnormal (being "infected" with microfilariae). The abnormal findings in skin tests might be relevant to susceptibility to other skin-associated infections, but whether they imply anything more general about systemic cellular immune abnormalities can be determined only after the effects of such vaccinations are assessed systemically rather than cutaneously.

4.3.2 *Pathogenesis*

Perhaps the single most revealing observation relating to the pathogenesis of onchocerciasis is the remarkable ease with which living microfilariae appear to glide through the skin and other tissues unaffected by immune or other inflammatory responses of the host (*17*). Similarly, live adult worms encapsulated in their nodules evoke little inflammatory response. In fact, it is only around dying parasites, whether microfilariae or adult worms, that there appears to be significant inflammation. Which came

first – parasite death or the inflammatory response – can only be a matter of speculation; since the pathological consequences to the host are so much more severe, however, when inflammatory reactions surround the worms, it is likely that, to achieve a harmonious state of parasitism, evolution selected primarily for regulatory mechanisms in the host that inhibit or modulate inflammatory responses to the parasites.

Identification of such modulating or "down-regulating" mechanisms has been a major focus of immunological studies of patients with onchocerciasis, and mechanisms limiting both allergic responsiveness and lymphocyte-mediated inflammation have been well described. Full activation of these mechanisms *in vivo*, however, seems to require the presence of living parasites. Whether this observation implies that the parasites elaborate molecules that inhibit host inflammatory responses directly, or whether the death of the parasite merely exposes antigens that were otherwise hidden from the host is not known. In either case, the presence of dying or dead parasites permits (or perhaps induces) the development of inflammatory reactions, especially around microfilariae, the probable result being some amount of localized "bystander" tissue damage to the host. Though anti-inflammatory host mechanisms must certainly limit the damage induced around each dying parasite, the calculation that, even in lightly infected individuals, microfilariae normally die at the rate of 20000 per day and that, in heavily infected adults, they die at the rate of half a million per day (7) implies that the major driving force directing the host's immune response to onchocercal infection is the need to contain or restrict inflammatory responses. Where containment responses are poorly developed or where they are overwhelmed by dying parasites (eg. after rapid killing by diethyl-carbamazine or certain other microfilaricidal drugs), acute inflammatory reactions develop and tissue damage may ensue.

Thus, if the essential function of the patient's immune system is to inhibit inflammatory responses to dying microfilariae, it is not surprising that, in the few instances where eye tissue has been examined immuno-histologically, a preponderance of CD8+ suppressor T-cells has been seen infiltrating the conjunctivas of patients with chronic ocular onchocerciasis or that there is an abundance of T-cells producing interleukin-4 (a "down-regulating" cytokine) in the same tissues. The fact that auto-antibodies to ocular tissue are also found in such patients is intriguing and might relate to exacerbation of ocular damage in these patients, but it remains unclear whether such antibodies actually initiate chorioretinal damage or are the consequence of such damage, induced in this "bystander" tissue by inflammatory responses to dying microfilariae. Similarly, while animal models of immune-mediated ocular inflammation induced by onchocercal microfilariae or their antigens have been developed – some emphasizing the importance of IgE-mediated inflammation and others T-cell-mediated inflammation – the relevance of these models to the human disease of the eye, whose major immunological features have not been defined, remains uncertain.

The pathological changes in the skin in onchocerciasis are a mixture of acute localized inflammatory reactions and chronic tissue damage (e.g. atrophy, hypopigmentation). The latter changes can readily be understood as the final product of repeated insults to this tissue, which serves over the course of infection as the major battlefield for the confrontation between the host and dying microfilariae. Acute dermal involvement can be viewed as the active stage of the inflammatory response to these microfilariae by the host. It is still uncertain whether individuals with the "hyperresponsive" sowda form of localized dermatitis actually have heightened responsiveness to microfilariae (i.e. "tolerate" them less well and thus attack them more aggressively), or whether the inflammation-containment mechanisms of such individuals are relatively deficient. Furthermore, it is not known why certain people manifest this particular clinical presentation while others with similar intensities of infection have a very different clinical expression of disease, though possible reasons include: (a) differences in the particular character of exposure to infection; (b) an inherited predisposition to certain types of antigen processing and immune responsiveness (*18*); and (c) prenatal sensitization (or acquisition of tolerance) to onchocercal antigens (*19*).

4.4 Clinical and immunological changes following treatment with ivermectin

4.4.1 Ocular changes

During the first 3-4 days following a single dose of ivermectin, the number of microfilariae in the anterior chamber of the eye either remains unchanged or increases temporarily. Corneal microfilariae are not increased in the first few days. A reduction in the number of ocular microfilariae does not occur for at least 2 weeks, and microfilariae may not be eliminated for 3 or more months.

The effect of repeated doses of ivermectin (150 µg/kg of body weight given annually or semi-annually) on ocular onchocercal disease was examined in four community-based studies in Cameroon, Ghana, Nigeria and Sierra Leone. The conclusions reached (*20*) are described below.

Ocular microfilarial loads
There was a significant reduction in ocular microfilarial loads and a 90% decrease in prevalence after 2-4 years. This reduction coincided with a decrease in the prevalence of punctate keratitis.

Lesions of the anterior segment of the eye
There was at least a 50% reduction in the prevalence of early iridocyclitis and a reduction of up to one-third in the prevalence of sclerosing keratitis after 2-4 years. Ivermectin probably reversed advanced sclerosing keratitis by reducing the corneal haze caused by large numbers of invading microfilariae.

Lesions of the posterior segment of the eye

The impact of ivermectin on posterior segment lesions appears to be less marked than that on anterior segment lesions. This may reflect the irreversibility of most posterior segment changes or may indicate that the pathogenic mechanisms are different from those involved in anterior segment disease.

In the Nigerian study, which was specifically concerned with the effect of ivermectin on optic nerve disease, no evidence was found that it precipitated or exacerbated optic neuritis in the period shortly after treatment. Furthermore, after four annual treatments, this study showed a significant reduction of about one-third in the overall incidence of optic atrophy (as compared with patients receiving a placebo), which is suggestive of a substantial reduction in *O. volvulus*-specific lesions.

The results of the studies in Cameroon, Ghana and Sierra Leone did not provide any convincing evidence of an impact of ivermectin on the prevalence of chorioretinitis, which appeared to remain stable.

Visual function

In none of these studies was a significant benefit in terms of visual acuity associated with ivermectin therapy. Visual acuity is, however, a simple, but rather crude measure of central visual function, which often deteriorates late in the course of onchocerciasis. There was, in contrast, a significant reduction in the occurrence of marked loss in paracentral visual fields, especially in those with pre-existing optic nerve disease.

Blindness

In none of these studies was there any evidence of a reduction in the prevalence of blindness and a few new cases due to onchocercal eye disease were observed. It may take a long time for the effect of ivermectin on the incidence of blindness to become apparent.

4.4.2 Skin and lymph node changes

Skin microfilariae are seen to migrate into the *dermis* about 24 hours after ivermectin is given, and elicit little inflammatory reaction (*21*). These findings are in marked contrast with what is seen after administration of diethylcarbamazine, when microfilariae migrate towards the *epidermis* as early as 1-6 hours after treatment and become the foci of microabscesses. These differences probably account for the much less severe cutaneous manifestations seen after treatment with ivermectin as compared with diethylcarbamazine.

Most microfilariae are probably killed in the lymph nodes after treatment with ivermectin, as their density there increases by a factor of about 1000 (*22*). It has been suggested that ivermectin must cause them to migrate from the subepidermal layer into the deeper layers of the dermis, then into fatty and connective tissue and finally into the regional lymph nodes.

Alternatively, however, if the microfilariae are normally resident in the lymphatics (see section 4.1.2), they could either move actively into the lymph nodes when "mobilized" by ivermectin or be swept passively along to the nodes. Almost all microfilariae in the nodes are dead or dying, surrounded by eosinophils in the early stages, and later by histiocytes and giant cells.

This predominantly lymphatic location of microfilarial death may explain the occurrence of the relatively painless transient oedema of the limbs and face that commonly occurs after ivermectin therapy.

There is very little information on the long-term effect of ivermectin on the dermal manifestations of onchocerciasis. Improvement in some skin lesions occurs, the most dramatic of which is in patients with chronic hyperreactive onchocerciasis. The effect on pruritus has been variable.

4.4.3 *Changes in the immune response*

Treatment of onchocerciasis with any microfilaricidal drug acutely disturbs the clinical and immunological balance between host and parasite (*17*). The post-treatment clinical changes have been called the Mazzotti reaction, and though the immunological changes that accompany it have been described in detail following treatment with diethylcarbamazine (*23*), no similar reports are available on the changes following ivermectin treatment.

Long-term immunological changes (evaluated 1–2 years after ivermectin treatment) do occur (*17*), but do not appear to include reversal of the profound lymphocyte hyporesponsiveness (in terms of proliferation and cytokine production) to onchocercal antigen. Rather, they appear limited to significant declines in blood eosinophil numbers, total serum IgG and IgE levels, and specific IgG anti-parasite antibody titres. There is also evidence for some non-parasite-specific changes in circulating blood lymphocyte populations.

4.5 Suggestions for further study

- Standardized methods for the evaluation and description of skin lesions, visual field loss and posterior segment lesions need to be developed, validated and field-tested.
- The relationship between onchocerciasis and certain symptoms/signs attributed to it, such as epilepsy, hyposexual dwarfism, low body weight and musculoskeletal complaints, should be clarified.
- The pathology of onchocerciasis, including the histopathology and immunohistology of the skin, ocular and other lesions, requires study at autopsy.
- The localization of dermal microfilariae in the lymphatics should be confirmed, and their localization in other tissues and the implications for the disease process explored.

- Studies are needed to determine whether the alterations in the immune system induced by onchocercal infection affect normal host responses both to other infections and to standard (non-parasite) vaccines.
- The pathogenesis of eye, skin and other onchocercal lesions should be studied, with special reference to their relation to parasite localization, host immune responses and factors that predispose to acquisition of infection or pathological changes.
- The pathogenesis of posterior segment lesions of the eyes should be specifically investigated, in particular chorioretinitis, which appears in some cases to progress despite the clearance of microfilariae.
- Studies are needed of the long-term clinical and immunological changes that occur after repeated treatment with ivermectin.

5. Geographical distribution, epidemiology and public health importance

5.1 Introduction

Onchocerciasis is still endemic in 34 countries, 26 in WHO's African Region, six in the Region of the Americas, and two in the Eastern Mediterranean Region (Figs 1 & 2). In Africa, in the original core area of the OCP, the disease has declined dramatically in both prevalence and public health importance. The main public health problem remains in the countries of sub-Saharan Africa outside the OCP area, where the disease is both widely prevalent and severe in terms of blindness and skin lesions, and where there is additionally the risk that savanna blackflies will become established in degraded forest habitats. In the Americas, new foci have been found, and the disease may spread still further as infected workers continue to exploit areas of virgin forest. A programme to eliminate onchocerciasis as a disease of public health importance in this region by the end of the century has recently been launched.

5.2 Numbers of cases

The available information for the endemic countries on the number of people infected and some estimates of the numbers of blind people are summarized in Tables 3-5. The quality of the data varies considerably from country to country; in some surveys, for example, visual impairment has not been assessed. Current estimates suggest that about 17.7 million are infected, of whom some 270 000 are blind; in addition, a further 500 000 are severely visually disabled.

These figures are certainly an underestimate and do not fully reflect the importance of the disease and its implications; more accurate data are needed from a number of countries. Furthermore, it is difficult to estimate the visual disability caused by onchocerciasis, since the

Figure 1

Geographical distribution of onchocerciasis in Africa and the Arabian peninsula

Endemic onchocerciasis

Area covered by the OCP

10°E

0°

0°

WHO 94910
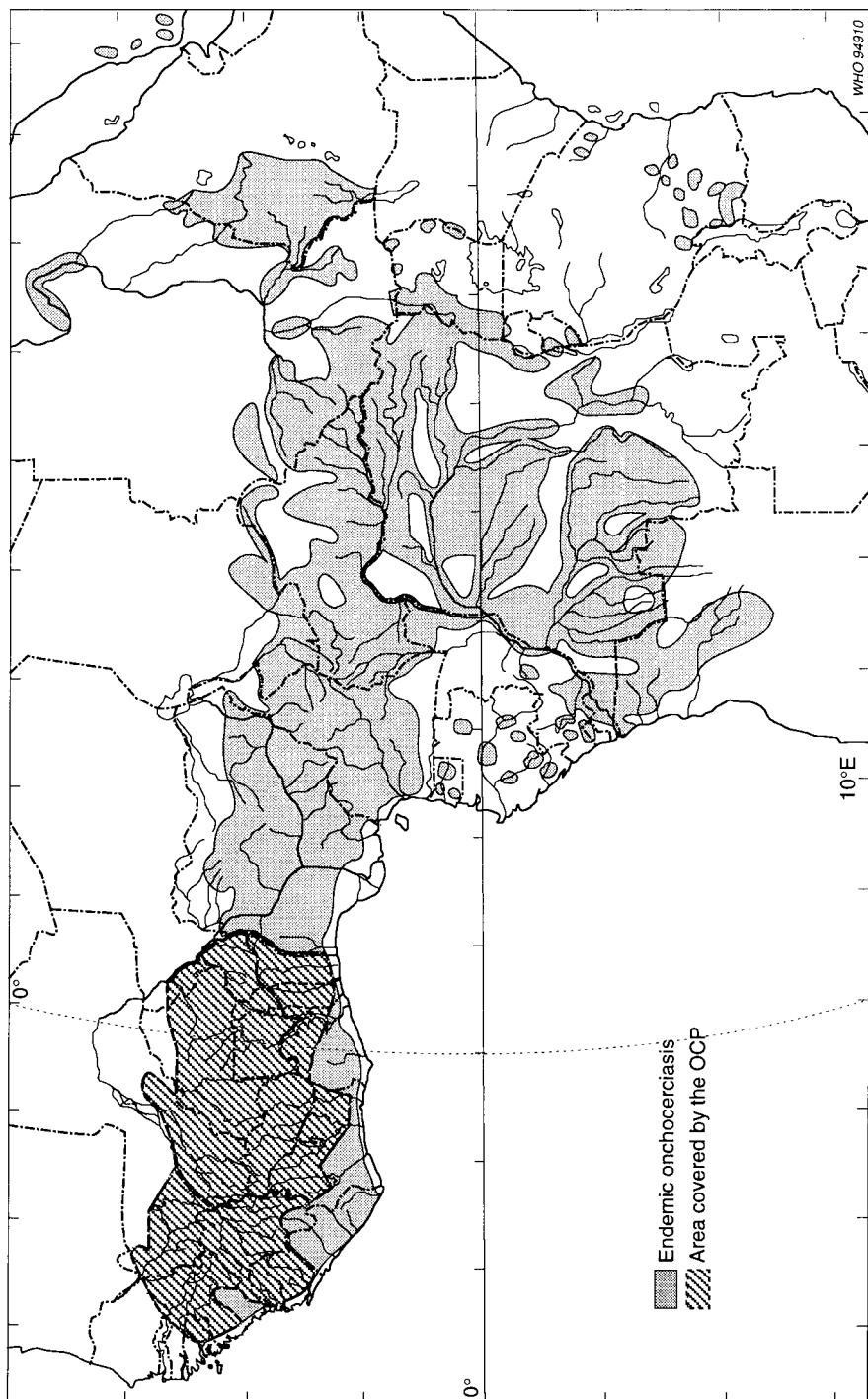
Figure 2

Geographical distribution of endemic onchocerciasis in the Americas

Endemic onchocerciasis

1. Oaxaca focus
2. Northern Chiapas focus
3. Southern Chiapas focus
4. Huehuetenango focus
5. Solola–Suchitepequez focus
6. Escuintla focus
7. Santa Rosa focus
8. North-central focus
9. North-eastern focus
10. Southern focus
11. Amazonas–Roraima focus
12. López de Micay focus
13. Nariño focus
14. Esmeraldas focus

WHO 94911

Table 3

Estimates of the number of people infected and blind in the African and Eastern Mediterranean Regions[a]

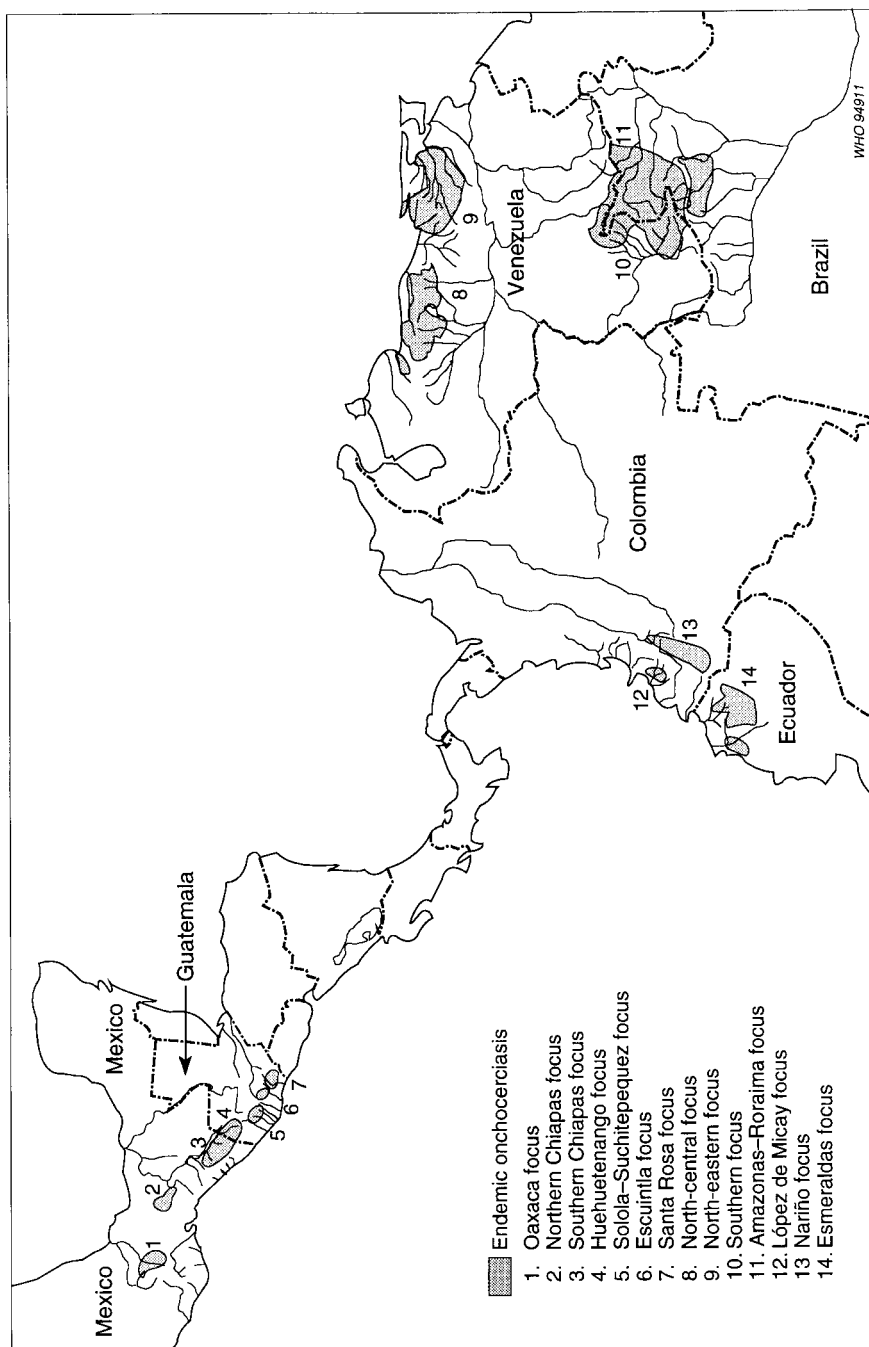| Country	Total population (millions)[b]	Number infected with *O. volvulus*	Number blind as a result of oncho-cerciasis	Source of information
Angola	10.0	100 000	2 000	Most recent information dates from 1962; Ministry of Health estimate[c]
Benin	4.6	162 000	2 800	OCP surveys
Burkina Faso	9.0	500	3 000	OCP surveys
Burundi	5.5	143 000	?[d]	Extensive surveys by Ministry of Health
Cameroon	11.8	1 300 000	26 000	Ministry of Health estimate; mapping in progress
Central African Republic	3.0	390 000	19 000	Ministry of Health[c]
Chad	5.7	870 000	20 000	Ministry of Health estimate; limited surveys
Congo	2.3	50 000	600	Ministry of Health estimates
Côte d'Ivoire	12.0	403 000	4 300	OCP surveys
Equatorial Guinea	0.4	60 000	?[d]	Extensive surveys by Ministry of Health
Ethiopia	49.2	929 000	?[d]	Ministry of Health estimates
Gabon	1.2	60 000	?[d]	Ministry of Health[c]
Ghana	15.0	123 000	7 400	OCP surveys
Guinea	5.8	510 000	9 000	OCP surveys
Guinea-Bissau	1.0	3 300	100	OCP surveys
Liberia	2.6	600 000	2 600	Ministry of Health[c]
Malawi	8.8	150 000	?[d]	Surveys by Ministry of Health
Mali	9.2	196 000	2 700	OCP surveys
Niger	7.7	32	300	OCP surveys
Nigeria	99.0	3 302 000	100 000	National sample survey 1988/1989
Senegal	7.3	65 000	2 800	OCP survey
Sierra Leone	4.2	701 000	8 300	OCP survey
Sudan	25.8	620 000	10 000	Ministry of Health estimate[c] multiplied by population growth rate
Togo	3.5	334 000	8 800	OCP surveys

Table 3 *(continued)*
Estimates of the number of people infected and blind in the African and Eastern Mediterranean Regions[a]

Country	Total population (millions)[b]	Number infected with *O. volvulus*	Number blind as a result of onchocerciasis	Source of information
Uganda	18.8	1 200 000	?[d]	Extensive surveys by Ministry of Health
United Republic of Tanzania	27.3	650 000	?[d]	Surveys just started
Yemen	12.5	30 000	0	Ministry of Health, 1991
Zaire	35.6	4 565 000	37 500	Ministry of Health estimate[c] multiplied by population growth rate
Total	398.8	17 516 832	267 200	

[a] 1985–1993, except for Angola (1962).
[b] Source: *World development report 1993: investing in health.* New York, Oxford University Press (for the World Bank), 1993.
[c] See reference *1*.
[d] Onchocerciasis not considered to cause significant blindness in these countries.

Table 4
Estimates of the number of people infected and blind in the Americas[a]

Country	Total population (millions)[b]	Number infected with *O. volvulus*	Number blind as a result of onchocerciasis	Source of information
Brazil	150.4	707[c]	NA	Ministry of Health, 1993
Colombia	33.0	70[c]	NA	Ministry of Health, 1993
Ecuador	10.6	5 930	36	Ministry of Health, 1992
Guatemala	9.2	62 961	600	Ministry of Health, 1993
Mexico	85.9	26 182	105	Ministry of Health, 1993
Venezuela	19.7			
southern		2 884[c]	9	Ministry of Health, 1993
northern		41 721	NA	Ministry of Health, 1993
Total	308.8	140 455	750	

NA, not available.
[a] Recorded cases according to 1992/1993 surveys, except for northern Venezuela, for which cumulative figures are given for the period 1959–1986.
[b] Source: *World development report 1993: investing in health.* New York, Oxford University Press (for the World Bank), 1993.
[c] Certain to be underestimates of true prevalence because figures are based on surveys of only 1–23% of the endemic populations and have not been extrapolated to the total populations of the endemic areas.

Table 5
Global estimates of the population at risk, infected and blind

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.

constriction of the visual field as a result of optic nerve involvement is not usually assessed in routine survey procedures.

It should be noted that the present estimates are close to those given in the third report of the WHO Expert Committee on Onchocerciasis (1). New data on onchocerciasis for some African countries are available which indicate that the prevalence and severity of the disease in those countries are greater than previously believed; accordingly, the global estimates remain almost unchanged despite the success of the OCP in West African countries.

Overall, the following trends can be observed:
- a significant reduction in the number of infected and blind persons in the original OCP area;
- markedly increased estimates of the numbers of infected people in Equatorial Guinea, Uganda, the United Republic of Tanzania and Zaire, partially supported by population-based assessment;
- an apparent reduction in the numbers of infected people in Nigeria, following a reassessment based on a sample survey.

5.3 Geographical distribution and trends

5.3.1 *The overall situation in Africa*

The prevalence figures given in the third report of the WHO Expert Committee on Onchocerciasis (1) indicated that, of the global total of persons infected and of the numbers blind as a result of onchocerciasis, more than 99% lived in the tropical belt of Africa.

Two factors have influenced the intensity and prevalence of onchocerciasis over the past 6–8 years, the first being the maintenance and expansion of the vector-control activities of the OCP and the second the advent of the Mectizan Donation Program and the Mectizan Humanitarian Program of Merck and Co., Inc., which have led to the widespread distribution of ivermectin for the treatment of onchocerciasis in the majority of countries where the disease is endemic.

5.3.2 *The OCP area in West Africa*

Vector control has achieved the virtual interruption of transmission in 90% of the original OCP area. As a result, the incidence of infection in children has been reduced by 99% in this area (see Table 6). After a few years of control, the intensity of infection as measured by the community microfilarial load started to decline in a linear fashion, reaching very low levels after 10 years. This was followed by the predicted accelerated fall in the prevalence of infection (Fig. 3). After 14 years of control, the prevalence of infection was close to zero in most of the original Programme area (see Figs 4 & 5). It is estimated that the number of infected persons in this area fell from more than 1 million in 1975 to less than 10 000 in 1992 (*24*).

These reductions in the incidence and prevalence of infection in the central OCP area have been accompanied by dramatic improvements in ocular onchocerciasis. After 13 years of vector control, microfilariae were no longer seen in the eye, and the incidence of ocular lesions and onchocercal blindness had ceased to rise.

In the remaining part of the original Programme area, transmission has not been fully interrupted because of problems such as reinvasion by infective blackflies or the development of insecticide resistance. Nevertheless, the incidence of infection in children has been reduced by 80–90% and the recent introduction of ivermectin has further improved the epidemiological situation even in these problem areas.

In the extension areas, control began in 1986 and has had limited epidemiological impact to date, as compared with the original OCP area. However, there are indications, in areas where both ivermectin and vector control are being used, of a synergistic effect on the community microfilarial load or more rapid reductions in ocular morbidity. Vector control in the western extension area has prevented reinvasion of the core area.

5.3.3 *African countries not participating in the OCP*

Nigeria, since it has the largest population of any sub-Saharan African country, also has the largest number of infected persons, but it is a measure of the lack of accuracy of country-wide endemicity figures that

Table 6

Results of skin-snip examinations in children born in the OCP area since the start of control

| Zone	Number of villages	Number of villages with infected children	Number of children examined	Number of infected children		Ratio of observed to expected
				Observed[a]	Expected[b]	
Central OCP area	128	12	12 891	29	2 303.7	0.013
Reinvaded west	22	9	1 265	38	340.6	0.112
Reinvaded east	13	8	954	33	154.3	0.214
Intermediate zone[c]	18	6	1 244	28	206.0	0.136
Total	181	35	16 354	128	3 004.6	0.043

[a] For each village, observations are recorded from surveys conducted between 1987 and 1991 after 12–14 years of vector control.
[b] Number of children expected to be infected if there had been no control and the conditions of infection had remained unchanged from the time of the initial (pre-control) survey carried out between 1975 and 1979.
[c] Savanna–forest interface (vegetation).

Figure 3
Predicted and observed trends in the prevalence of microfiladermia during vector control in the original OCP area[a]
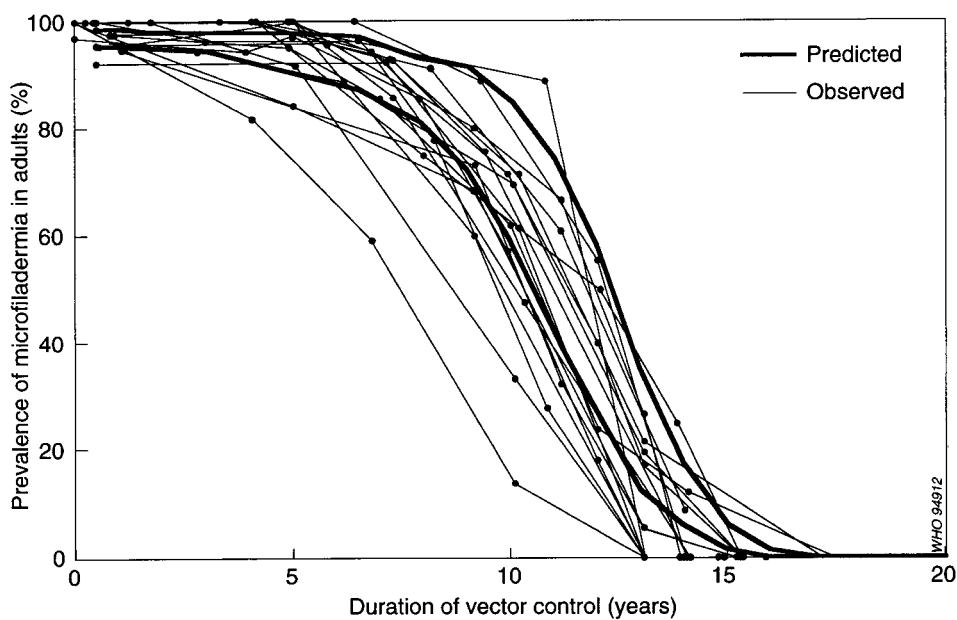
the estimate of nearly 7 million infected persons made by the WHO Expert Committee on Onchocerciasis in its third report (*1*) was reduced to about 3 million in the national sample survey conducted in Nigeria in 1988–1989.

The disease varies in endemicity in Nigeria but is present in all states and the Federal Capital Territory, with the exception of Lagos, Rivers and Akwa-Ibom states, where infections are sporadic. Large-scale ivermectin distribution is being organized by UNICEF and NGOs in cooperation with the state governments.

In central Africa, the serious blinding form of the disease extends from the eastern Nigerian states of Taraba, Adamawa and Borno across northern Cameroon into the six south-western prefectures of Chad, the three north-western prefectures of the Central African Republic, and south-eastern Sudan.

Figure 4
Pre-control prevalence of skin microfilariae in villages in the original OCP area
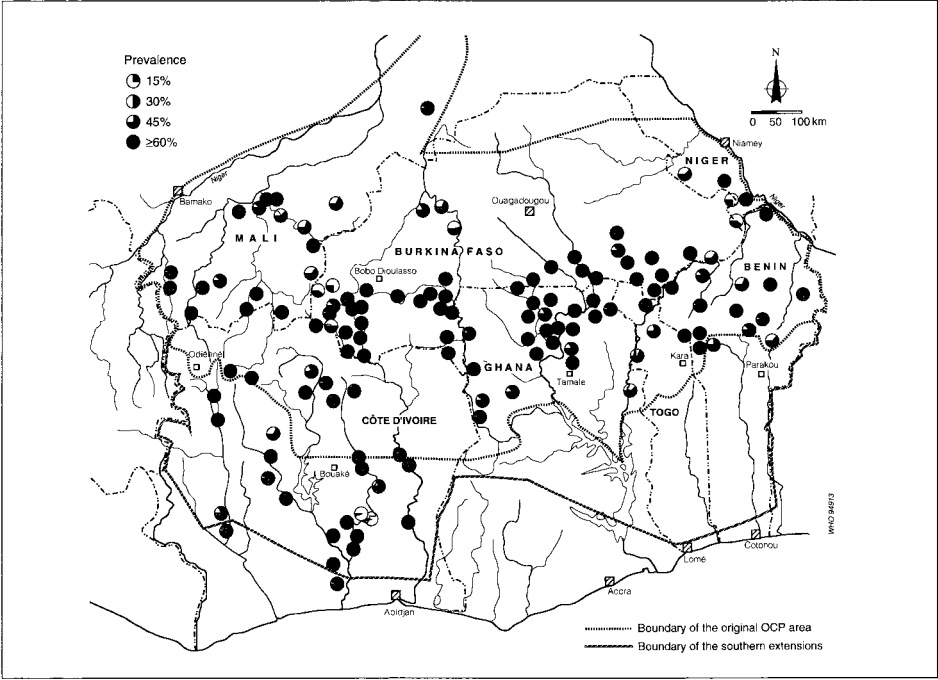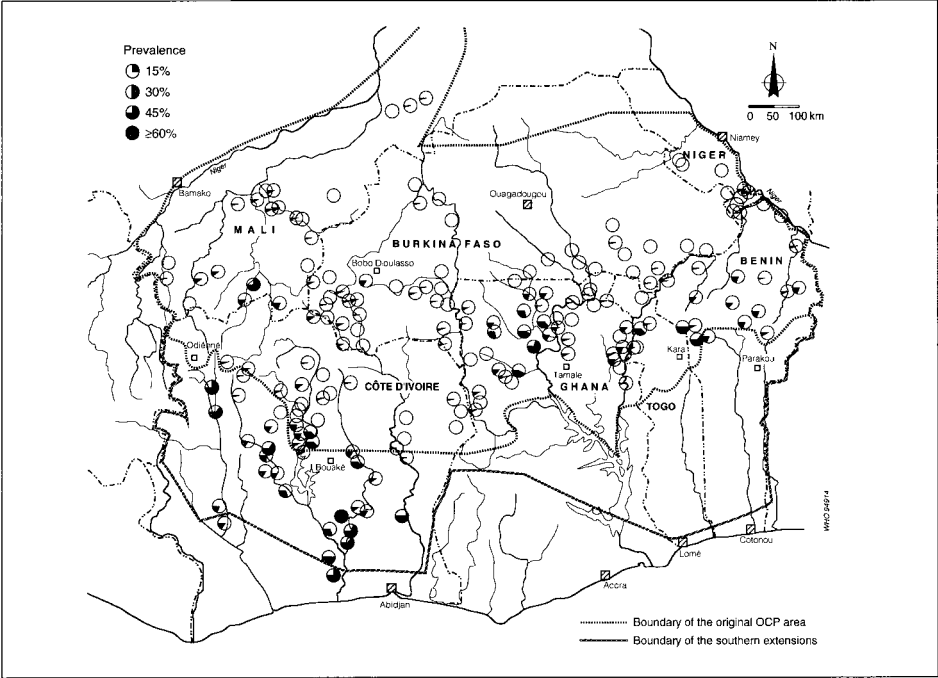

Figure 5
Prevalence of skin microfilariae in villages in the original OCP area: 1992–1993

In Uganda, deforestation following subsistence agricultural development and timber exploitation has reduced the cover available to the *S. neavei* vector, thereby reducing the transmission of *O. volvulus*; however, if *S. damnosum* colonizes these foci, transmission will return.

In Angola, Liberia and Zaire, the current situation is uncertain.

In Ethiopia, there appears to be almost no blindness due to onchocerciasis, but there is substantial disfiguring skin disease, especially in coffee and tea plantations along the Baro River in Ilubabor as well as in areas of Kaffa and Gojam. Control programmes are so far being developed on a regional basis.

In Malawi, the principal disease focus is in Thyolo in the south. The disease is currently being controlled by ivermectin distribution.

In Sudan, known endemic zones extend over Bahr al Ghazal, the western part of Equatoria, the Radom area of southern Darfur, the southern and eastern parts of Upper Nile, the Khor Yabus area of Blue Nile, parts of the Atbara and Setit rivers in Kassala and the Abu Hamed focus in Nile Province. The real extent of onchocerciasis infection and disease is at present not well known and, since the last report, demographic changes may have considerably affected the situation.

5.3.4 *The Arabian peninsula*

Onchocerciasis is found in Yemen. Studies have revealed its existence along the wadis, between the Wadi Ghayl to the south and the Wadi Surdud to the north. However, the distribution may extend further south into the Wadi Aggan in Karish District and north around Al Mawit on the upper reaches of Wadi Mawr.

Although there are reports of onchocerciasis in Saudi Arabia, transmission in that country has not been confirmed. It is probable that cases in Saudi Arabia have been imported. Furthermore, no vector of onchocerciasis has been identified; hence it is unlikely that there is any significant focus of the disease in the country.

5.3.5 *The Americas*

In Mexico, there are three endemic foci in mountainous areas in the south, namely one in the state of Oaxaca and two in Chiapas. The population at risk is 261 660, and there are over 25 000 reported cases.

In Guatemala, active foci are concentrated on the western slopes of the volcanic range. There is also a focus in the north-west near to the border with Mexico. However, migrant workers who cross the Mexico-Guatemala border may spread the disease to other areas. Almost 450 000 people live in the foci in Guatemala, the largest and most intensively infected being the central focus comprising the departments of Chimaltenango, Solola and Suchitepequez, where 30% of communities are hyperendemic.

Onchocerciasis was first recognized in Venezuela in 1948, in Colombia in 1965, in Brazil in 1967, and in Ecuador in 1982. Since 1985, there has been no convincing evidence of any expansion of the existing foci. However, studies in Amazonas State in Venezuela have indicated that the geographical distribution of competent vectors is considerably larger than that of the disease, so that, if infected individuals migrate, new foci could be created.

In Brazil, onchocercal foci are located in the northern part of Amazonas State and in the western part of Roraima State, which borders Venezuela. It is estimated that 200 communities scattered in the onchocerciasis area, including Auaris, Surucucu, Tootobi, Marari, Mucajai, Catrimani, Xidea, Paapiu and Homoxi, are infected. The disease is confined to isolated, itinerant Amerindian ethnic groups, namely the Yanomami and Yek'wana, of whom approximately 10 000 are at risk of infection. However, immigration by miners may put other areas of Brazil at risk. Since 1990, more than 50 000 miners have been present in the Yanomami onchocerciasis area for 1–9 months and have then resettled in other areas of Brazil, including regions bordering Colombia and Guiana, where competent vectors are present.

In Colombia, the main known focus is the López de Micay area on the Pacific coast, where 16 300 individuals are at risk of infection in 155 communities. The total number of cases identified between 1965 and 1991 was only 70, but the communities of Tumaco, Barbacoas and Ricaurte in Nariño department bordering on Ecuador are also suspected to be an onchocerciasis transmission zone.

In Ecuador, the onchocerciasis focus is located in the north-western coastal province of Esmeraldas. The major focus involves blacks and Chachi Amerindians living in the Santiago River basin. In 1993, there were 192 known infected communities and 20 089 individuals at risk of infection.

In Venezuela, three main foci of the disease have been detected: one in the north-central region, which includes Aragua, Carabobo, Cojedes, Falcón, Guárico, Miranda and Yaracuy states; another in the north-east region, which includes Anzoátegui, Monagas and Sucre states; and a third in the southern region, which includes Amazonas and Bolívar states. In the north-east region 25 461 inhabitants were found to be infected between 1959 and 1986, and in the north-central region 16 260 infected individuals were identified between 1959 and 1970.

The southern focus is in the states of Bolívar and Amazonas, involving three Amerindian groups, the Yanomami, the Sanema and the Yek'wana. Approximately 82 000 individuals are at risk, while 17 574 are living in the hyperendemic areas of the focus, which extends from the Caura River to the basins of the Ocamo and Mavaca rivers to the east and to the Orinoco and Ventuari rivers to the west. A positive correlation has been found between the altitude of a given locality and the prevalence of the disease.

Studies over the last decade have indicated that, while the geographical borders of the southern focus have been extended, the epidemiological characteristics have remained stable. The focus is characterized by a high prevalence of infection among certain Amerindian populations; 60% of the communities are hyperendemic, with a community microfilarial load of up to 36 microfilariae per skin snip.

5.4 Epidemiology

The epidemiology of onchocerciasis is that of a vector-borne disease of which human beings are the only vertebrate host. Infection with *O. volvulus*, like other filarial infections, is also characterized by coincidence between the degree of human infection and the intensity of exposure to infected vectors.

However, the epidemiology of onchocerciasis is not uniform throughout its distribution because different disease patterns are associated with different variants or strains of the parasite, with differences in the vector competence and feeding characteristics of local blackfly populations, with the abundance of the vector, and with differences in the human host responses to the parasite. These factors, together with those related to environmental, geographical, social and demographic influences, increase the complexity of the epidemiology of the disease in the different areas of its distribution.

An analysis of the epidemiology of onchocerciasis, including risk-factor analysis, may provide vital information needed in deciding which control measures should be adopted. The recent identification of a relationship between geographical forms of the parasite, which are genetically distinct, and patterns of blinding and non-blinding ocular disease is a major finding. The development and use of mathematical models over recent years in the OCP have enabled predictions to be made about the impact of control measures and thus facilitated strategic planning (see section 9.4).

Factors influencing the epidemiology of onchocerciasis can be divided into those relating to the host, the parasite and the vector, but behavioural and community factors also need to be taken into account.

With respect to host factors, there are no known sex differences in acquisition of infection, and age merely determines cumulative exposure to infection. Variations in the immune response to infection are apparent in individuals with sowda lesions, but more detailed studies on different aspects of the status of the human immune system under different pathological conditions are needed. Parasite factors such as genotype may explain the pattern of disease in certain foci. For example, two different types of *O. volvulus* (forest and savanna) exist in Africa; this is of importance in setting priorities for control measures.

Vector factors are important inasmuch as they affect the transmission of the parasite. Transmission rates may vary both seasonally and by

geographical location. Vector abundance depends on hydrological conditions, which determine the number and productivity of blackfly larval habitats. Vector density is also determined by dispersal habits. Ecological factors, such as prevailing winds and humidity, also contribute to passive dispersal and migration; some species of African savanna flies travel up to 400 km from their breeding sites. There are also major differences between vector species in their feeding habits, e.g. in the degree of preference for human as opposed to animal hosts. Furthermore, the intensity of microfilarial infection in the skin may play a critical role in determining the infection of the vector, since each species has an infection threshold.

Behavioural and community factors are most important in the planning, implementation and evaluation of control measures. In savanna areas, the intensity of exposure to transmission is determined by the distance between a community and a fly breeding site and by the presence or absence of other human settlements in the intervening area; these considerations have led to the characterization of villages as first-, second- and third-line. Furthermore, individuals who frequently visit the breeding site(s) or whose work requires them to spend long periods on the river bank (e.g. fishermen) tend to have very severe manifestations of onchocerciasis.

The density of the human population in relation to the vector population emerging from local breeding sites is also an important determinant of intensity of infection, as is the presence of cattle near rivers, since it reduces the contact of the human population with zoophilic vectors of *O. volvulus*. In addition, the regular inoculation of the human population with bovine/animal *Onchocerca* L_3 larvae may provide an immunological stimulus to the host and thus help prevent infection with *O. volvulus*.

5.5 Public health importance

The public health importance of onchocerciasis has been highlighted by the significant economic and social benefits as well as the reduction in disease-associated morbidity that have followed the success of the OCP in controlling the disease in 11 West African countries. Until 1987, other countries afflicted by onchocerciasis could not benefit from the type of economic development that had taken place over the previous decade in the OCP area as a result of the interruption of transmission by vector control. However, with the advent of ivermectin in 1987 and the Mectizan Donation Program which provide an opportunity to suppress and control the disease by chemotherapy, onchocerciasis has been recognized as a problem for which there is now a relatively easy and economical solution. Many governments are therefore now undertaking ivermectin-based control campaigns and, in both Africa and the Americas, are even using them to spearhead the development of primary health care programmes.

The serious eye lesions, which occur when the intensity of infection is high and where the strain of the parasite is pathogenic for the eye, and the prominent skin lesions are responsible for the major public health impact of the disease. The consequences of onchocerciasis have repercussions beyond the individual and directly affect the family, community and country. In the usually remote, rural areas of the savanna zones of Africa, the effects of river blindness have led to the decline and desertion of villages, where it is without doubt the most important disease afflicting the communities. Blindness rates of 5–10% reduce the viability of communities; when the majority of men over 40 years of age are blind, villages rapidly cease to be economically viable. Populations move to healthier local environments, away from the rivers where the vectors breed but where the soil is usually not so fertile. Furthermore, since blindness leads to a reduction of some 10 years in life expectancy, onchocerciasis is a disease that not only disables but is indirectly responsible for considerable premature mortality. Similar effects are seen in Amazonian communities, where eyesight is a fundamental requisite for hunting and tribal migration, and thus for nutrition and survival.

In persons with prolonged intense infections, the skin lesions and itching are responsible for much chronic misery and disfigurement, and can lead to a degree of social isolation, with detrimental psychological effects (25).

There is also increasing evidence that, in Africa, as previously mentioned, onchocerciasis is associated with an increased incidence of both epilepsy and hyposexual dwarfism. Although no causative association has been clearly demonstrated, this possibility should no longer be ignored.

5.6 Suggestions for further study

- The continued use of mathematical modelling in different epidemiological settings is required to guide the choice and predict the outcome of different interventions for the control of onchocerciasis.
- In countries outside the OCP area, studies are needed on the epidemiological characteristics of onchocerciasis, and on its prevalence, severity and distribution.
- The recently introduced methods of rapid epidemiological assessment (see section 11.4) should be evaluated in different areas (including the Americas) and, if possible, in parallel with standard methods, so that their value can be compared with the use of parasitological and ophthalmological criteria.
- Microfilarial infection thresholds should be determined for major vectors in areas where ivermectin is being used for the control of transmission.
- Studies are required on the zooprophylactic effect of regular inoculation of the human population with *O. ochengi* L_3 larvae, including an assessment of its impact on the epidemiology of onchocerciasis and the development of disease due to *O. volvulus*.

6. Social and economic impact

6.1 Socioeconomic consequences

The socioeconomic consequences of onchocerciasis are most marked in the hyperendemic belt that extends across sub-Saharan Africa, excluding the West African countries in the original OCP area, where the burden of onchocercal blindness has been greatly reduced as a result of control.

Within Africa, blindness rates in hyperendemic communities not under control may rise to 15%, and up to 40% of adults may show severe ocular impairment. When there are high rates of visual impairment, communities become unstable, their agricultural capacity declines, and eventually the villages are abandoned.

In Guinea, for example, the impact of onchocerciasis-related blindness on the household is severe, most often resulting in the family's inability to support itself. The disruption of family life is directly related to stress within the household, contributing to its destitution. The extra burdens placed on other members of the family, once the main breadwinner is blind and can no longer continue with normal activities, have adverse effects on their physical, psychological and emotional health. The older children often choose to migrate, fearful of becoming blind themselves.

In the hypo- and mesoendemic areas in Africa and in the Arabian peninsula, where blinding onchocerciasis is less prevalent, the socio-economic consequences of onchocerciasis are less striking and less well studied.

In the Americas, the socioeconomic consequences of onchocerciasis require further study particularly with regard to the impact of blindness and skin disease on productivity.

6.2 Community knowledge, beliefs and attitudes

Knowledge of onchocerciasis, including its name, the method of trans-mission, and the complex of signs and symptoms of the disease, is poor in endemic communities in Africa and the Americas. Nevertheless, the studies conducted to date indicate that populations are aware of, and concerned about, the signs and symptoms of the disease, especially blindness and the skin lesions, as well as the stigmatization associated with these conditions and the psychosocial consequences. The conse-quences of the skin lesions have been less well studied because research has focused mainly on the OCP area and on blindness as a public health problem. However, in Nigeria, there have been reports of social stigmatization and rejection of those with skin disease because of the belief that it is caused by dirtiness (26).

The psychological repercussions of social marginalization in some Amerindian cultures are not well known but cause serious difficulties for

the affected individuals in their interactions with other members of the community. In the southern Venezuelan foci, cultural interpretations of the origin of some of the disease signs and symptoms, as well as the mechanisms of onchocerciasis transmission, are sometimes a source of conflict between communities. These cultural factors also determine the social acceptance of the changes in physical appearance associated with the disease. Individuals with severe skin manifestations (e.g. hanging groin) are socially isolated (27).

In a survey conducted in several communities in the central onchocerciasis zone in Guatemala, the term "filaria" was recognized and routinely associated with the presence of nodules and eye disease (28). However, while half of those surveyed associated infection with insect bites and a third knew that nodules contained worms, the overlap between the two groups was less than 40%. The findings indicated that overall community knowledge of onchocerciasis was fragmentary and based primarily on awareness of nodules. Thus, in a chemotherapy campaign in which a microfilaricidal drug such as ivermectin is used, the drug's effects must be clearly explained since its direct impact on nodules (the recognized marker of infection for many) is minimal.

6.3 Socioeconomic benefits of control in the OCP area

Before 1975, in the area of West Africa now covered by the OCP, desertion of villages and fertile valleys was a common feature. After 19 years of control operations, significant changes have occurred in terms of both resettlement and agricultural development, although these may themselves create problems because of their environmental consequences.

In the countries covered by the OCP, an estimated 30 million people are now protected from onchocerciasis. About 9 million children born within the original Programme area since 1974 have not been infected and are not at risk of onchocercal blindness, 1.25 million people are rid of their onchocercal infections, and 100 000 people have been prevented from going blind; it is estimated that, when OCP operations end in 2000, the corresponding figures will be 15 million, 2 million and 150 000, respectively.

In terms of agricultural development, 15 million hectares of riverine tillable land, suitable for cultivation to feed up to 10 million people, have so far been made available for resettlement in the Programme area. By 2000, this area will be increased to 25 million hectares, capable of meeting the food requirements of 17 million people.

The impact of OCP operations on the economy of Burkina Faso is exemplified by the development of an area of 2500 km^2 that has been settled by a population of 400 000, with the support of the Volta River Valley Authority, the agency responsible for the development of areas

where onchocerciasis has been controlled. Under the auspices of the Authority nearly 100 villages have been constructed and about 230 existing traditional villages have been economically strengthened. Some 8000 new farms have been created and more than 5600 traditional holdings have benefited from improvements in agricultural practices. In addition, more than 1000 km of roads have been constructed and almost 700 wells and bore-holes have been drilled, allowing for the supply of 400 litres of water per family per day. Infrastructure improvement resulted in the construction of 41 schools, 22 outpatient clinics and 11 village stores, at a total cost of US$ 30 million.

In output terms, overall production within the area in 1990 reached an annual level of 7000 tonnes of cotton, 110 000 tonnes of cereals, 1000 tonnes of rice, 650 tonnes of French beans, 300 tonnes of potatoes, 800 tonnes of onions, 500 tonnes of other vegetables and 2163 tonnes of meat. The total value of the agricultural products is about US$ 37 million or US$ 2700 per farm per year.

In the course of a pilot project on environmental impact assessment in the OCP area, aerial reconnaissance and photographic flights were made in the upper Léraba Valley (in Burkina Faso and Côte d'Ivoire), and large-scale maps drawn on the basis of these flights were compared with maps of the same areas prepared on the ground in 1972 and 1983. From such comparisons, it appears that in the areas in question, where the Programme has operated since the early 1970s, there has been a considerable extension of homestead settlements and smallholder farms and a significant extension of the zones containing established villages with adjoining areas of intensive cultivation, in particular of cotton.

6.4 Cost-benefit analysis of OCP operations

As a result of the long-term support of international donors together with exemplary collaboration between the sponsoring bodies (The World Bank, UNDP, WHO and FAO) and the participating countries,[1] the OCP is recognized as an excellent and successful development programme. It benefits rural populations by improving their health and environment, while enabling previously endemic zones to be developed for agriculture.

Recently, a cost-benefit analysis of the Programme was undertaken in which the costs of investing in it were compared with the economic benefits likely to result from it (29). The costs included the actual expenditures since 1974, plus projected expenditures until the planned end of the programme in 2000. Only the costs of the activities directly

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[1] Benin, Burkina Faso, Côte d'Ivoire, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Senegal, Sierra Leone and Togo.

related to disease control were included. No attempt was made to determine the value of the time spent by people in the community in participating in OCP activities, such as epidemiological mapping.

Two types of economic benefits were measured, the first being the increase in agricultural output in endemic areas resulting from an effective increase in the size of the labour force, and the second the net increase in agricultural production made possible because people have been able to cultivate land in formerly endemic areas where no agricultural activities were previously possible.

The available labour force was assumed to have increased because fewer people have become blind since the commencement of the Programme and those whose sight has thus been preserved will spend more years working in agriculture. To obtain a monetary value for this benefit, the estimated number of cases of blindness prevented by the OCP was multiplied by the number of years of productive life added per case of blindness prevented to give the additional years of labour made available. This figure was then multiplied by the value of the additional output expected to be produced by each extra unit of labour. This calculation may underestimate the real increase in labour supply and its consequent effect on output because no attempt was made to measure the impact of such factors as the reduction in other onchocerciasis-related symptoms and in the production time lost by family members in providing care for the blind.

The value of the increased production resulting from the settlement of new land was calculated as the area of land that would be brought under production, multiplied by the value of the output produced by each extra unit of land. Account was taken of the fact that the people working this land would have produced some output elsewhere before moving to the new land, and the value of that production was therefore subtracted from the total output in the new areas. The resulting figure is the net increase in production as a result of the availability of new land.

Costs were projected up to the end of the OCP in 2000, while it was assumed that benefits would accrue until 2010 – probably a conservative assumption. To allow values to be summed over the different years, and to take account of considerable changes in cost and price structures, both costs and benefits were expressed in constant (inflation-free) prices, in terms of 1987 US dollars.

The results were presented in two ways. The first required the calculation of the sum of the yearly costs and benefits. This in turn required recognition of the fact that US$ 1 received today is more valuable than US$ 1 received at some time in the future and, conversely that people would prefer to pay a cost of US$ 1 at some time in the future than to pay it today. To reflect the fact that the value of US$ 1 depends on when it is received or paid, "discounting" was used; the resulting "net present value" calculation reflects the extent to which the economic benefits of the

programme exceed the costs. At realistic discount rates (3% and 5%),[1] the benefits from the increase in the labour supply alone were estimated to exceed the costs of the Programme by between US$ 55 million and US$ 210 million, while the benefits of the increased availability of land were many times greater. Taken together, the net benefits could be as large as US$ 3887 million and, even on the most pessimistic assumptions that the benefits do not extend beyond 2000, that only 70% of the available new land is actually cultivated, and that the discount rate is 15%, they exceed US$ 5 million. This suggests that the investment has more than paid its way and that the benefits more than justify the costs even in purely economic terms (29).

This conclusion is supported when the results are presented in another way. On best-guess assumptions, the total benefits were calculated to represent a rate of return on the investment in the OCP of between 18% and 21%, after controlling for inflation. This internal rate of return is extremely high when compared with the returns available from alternative investments, again suggesting that the Programme has been a good investment even in purely economic terms.

6.5 Socioeconomic consequences in the Americas

In the Americas to date, only limited studies have been undertaken on the socioeconomic consequences of onchocerciasis.

Although certain social consequences have been identified in some of the most severely affected countries, mainly related to work at the less developed coffee plantations, these observations are limited and not well documented. Attention has been drawn to this problem, and some studies designed to determine the social and economic impact of onchocerciasis on migrant workers are being promoted.

A major consequence of the exploitation of forested areas in the Amazon basin through mining activities will be the infection of migrant workers with *O. volvulus*. Over the next decade, the movement of these workers into previously non-endemic areas of South America, where potential vectors exist, as mentioned in section 5.3.5, may have severe long-term social and economic consequences for several countries in the region.

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[1] The discount rate permits a comparison of values over different periods of time. The 3% and 5% discount rates are "social" discount rates that take into account additional benefits that may accrue to society as a whole from undertaking a given project. In the case of health projects, the social discount rate is typically lower than the market discount rate in order to reflect additional economy-wide gains that frequently occur, such as benefits accruing to future generations as a result of disease control. For the "productive" sectors, such as agriculture, industry, energy and transport, the World Bank typically uses a 10% discount rate in present-value analyses.

Suggestions for further study

- Socioeconomic studies, in particular cost–benefit studies, should be carried out in areas where onchocerciasis control is based exclusively on ivermectin distribution. The results should be compared with findings in OCP areas where reliance has been placed primarily on vector control.
- Research on the sociological importance of onchocerciasis, and especially of skin lesions, should be intensified in all endemic areas, including the forest zones of Africa and America.
- Further socioeconomic studies should be conducted in zones that have been freed from onchocerciasis in order to assess the extent and impact of new settlements and changes in land use.

7. Diagnosis and surveillance

7.1 Clinical diagnosis

Clinical diagnosis is not difficult in endemic areas, especially when patients present with clinical manifestations such as subcutaneous nodules, hanging groin, "leopard skin" and skin atrophy. Pruritus in the absence of skin lesions may be onchocercal in origin.

Onchocercal skin lesions are seldom pathognomonic. Conditions that need to be excluded are streptocerciasis, scabies, insect bites, miliaria rubra (prickly heat), contact dermatitis, hypersensitivity reactions, post-traumatic or inflammatory depigmentation, tuberculoid leprosy, dermatomycoses and treponematoses. Nodules need to be differentiated from lymph nodes, lipomas, fibromas, ganglions, other parasitic cysts, and juxta-articular nodes in yaws.

In non-resident visitors to an endemic area, asymmetrical pruritic lesions with or without limb swelling or lymphadenitis are suggestive of onchocerciasis. The diagnosis may be missed because of the long interval of 1–3 years that may elapse between exposure and the onset of symptoms.

Musculoskeletal pain, sometimes producing significant morbidity in both visitors to and residents in endemic areas, has been attributed to onchocerciasis, but this relationship needs to be further evaluated.

The diagnosis of ocular onchocerciasis requires ophthalmological evaluation to determine visual function, the presence of intraocular microfilariae and pathological changes attributable to the infection. Visual function can be assessed by the measurement of visual acuity and pupillary reactions and by visual field examination.

Slit-lamp examination of the eye under magnification ($\times 16$) after patients have sat with their heads down for at least 2 minutes allows microfilariae in the anterior chamber and dead corneal microfilariae to be visualized and counted. With a higher magnification ($\times 25$) and retro-illumination, live corneal microfilariae can also be counted. Punctate

keratitis, limbitis, sclerosing keratitis and anterior uveitis should also be assessed by slit-lamp examination and the intraocular pressure measured with an applanation tonometer. For posterior segment lesions, the patient's pupils should be fully dilated (1% tropicamide and 10% phenylephrine are the drugs generally used for this purpose), after which direct and indirect ophthalmoscopy should be performed and any optic disc or chorioretinal changes recorded. Fundus changes can also be documented by fundus photography, which is useful for future comparisons, while fluorescein angiography can be used in selected cases to detect early lesions.

Although ocular examinations are time-consuming and require specialized techniques and an ophthalmologist, demonstration of microfilariae in the eye enables a definite diagnosis of onchocerciasis to be made.

Onchocercal corneal lesions need to be differentiated from viral keratitis, exposure keratitis, nutritional keratopathy and phthisis bulbi from other causes.

Other causes of optic nerve disease that need to be excluded in an endemic community are primary glaucoma, nutritional optic atrophy, syphilis and other ocular diseases causing optic atrophy.

Onchocercal chorioretinitis must be differentiated from choroiditis, especially of toxoplasmic, syphilitic and tubercular origin.

7.2 The Mazzotti test

This test should be used only when onchocerciasis is suspected but the parasite cannot be demonstrated in the skin or eye; it is probably the only indication for the use of diethylcarbamazine in onchocerciasis. The patient is given 50 mg of diethylcarbamazine by mouth and is observed for the effects of microfilarial death, such as itching, rash and lymphadenitis, which may occur after 1–24 hours. In properly selected patients, the itching is short-lived and the rash is limited and often asymmetrical. *Mansonella streptocerca* infection can give false-positive results with diethylcarbamazine. Ivermectin is not generally suitable for use in the Mazzotti test because of a high incidence of false-negative reactions.

7.3 Parasitological diagnosis

7.3.1 *Microfilariae*

The demonstration of microfilariae in skin snips is the classic method of determining the prevalence and intensity of infection. As already mentioned, microfilariae may be seen in the cornea and anterior chamber of the eye, and may also be found in urine and blood in heavy infections.

The preferred sites for obtaining skin snips, the number of snips to be taken, and the handling of samples and instruments have been well documented (*1*).

7.3.2 *Adult worms*

Palpable nodules can be excised under local anaesthesia using aseptic techniques and examined for adult worms directly after digestion with collagenase or by routine histology.

Ultrasonography is a non-invasive technique that can be used to distinguish an onchocercal nodule from lymph nodes, lipomas, fibromas and foreign body granulomas. A typical nodule appears as a central, relatively homogeneous echogenic area containing echodense particles with a lateral acoustic shadow. The latter is absent in very small nodules. The worm burden can be determined more precisely by ultrasonography since it detects impalpable nodules, and the number of nodules in a conglomerate mass can be accurately assessed by counting the number of worm centres. Since expensive equipment and highly trained staff are required, ultrasonography is currently limited to a few centres in endemic areas.

7.3.3 *Use of DNA probes for diagnosis*

Techniques based on the polymerase chain reaction using species-specific probes for the "Oncho-150" repeat (see section 7.4.2 below) have recently been shown to be effective for diagnosing *O. volvulus* infection by detecting parasite DNA in routine skin snips (*30*). The technique is more sensitive in detecting low-level infections than standard skin-snip methods, but does not give any indication of the number of skin microfilariae. How long parasite DNA remains in the skin, how extensively it is distributed in light infections, and how feasible the technique will be in central field laboratories must all be determined before the ultimate usefulness of this technique can be assessed.

7.4 Use of DNA probes for surveillance

7.4.1 *Potential use of DNA probes*

In its third report (*1*), the WHO Expert Committee on Onchocerciasis identified two particular areas where it was thought that DNA probes might be of use in the surveillance of onchocerciasis. The first was in providing a means of identifying *O. volvulus* in infected vector blackflies (*S. damnosum* s.l.). In particular, DNA probes could be of use in distinguishing *O. volvulus* infective larvae from non-human filarial larvae, such as those of *O. ochengi*, which are carried by the same species of blackfly. The second potential use of the DNA probes would be in differentiating between the so-called forest and savanna forms of the parasite. Since 1988, strain- and species-specific DNA probes have been developed, and methods of using them devised.

7.4.2 *Development of DNA probes for Onchocerca volvulus*

DNA probes for *O. volvulus* have been isolated by the differential screening

of genomic DNA libraries. All the probes developed contain closely related DNA sequences that form a family of tandem-repeat sequences with a unit length of 150 base pairs (the "Oncho-150" repeat mentioned above). The individual DNA probes contain distinctly different versions of this 0–150 repeat, such that the species and strain of the parasite can be identified (*31*).

Primers for use in the polymerase chain reaction and capable of recognizing all known examples of the 0–150 family have been devised. The amplified products can be reacted with species-specific (e.g. *O. volvulus* versus *O. ochengi*) and strain-specific (e.g. savanna versus forest) probes for parasite identification. Furthermore, use of the polymerase chain reaction has made it possible to adapt the DNA probes so as to enable a variety of non-radioactive detection techniques to be employed, a step necessary in the transfer of the technology to laboratories situated in endemic areas.

Within the OCP area, these strain-specific probes have been used successfully to predict the pathogenic potential of a given parasite population with a sensitivity and specificity exceeding 90%.

## 7.5 Recent advances in immunodiagnosis for surveillance

The WHO Expert Committee on Onchocerciasis, in its third report (*1*) recommended that immunodiagnostic tests should be developed capable of detecting early infections. Such tests would be of special interest for identifying new infections in areas under vector control (particularly in the OCP area) and serve as a tool for onchocerciasis surveillance.

As the first step in developing such immunodiagnostic tests, seven collaborating centres evaluated 37 recombinant antigens against coded serum samples from the WHO Filariasis Serum Bank (*32*). Of these, 10 were selected for further study because of their high specificity (i.e. absence of cross-reactivity with sera from other filarial infections). These antigens were evaluated in a second round of testing both against sera serially collected from children shown to have acquired onchocercal infection during a longitudinal study in a hyperendemic area of Mali, and against sera of experimentally infected chimpanzees. From this second screening, antigens were selected for high sensitivity in detecting early infections during either the prepatent or the early patent period. In addition, individual sera were screened for complementary patterns of reactivity among the antigens, so that the sensitivity of the final assay could be enhanced by creating an "antigen cocktail". As a result of this selection process (*32*), three recombinant antigens, namely Ov-7, Ov-11 and Ov-16, were chosen as components of such a "cocktail".

Preliminary results with the "tri-cocktail"-based antibody-detection assay in a study of a recrudescence focus within the OCP area (Pendié, Burkina

Faso) and in a study on transmigrants exposed to onchocerciasis in the Vina Valley (Cameroon) are given in Fig. 6. Seropositivity rates were directly correlated with the rate of parasitologically confirmed new infections, but in all villages studied were higher than the prevalence of positive skin snips. This discrepancy resulted from the fact that 30-50% of the exposed individuals who subsequently converted to having a positive skin snip within the following 12 months were found to be serologically positive, in addition to 60-80% of those with early patent infection. Seropositivity rates were low (under 2%) for children living either in a Programme area without transmission of *O. volvulus* or in one where *O. ochengi* is transmitted. However, more data need to be collected before a final assessment can be made of the specificity of the "tri-cocktail" test.

Figure 6
Relation between onchocercal seropositivity and parasitological results in six villages in Cameroon and in Pendié, Burkina Faso[a]

$r = 0.82$
$P < 0.05$

M1, Mafaré 1992
M2, Mafaré 1993
P, Pendié 1989

WHO 94915

Seropositivity (%)

Positive skin snip (%)
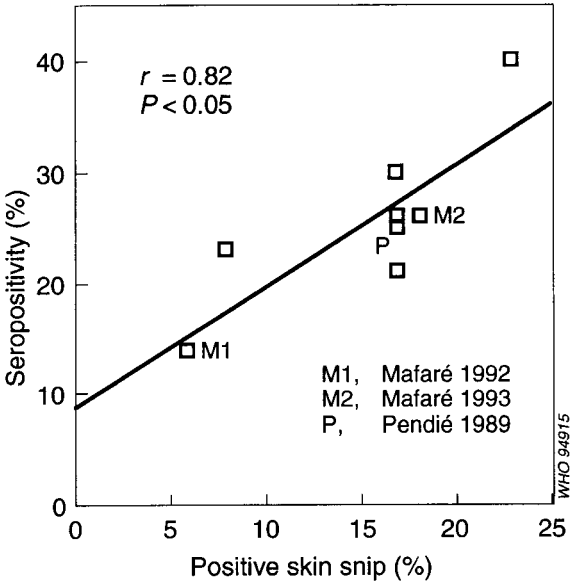
[a] Study populations (newly exposed transmigrant populations in Cameroon and children born during OCP vector control but recently exposed because of recrudescence of onchocerciasis in Pendié, Burkina Faso) had been exposed to onchocerciasis for less than 2 years. Seropositivity rates were determined by means of an antibody-detection assay based on the "tri-cocktail" Ov-7, Ov-11 and Ov-16. The study population in Mafaré, Cameroon, was tested at two time points, after 1 and 2 years of exposure.
Source: J.P. Chippaux & N. Weiss, unpublished data.

7.6 Suggestions for further study

- Diagnostic techniques based on parasite DNA detection should be developed and evaluated as means of complementing or replacing existing methods, especially for application to specimens that can be collected non-invasively from patients.
- The development, field-testing and application of immunodiagnostic tests to detect early infections (e.g. in areas of potential recrudescence) should be continued.

8. Treatment

8.1 Introduction

Although five classes of chemotherapeutic agents are potentially available for the treatment of onchocerciasis, only one drug, ivermectin, is actually being used regularly for this purpose. Of the remaining drugs, diethyl-carbamazine and suramin are considered unsuitable for large-scale therapy, while two groups of potentially macrofilaricidal compounds, thioureas and benzimidazoles, are still at the stage of experimental drugs.

8.2 Ivermectin

The clinical trials of ivermectin required for purposes of licensing and to develop a safety profile have, since 1987, been followed by extensive use of the drug within the OCP area of 11 countries as well as in all 23 other endemic countries.

8.2.1 Treatment schedule

Ivermectin is given as a single oral dose of 150 µg/kg of body weight once or twice a year. It should not be given to children under the age of 5 years or weighing less than 15 kg, during pregnancy, to mothers nursing infants during the first week of life, and in severe illness, as specified in the manufacturer's exclusion criteria.

Preliminary observations indicate that different regimens may be required to achieve different objectives, such as the improvement of specific severe ocular or skin manifestations, the control of transmission, and more pronounced effects (macrofilaricidal or sterilizing) on the adult worms.

8.2.2 Toxicity and adverse reactions

Ivermectin has no pharmacological activity in humans or intrinsic toxicity in single doses of up to 600 µg/kg of body weight or in multiple doses of 100-150 µg/kg of body weight given every 2 weeks, monthly or every 3 months up to a total dose of 1.8 mg/kg of body weight.

Before mass distribution began, more than 100 000 persons had received ivermectin. The reactions seen were qualitatively similar to those following the use of diethylcarbamazine (i.e. the Mazzotti reaction) but were much less frequent and less severe; common side-effects included itching and rash, musculoskeletal pain, relatively painless swelling (oedema) of the limbs and face, fever, and gland pain and swelling. There have been no life-threatening side-effects or mortality attributable to ivermectin. Severe reactions are uncommon (approximately 1 per 1000) and those requiring the use of corticosteroids are rare. Most reactions can be managed with simple analgesics and antihistamines. The incidence of severe symptomatic postural hypotension can be reduced from approximately 1 per 1000 to nearly zero if those receiving ivermectin are advised to rest in bed when feeling weak or dizzy. Reactions usually commence on the first day after treatment, most of the severe reactions occurring by the second day. There is a direct correlation between infection intensity and the severity of musculoskeletal pain, fever and lymphadenitis, but there is no such relationship for cutaneous reactions. Reactions are prominent in localized onchodermatitis and may be more frequent in non-resident visitors to endemic areas despite low skin microfilarial counts. Previous constraints on the use of diethylcarbam-azine, such as careful patient selection, individualized treatment, hospital management of the heavily infected, pretreatment with corticosteroids, and close clinical and ophthalmological monitoring, do not apply to ivermectin. Reactions are greatly diminished on repeated dosings of populations or individuals.

Reactions such as acute laryngeal oedema, attacks of asthma in known asthmatics, bullae, and the late development of abscesses have also been reported, but possibly represent pre-existing or coincidental illnesses that appeared at the same time as ivermectin administration. There are no reported adverse effects on the outcome of pregnancy or on the course of epilepsy.

The treatment of patients with concomitant nematode infections has not been fully studied, but investigations to date in onchocerciasis patients who also have loiasis have not shown any increased morbidity or adverse experiences.

8.2.3 *Activity against the parasite*

Microfilariae
Ivermectin has a potent, rapid action against skin microfilariae. Massive reductions in microfilarial counts occur during the first few days; the maximum reduction may, however, not be achieved for 2 or more weeks. A reduction in the number of ocular microfilariae also occurs, but not for at least 2 weeks, and microfilariae may not be eliminated for 3 or more months. The drug's effects on microfilariae in the eye, skin and lymph nodes are discussed in section 4.4.

Adult worms

When given in a single standard dose of 150 µg/kg of body weight, ivermectin appears neither to be macrofilaricidal for *O. volvulus* nor to affect embryogenesis or spermatogenesis. Its most marked effect in adult worms is a block in the release of stretched microfilariae from the uterus followed by microfilarial degeneration. These effects last for more than 6 months and are mainly responsible for the prolonged suppression of skin and ocular microfilarial counts. Other effects include a reduction in the number of male worms per nodule, an increase in the number of nodules not containing male worms, and a reduction in the percentage of nodules in which intact microfilariae are present in the nodular tissue.

Multiple doses of the standard regimen have been given at varying intervals up to a total of 12 doses and 1.8 mg/kg of body weight. Even repeated yearly doses appear to have some macrofilaricidal activity, but the greatest effects against adult worms followed 11 doses given at 3-monthly intervals. This resulted in an excess mortality of female worms (32.6% greater than in the control group who received no drug treatment), a reduction in the number of live male worms and in the proportion of inseminated females, and a cessation of microfilarial production (*33*).

Kinetics of skin microfilarial numbers

There is a rapid fall in the numbers of skin microfilariae, followed by the maintenance of very low levels over a period of several months, after which there is a gradual increase.

This pattern probably reflects an initial potent microfilaricidal effect, followed by a failure to release intrauterine microfilariae, impaired fertilization of ova, and a subsequent decline in these effects on the adult worms.

8.2.4 Mechanism of action

Recent studies of the ivermectin receptor in the free-living nematode *Caenorhabditis elegans* show that, in this nematode, ivermectin binds at extremely low concentrations to a membrane chloride channel normally controlled by glutamate. It is still uncertain how these findings relate to *O. volvulus*.

8.2.5 Resistance

To date, resistance of *O. volvulus* to ivermectin has not been described; constant surveillance must be maintained to ensure that any such development is detected.

8.3 Suramin

Despite its appreciable intrinsic toxicity and the complexities of its administration, suramin remains the only macrofilaricidal drug currently

recommended for use in onchocerciasis. However, its use should be considered only for: (a) the curative treatment of selected individuals in areas without transmission of onchocerciasis and of individuals leaving an endemic area; and (b) severe hyperreactive onchodermatitis, where symptoms are not adequately controlled by repeated treatment with ivermectin.

8.3.1 *Treatment schedule*

Suramin is not absorbed from the gastrointestinal tract, and causes irritation when given intramuscularly. Thus it needs to be given by intravenous injection. A freshly prepared 10% solution is used.

A recommended suramin regimen was presented in the third report of the WHO Expert Committee on Onchocerciasis (*1*). A total dose of 4.0 g of suramin sodium is given to an adult weighing 60 kg or more. This dose is the minimum that combines anti-parasitic efficacy with an acceptably low incidence of side-effects. Results are improved by administering an additional 1.0 g if the regimen is well tolerated. Suramin sodium should be given as follows:

1st week	200 mg or	3.3 mg/kg
2nd week	400 mg or	6.7 mg/kg
3rd week	600 mg or	10.0 mg/kg
4th week	800 mg or	13.3 mg/kg
5th week	1000 mg or	16.7 mg/kg
6th week	1000 mg or	16.7 mg/kg
Total dose:	4000 mg or	66.7 mg/kg

The doses can be reduced proportionately for those weighing less than 60 kg.

8.3.2 *Monitoring of suramin therapy*

After the first dose of suramin, patients should be carefully monitored for idiosyncratic reactions. During subsequent therapy, they must be questioned about adverse reactions to previous injections. A complete physical and ocular examination, and urine, haematological and biochemical tests should be performed before each dose of suramin. Side-effects are most prominent after the third dose, but some occur weeks after the completion of therapy, so that the patient should continue to be monitored even after treatment is completed.

Mild albuminuria is common during therapy and is not an indication for cessation of treatment. If albuminuria reaches moderate levels, suramin administration should be suspended for 1–2 weeks, by which time the albuminuria is usually only mild or is completely absent. When suramin injections have had to be temporarily interrupted, the total course may

take much longer to administer. Heavy albuminuria, particularly if associated with granular casts, or the occurrence of any other severe reaction is an indication for stopping therapy.

8.3.3 *Toxicity*

The side-effects of suramin result from its intrinsic toxicity as well as from the effects of killing the microfilariae and adult worms. Information on such side-effects has been published (*1, 34*), and should be consulted before the drug is used.

8.3.4 *Activity against the parasite*

Microfilariae
Suramin is a potent microfilaricide for *O. volvulus*, but the microfilariae in the skin and eye are not killed for several weeks, after which the numbers of both are rapidly reduced.

Adult worms
Suramin is a potent macrofilaricide for *O. volvulus*. This effect may be delayed for 6 or more months, and even 1 year after a total dose of 5 g of suramin sodium some adult worms may still survive. A reduction in the reproductive activity of both male and female worms precedes adult worm death.

Kinetics of skin microfilarial numbers
Skin microfilarial counts remain essentially unchanged over the first 5–6 weeks, after which there is a rapid and massive reduction. Counts then remain very low, and skin snips ultimately become negative. This pattern is the result of an initial delayed but potent microfilaricidal effect; microfilarial counts are then kept low by the effect on reproductive activity in adult worms and subsequently by the delayed macrofilaricidal effect of suramin.

8.3.5 *Mechanism of action*

Although many metabolic processes are inhibited by suramin, its major mechanism of action, it is suggested, is interference with the binding of general growth and angiogenic factors to their cellular receptors.

8.4 Amocarzine

The piperazinyl derivative of amoscanate, amocarzine (CGP 6140), has been shown to have good macrofilaricidal activity in animal infections, and has recently been developed to the stage of Phase II–III clinical trials (*35*). Most of the trials have been carried out in Ecuador and Guatemala.

8.4.1 *Treatment schedule*

Amocarzine is active orally; absorption is improved and is more predictable when it is administered after meals rather than when the patient is in the fasting state. Of the several dose regimens examined in early studies, the most effective and best tolerated was a dose of 3 mg/kg of body weight given twice daily after meals for 3 days. It appears from studies reported more recently that large-scale therapy in a village situation is possible using a schedule of a single dose of 5 mg/kg of body weight given on two consecutive days after a meal.

8.4.2 *Toxicity*

In the trials in South America in which amocarzine was given at 3 mg/kg of body weight twice daily for 3 days (total dose 18 mg/kg of body weight), intrinsic toxicity was manifested by slight dizziness in most patients, a positive Romberg sign in 12% and impaired coordination in 4%. These neurological side-effects were fully reversible. Mazzotti-type reactions were mild and consisted mainly of pruritus and rash. No serious adverse ophthalmological, haematological or biochemical changes were observed.

In West Africa, where much higher doses were used in initial dose-finding studies (up to 45 mg/kg of body weight), more severe neurological and Mazzotti-type reactions were observed.

8.4.3 *Activity against the parasite*

Microfilariae
Amocarzine is a potent microfilaricide. In the clinical trials, microfilarial numbers in the skin usually fell to low levels within 1 week. The number of microfilariae in the eye was reduced slowly and reached zero by day 90 after treatment.

Adult worms
Examination of nodules 4 months after treatment with amocarzine at 3 mg/kg of body weight twice daily for 3 days showed that 65–73% of adult female worms had been killed or were moribund.

Kinetics of skin microfilarial numbers
After amocarzine treatment, there is a rapid fall in the number of skin microfilariae, followed by the maintenance of extremely low levels over a period of 2 years. This pattern is attributed to the combined effects of potent micro- and macrofilaricidal activity against the parasite.

8.4.4 *Mechanism of action*

The primary site of action of amocarzine is the mitochondrion, where it inhibits electron transport at the level of NADH dehydrogenase (quinone).

8.5 Benzimidazoles

As a chemical class, benzimidazoles have always shown good macro-filaricidal activity in screening models for filariasis. However, to date, this activity has not been observed in onchocerciasis patients. Benzimid-azoles designed to act as anthelminthic agents against nematodes are poorly absorbed, and antifilarial activity is usually demonstrated in animal models by subcutaneous injection, presumably with depot formation and sustained release of the drug. Benzimidazoles bind to the tubulin making up the microtubules of the mitotic spindles of the submembrane network, and so interfere with cell division and substrate transport.

Multiple doses of mebendazole and albendazole given orally and flubendazole given by intramuscular injection show little or no macrofilaricidal activity in human onchocerciasis. Their primary action is a toxic effect on the embryonic stages of the parasite. Flubendazole, when studied, induced severe inflammation and sterile abscesses at the injection site.

A flubendazole prodrug (UMF 078) has been developed that is macro-filaricidal by both oral and intramuscular routes in animals. When the prodrug is given intramuscularly as a suspension in oil, the inflammatory response seen with flubendazole itself is absent. Two or three doses of UMF 078 are required for full macrofilaricidal activity in animal models; this compound is currently entering the preclinical toxicology phase of development.

8.6 Diethylcarbamazine

Diethylcarbamazine is no longer recommended for the treatment of onchocerciasis. Its toxicity, side-effects and activity in the parasite were reviewed in 1987 (*1*). If it is used for the treatment of lymphatic filariasis in patients who also have onchocerciasis, ivermectin should be administered first and diethylcarbamazine given only after microfilariae have been cleared from the skin and eye.

8.7 Evaluation of the effectiveness of chemotherapeutic agents

During the development of a drug for use in the treatment of onchocerciasis, its effects on the following should be monitored: (a) microfilariae; (b) adult worms; (c) the ability of microfilariae from treated patients to develop in the vector; (d) infective larvae; (e) the symptoms, lesions and systemic manifestations of onchocerciasis; (f) the results of clinical laboratory tests on specimens obtained from patients; and (g) host immune responsiveness.

When a drug becomes generally available and is in use in community therapy, however, assessment of efficacy can be limited to the effects on

patients' symptoms (such as pruritus), easily recognizable lesions, general well-being, weight gain in both children and adults, and the prevalence of visual symptoms and blindness. This overall evaluation can be supplemented by the judicious use of skin-snip and ocular examinations, where practicable.

8.8 Suggestions for further study

- Indirect methods are needed for determining the macrofilaricidal activity of novel chemotherapeutic agents, including the use of antigen, antibody or DNA assays.
- Methods should be established for detecting the development of resistance by *O. volvulus* to ivermectin, and possible underlying mechanisms should be studied.
- The role of amocarzine in the community treatment of onchocerciasis requires investigation.
- Data should be collected on:
    - tolerance to ivermectin in patients infected with both *O. volvulus* and other tissue-dwelling filarial parasites, especially *Loa loa* and *Wuchereria bancrofti*;
    - the outcome of pregnancy in women inadvertently treated with ivermectin.
- The effect of different dose regimens and schedules of ivermectin on adult worm viability and reproductive capacity should be studied.
- There is a need to define the mechanisms underlying the adverse reactions that sometimes occur after ivermectin treatment of infected patients and the long-term immunological changes in the host.

9. Control: objective, strategies and epidemiological modelling

9.1 Objective

The overall objective of onchocerciasis control is to achieve the sustained control of onchocerciasis as a public health and socioeconomic problem.

The definition of what constitutes a public health and socioeconomic problem will vary from one endemic area to another. In the West African savanna, onchocercal blindness is the dominant problem. In other areas, such as the West African forest belt, East Africa and the Americas, onchocercal skin disease and lymphatic disease are more important, not least because of their psychosocial repercussions.

According to the criteria mentioned on p. 144 of the third report of the WHO Expert Committee on Onchocerciasis (*1*), an area under vector control in the West African savanna could be considered safe for

resettlement if the annual biting rates were less than 1000 per person and the annual transmission potentials less than 100 for 2 consecutive years.[1] These entomological criteria can be supplemented by the medical criterion that blindness ceases to be considered a public health problem in a given area when the prevalence of all blindness, including blindness due to onchocercal infection, is less than 1% in all endemic communities and less than 0.5% in the country as a whole (36). Too little is known about the importance of skin disease and its psychosocial consequences for a similar criterion to be established for this aspect of the disease.

9.2 Factors affecting control strategies

Until 1987, the control of onchocerciasis was based exclusively on the control of the vector. However, with the introduction of ivermectin, a new tool has become available which has radically modified control strategies. If a safe, easily administered macrofilaricide is ever developed, a further review of the role of vector-control activities will be necessary.

The current strategies for onchocerciasis control are largely determined by two factors, namely the focal nature of severe onchocercal disease and the availability, effectiveness and affordability of intervention tools. Ivermectin delivery calls for a comprehensive approach, covering all those eligible in endemic foci who are at risk of infection.

9.2.1 Focal nature of severe disease

The risk of severe onchocercal morbidity, and therefore the public health and socioeconomic importance of onchocerciasis, is directly related to the level of endemicity at the community level. This relationship has been demonstrated convincingly for ocular onchocerciasis in the West African savanna. For other parts of the world, and for other forms of onchocercal morbidity, information on the relationship with endemicity is limited. However, several studies have shown that the prevalence of certain severe skin lesions, notably leopard skin, is also related to the level of endemicity in the community.

The level of endemicity before control measures are introduced depends on the intensity of *O. volvulus* transmission to which the members of a given community are exposed. The level of transmission varies greatly between different endemic foci and, within a given focus, between communities located at different distances from the vector breeding sites or having different vector contact patterns. This explains the great variation in endemicity levels observed, and the highly focal nature of the prevalence and intensity of onchocerciasis infection and the risk of severe complications.

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[1] For definitions, see section 12.2.4.

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The population of endemic areas is not evenly distributed with respect to endemicity level, and the most severely affected communities, where control is most urgently needed, usually account for only a minority of the population. It has been estimated, for example, that before the start of control in the western extension of the OCP, over 85% of all those blind as a result of onchocerciasis were from villages with a community microfilarial load greater than 10 microfilariae per skin snip, but only 12% of the total rural population in the endemic areas lived in these villages.

Since the risk of severe disease depends in general on the endemicity level, the highest priority for onchocerciasis control must be to introduce control measures first in those communities where the endemicity is greatest.

9.2.2 *Available intervention tools*

The second factor determining current control strategies is the availability of intervention tools and their effectiveness and affordability in different epidemiological and economic settings. The two principal tools or methods now available are vector control through larviciding, and chemotherapy with ivermectin. While it would be highly desirable to have a vaccine that protects against onchocerciasis, vaccine development is still in the research phase. Other possible interventions are of very limited practical value for onchocerciasis control. For example, personal protection from exposure to vector biting by wearing adequate clothing is usually impractical and repellents are of limited effectiveness and too expensive. Large-scale nodulectomy campaigns are said to have had a significant impact on morbidity and on the control of the parasite reservoir in Guatemala and Mexico, but it is generally accepted that large-scale nodulectomy is not a practical alternative in other endemic areas.

Vector control
Experiences in East and West Africa have shown that vector control through larviciding can be very effective in achieving the interruption of transmission and the eventual elimination of the parasite reservoir. However, vector control is expensive and, at least in the many foci where *S. damnosum* s.l. is the vector, has to be maintained over a very large area in order to reduce the risk of reinvasion by infective vectors from outside the zone under control. In general, this implies that, in most endemic areas, interruption of transmission by means of vector control is feasible only through large-scale national or multinational activities such as those conducted by the OCP, and is beyond the means of the endemic countries themselves.

Ivermectin
Since 1987, chemotherapy with ivermectin has proved to be a practical alternative to vector control. Ivermectin is a highly effective microfilaricide

and, since the pathological manifestations of onchocerciasis are directly related to the microfilarial load, treatment with it is of direct benefit to the infected patient. However, at the required dosage of 150 µg/kg of body weight and the usual treatment interval of one year, ivermectin appears to have only a limited cumulative effect on the adult worm and its reproductive capacity. After six annual treatments, partial repopulation of the skin by microfilariae has been observed. Because of this, and because of the limited effect of ivermectin on transmission, treatment may have to be given repeatedly over a long period of time.

9.3 Strategies

The main control strategies in current use are morbidity control by ivermectin treatment, elimination of the parasite reservoir, and prevention of recrudescence.

9.3.1 Morbidity control by ivermectin treatment

The principal aim of this strategy is the prevention of severe onchocercal morbidity, both directly through ivermectin treatment of individuals at risk, and indirectly through the reduction in transmission following large-scale treatment. Two specific approaches are described below.

Large-scale annual ivermectin treatment in high-risk communities
This is the main strategy currently used. Its adoption is considered urgent for communities where the prevalence of infection is greater than 60% or that of palpable nodules in men is greater than 40%, and highly desirable for communities where the prevalence of infection exceeds 40% or the nodule prevalence in men is greater than 20% (*37, 38*). No lower limit has been set below which large-scale ivermectin treatment should not be considered, as any decision to proceed with such treatment will depend on the resources available for control and the local pattern of morbidity.

Treatment of patients reporting to existing health posts ("passive" drug distribution)
This strategy is currently recommended only for low-risk communities. Experiences to date suggest that it is not very effective, and that it is particularly difficult to ensure the regular treatment of all those at risk in the communities selected for treatment. However, it is hoped that, in general, the effectiveness of this strategy may be increased by improved public health education, and that, in areas where skin disease is highly prevalent, patients will be more likely to seek treatment because of symptoms.

9.3.2 Elimination of the parasite reservoir

The aim of this strategy is to eliminate onchocerciasis transmission, infection and disease within a defined period of time.

Elimination through vector control

This strategy involves the interruption of transmission through vector control for a period of time (about 14 years in West Africa) determined by the life span of the parasite, in order to ensure the elimination of the parasite reservoir. It has been highly successful throughout the greater part of the OCP area. However, partial interruption of transmission, even by 80–90%, is not sufficient, and will allow the parasite reservoir to remain at a viable level (as at Pendié in Burkina Faso). Interruption of transmission through vector control is feasible in certain areas, as has been shown in Kenya and the West African savanna, but not in others, e.g. the forested areas of south Sierra Leone and south Côte d'Ivoire.

Elimination through large-scale ivermectin treatment

This strategy aims at the progressive reduction of the parasite reservoir and ultimate interruption of parasite transmission by repeated large-scale ivermectin treatment.

Such repeated treatment achieved an 80–100% reduction in parasite transmission in three communities during a 3-year pilot study in Guatemala when the drug was given at 6-month intervals and overall coverage of those eligible was ≥81%. Treatment at 6-month intervals is currently being continued in both Guatemala and Mexico.

The results of community-level studies in Africa are variable and reflect both differences in measurement methodology and variations in patterns of transmission.

In a study in an area of Liberia, the intensity of *O. volvulus* transmission was reduced by 63–97% following the second of two annual treatments. This reduction was accompanied, over a 2-year period, by a decrease in the incidence of infection of as much as 45% in a cohort of 7–12-year-old children. Reductions in transmission of 50–70% were recorded in Ghana when some 65% of the total population in a community received three annual treatments.

Recent predictions based on the results of 5 years of annual treatment in a savanna focus in Africa suggest that it may not be possible to eliminate the parasite even by annual treatment for 15 years. However, these predictions require careful revision as new data emerge and the microsimulation model ONCHOSIM (see section 9.4) continues to be refined.

Elimination through vector control combined with ivermectin treatment

Combining ivermectin treatment with vector control has the advantage of providing an immediate benefit for the infected population. Furthermore, experience in the OCP shows that the use of ivermectin in this way provides a margin of safety for the vector-control operations. Temporary breakdowns in vector control tend to be less serious, while more selective vector-control operations, with fewer larviciding cycles and thus lower

costs, have been possible. However, it is predicted that the required duration of vector control cannot be significantly reduced as a result of the combination of vector control and chemotherapy.

9.3.3 *Prevention of recrudescence*

This strategy applies only to areas where control measures have virtually eliminated the parasite reservoir, as in the central OCP area.

Recrudescence is defined here as renewed transmission of a magnitude that would result in the gradual build-up of infection and disease to unacceptable levels in the absence of any intervention. Recrudescence may be the result of immigration of infected humans, reinvasion by infected vectors, or an undetected residual reservoir of infection.

The prevention of recrudescence initially involves only surveillance aimed at the early detection of new infection. When a significant incidence of infection has been detected, control by large-scale ivermectin treatment can be started. Predictions based on the model ONCHOSIM indicate that recrudescence of infection, if it occurs, will initially be very slow and that ivermectin treatment alone may be able to interrupt transmission again on condition that it is started early enough. An appropriate surveillance methodology is being worked out in detail and tested by the OCP.

9.4 Use of epidemiological models to predict trends in the prevalence of infection

The practical problems faced by the OCP in the planning and evaluation of control have led to the development of epidemiological models for this purpose, the most comprehensive one used in the Programme thus far being a microsimulation model called ONCHOSIM (*39*).

ONCHOSIM uses the technique of "stochastic microsimulation", which involves the explicit simulation of the individual life histories of both human hosts and adult parasites. Models based on microsimulation are flexible in design, which makes it easy to specify and simulate alternative assumptions. Furthermore, they can provide detailed output in the same format as field observations; this is useful in the validation of the model, while it also makes the model output more understandable to decision-makers.

In ONCHOSIM, the most important variables are: (i) human factors, namely population dynamics (birth, death, immigration), and hetero-geneity in exposure to the vector; (ii) vector factors, such as vector density, biting rates and seasonal variation; (iii) the life history of the parasite in the host (life span, prepatent period, age-specific microfilarial output, mating); (iv) larval uptake by flies as a function of human microfilarial load; (v) the development of blindness and associated excess mortality; (vi) the timing and coverage of epidemiological surveys

and ivermectin treatment; (vii) the timing and effectiveness of larviciding; and (viii) the microfilaricidal and possible macrofilaricidal effect of ivermectin.

Modelling has been successfully used by the OCP both in the integrated analysis of the evaluation data and to predict trends in the prevalence of infection after vector-control activities or ivermectin distribution, and action is being taken based on these predictions. For example, following the development and refinement of ONCHOSIM, it was predicted that vector control could be safely stopped after 14 years of interruption of transmission. Control was therefore stopped in the original Programme area and, according to the entomological evaluation, there was no significant transmission in this area during the following 3 years, even though the vector returned immediately.

It should also be possible to use ONCHOSIM outside the Programme area. The structure of the onchocerciasis transmission cycle and its components would remain unchanged in the simulation, but some adaptations would be necessary and would require appropriate expert knowledge and empirical data. For instance, for the American type of onchocerciasis, most of the assumptions concerning the fly, the parasite and the disease would have to be changed.

9.5 Suggestions for further study

- Further studies are needed on the cumulative effect of repeated large-scale ivermectin treatment on *O. volvulus* transmission, and on the viability and reproductive capacity of adult worms.
- Information on ONCHOSIM and the expertise necessary to use it should be communicated to other control programmes and to research groups in Africa and America.
- ONCHOSIM or other predictive epidemiological models should be used to address the following important issues relating to control programmes:
  - the potential development of ivermectin resistance in *O. volvulus*;
  - the availability of a macrofilaricidal drug;
  - the influence of control programmes on skin and eye disease.
- Research directed towards the development of vaccines that would confer protection from onchocercal infection or disease should be continued.

10. Control through vector control

In spite of the recent introduction of ivermectin, and in the absence of a macrofilaricide drug, vector control remains a technically valid method of interrupting parasite transmission. Nevertheless, it can be effective only if it is pursued until the parasite reservoir in the population is

exhausted, as was demonstrated in Africa, where the strategy, conducted for more than 15 consecutive years, was successful in ridding many regions of onchocerciasis. Vector control is based on the insecticide treatment of rivers in which the larvae of vector species develop. It rarely takes more than 1–2 weeks for the pre-adult stages to develop from egg to pupa, and this means that insecticide must usually be applied weekly. In Africa, because of the large areas and number of breeding sites to be treated, insecticides are sprayed mainly from the air. Ground treatment may, however, be undertaken in accessible and isolated areas.

10.1 Operational aspects and impact of insecticide treatments

10.1.1 Insecticides used

The formulations of the insecticides used for large-scale campaigns must satisfy a wide range of requirements. They must be highly effective against the vectors, but safe for the rest of the environment. Each formulation must be specially devised for blackfly control, the supply of the insecticide guaranteed over a long period of time, and the cost kept as low as possible. The constituents should be biodegradable but there must also be maximum "carry" downstream from the point of application. In addition, since the vectors are under constant insecticide pressure in very extensive control zones, alternative larvicides must be available (see below), preferably belonging to different chemical classes, so that any resistance to one or more compounds can be avoided or dealt with promptly.

Temephos is the preferred larvicide because of its effectiveness, its range (the distance over which it remains effective), and its safety for non-target fauna. However, the appearance in 1980 of resistance in West Africa required users to adopt a strategy of alternating insecticides with different modes of action, if possible, so as to forestall the appearance of new cases of resistance (Table 7). This rotation of insecticides has given ample proof of its worth, to the extent that today few *Simulium* populations in the OCP area are still truly resistant to organophosphorus compounds.

Because of the need for rotation, six insecticides are now used in the OCP area, namely temephos, pyraclofos, phoxim, permethrin, carbosulfan and *Bacillus thuringiensis* serotype H-14 (*B. thuringiensis* H-14). Temephos and pyraclofos, both organophosphorus compounds, are regarded as the most effective larvicides; they have fairly low operational doses, and a carry of as much as several tens of kilometres when water levels are high. Pyraclofos tends not to be used at river discharge rates above 300 m^3/s; it is never used at rates below 15 m^3/s because of its toxicity. Phoxim does not endanger the environment, but is less effective and has a limited range. Permethrin, a pyrethroid, has a more limited range than temephos and pyraclofos, though its operational dose (Table 7) is very low, so that its use is not limited by high rates of flow; however, because it is

Table 7
Blackfly larvicides currently used in the OCP

Insecticide name, formulation and concentration of active ingredient (g/l)[a]	Chemical group	Dosage (l) per m^3/s river discharge	Optimal range of river discharge (m^3/s)	Carry in large rivers (km)	Margin of safety[b] (fish and crustaceans)
Bacillus thuringiensis H-14 (water-dispersable concentrate)	Biological	0.72	0–15	< 3	Extremely safe in most situations
Temephos (EC200)	Organophosphate	0.15–0.30	0–450	20–30	100×
Phoxim (EC500)	Organophosphate	0.16	15–70	≤ 6	7×
Pyraclofos (EC500)	Organophosphate	0.12	15–300	20–30	4×
Permethrin (EC200)	Pyrethroid	0.045	≥ 70	≤ 10	2×
Carbosulfan (EC250)	Carbamate	0.12	70–150	≤ 11	2×

[a] EC200, for example, denotes an emulsifiable concentrate containing 200 g of active ingredient per litre of formulated material.
[b] Indicates the level of overdosing at which fish and shrimps may be endangered; the multiplication factors apply to the values for dosage (l) per m^3/s river discharge given in column 3.

somewhat toxic to non-target fauna, it is never used at less than 70 m^3/s and, if possible, is applied for no more than 6 weeks per year to the same stretch of water. Carbosulfan is a carbamate of carry and toxicity similar to those of permethrin, but both its price and operational dose are much higher; its use is therefore restricted to rates of flow between 70 m^3/s (the toxicity threshold) and 150 m^3/s (the cost threshold). Finally, *B. thuringiensis* H-14, a bacterial insecticide, is not particularly effective in rivers, since it has both a high operational dose and a low range. For these reasons, it is never used above 15 m^3/s, although its use is justified by its environmental safety and by the unlikelihood of resistance developing (*40*).

When river discharge rates are in the range 15–70 m^3/s, only organo-phosphorus compounds can be used, but there is then a high risk of resistance developing. In order to fill the gap, a non-organophosphorus larvicide is highly desirable. A new pseudo-pyrethroid compound (etofenprox) is currently undergoing field trials and has proved to be highly active against blackfly larvae. If approved by the OCP Ecological Group, this compound will become an important addition to the existing arsenal of larvicides.

10.1.2 *Operational decisions and impact of treatment choices*

In practice, to ensure effective vector management, two decisions will have to be taken. Thus, for each major location, it must first be decided whether insecticide should be applied from the air or on the ground. This decision depends, in part, on the results of an entomological evaluation aimed at determining the effectiveness of treatments on the pre-adult stages (by prospecting the rivers) and adult stages (by the capture and dissection of blackflies). It also depends on other factors, such as the movements of adult females, the vector capacity of the species concerned, the level of endemicity of onchocerciasis, and the therapeutic coverage in the zone concerned. The second decision concerns the selection of the most appropriate compound for each watercourse, based on a number of criteria relating not only to the insecticide itself but also to the river discharge rate and the blackfly population concerned.

The impact of larvicide treatments on the larval populations is checked by evaluating sites easily accessible by land along the rivers treated. These are selected both for their representative character and for larval productivity.

The high efficiency of aerial treatments means that insecticides are used to the full extent of their possibilities. The evaluation of carry for each insecticide application is the most critical factor in maximizing the efficiency of application, and intensive research has been devoted to improving its accuracy. For each operational insecticide, river transport models have been developed and validated by field experiments, taking into account basic parameters such as flow level and complexity.

Simplified field charts and tables derived from these models are used to determine the appropriate sites of insecticide application along rivers.

For ground treatment the preferred insecticide is either temephos or *B. thuringiensis* H-14; these insecticides, in particular the latter, present little risk to the environment.

10.2 Resistance and its management by the rotation of insecticides

Prolonged and intensive use of an insecticide encourages the development of resistance. Thus resistance to temephos by *S. damnosum* s.l. first appeared in 1980 in the OCP area in southern Côte d'Ivoire. Resistance to chlorphoxim, also an organophosphorus compound, arose in the same area soon after its introduction in the same year. The members of the complex involved were *S. sanctipauli* and later on *S. damnosum* s.s. Resistance to temephos (but not to chlorphoxim) spread from this original focus as a consequence of seasonal fly movements and continued selective pressure.

To overcome this problem, a testing and surveillance programme was established to evaluate the resistance risks for each river basin according to the time of year. Blackfly larvae used in the tests were identified at the species level and data on their insecticide susceptibility compiled in databanks, which provide extremely useful information for each species on seasonal distribution patterns and susceptibility ranges. This approach demonstrated from field data that different biochemical mechanisms were responsible for resistance to temephos, phoxim and pyraclofos (the three organophosphorus insecticides currently used in the Programme).

By 1986, resistance foci had been found in southern Ghana, and in northern Côte d'Ivoire and Guinea. By then, resistance was also present in *S. sirbanum*, a mobile species which is the main vector of human onchocerciasis in the sudanian savanna part of the Programme area. In contrast to the populations of *S. damnosum* s.s. and *S. sanctipauli* in southern Côte d'Ivoire, *S. sirbanum* usually showed lower and transient resistance to temephos when its use was not prolonged. In 1986, additional insecticides, such as permethrin and carbosulfan, became available. The transient nature of resistance to temephos in *S. sirbanum* suggested that a rotational use of insecticides could prevent resistance problems (*41, 42*). Thus phoxim has replaced chlorphoxim, and pyraclofos has come into use, bringing the number of operational insecticides to six, as previously mentioned. This rotational strategy has been implemented and gradually improved over the years. It can be summarized as follows:

 - *Dry season:* rivers are preferably treated with *B. thuringiensis* H-14, or treatments are stopped, if possible.
 - *Start of the rainy season:* applications of organophosphorus compounds, namely temephos, phoxim and pyraclofos, are gradually increased with emphasis on the last of these when river discharges are

high. To reduce the risk of resistance, no organophosporus compound is used for more than six successive weekly cycles.

- *Peak of the rainy season:* permethrin or carbosulfan (maximum of 6 weeks per year for each) is alternated with an organophosphorus compound with a long carry (temephos or pyraclofos). Treatments are interrupted whenever possible.
- *End of the rainy season and onset of the dry season:* the first two stages are repeated in reverse order, but with less emphasis on pyraclofos.

10.3 Impact of larviciding on the aquatic environment

Because of the potential risk to the aquatic environment, careful consideration must be given to the selection of larvicides and protocols for monitoring the aquatic environment. Such monitoring involves the continuous survey of fish populations (which are a source of essential protein in the diet of those living near rivers) and of the populations of benthic invertebrates on which most of the fish feed. Any insecticide used must be degradable and its toxicity must be minimal.

10.3.1 *Impact on the benthic fauna*

Short-term impact

Analysis of the impact of larvicidal treatment on benthic fauna, as measured by the downstream movement (drift) of organisms after larvicide application (*43, 44*), indicates that *B. thuringiensis* H-14 is the most selective of the six larvicides commonly used against blackflies. Among "non-target" insects, it does affect the Chironomidae (which, like blackflies, are dipterans) but not the Ephemeroptera or Trichoptera. Of the organophosphorus compounds, temephos is the most selective for blackfly larvae (*45*), followed by pyraclofos, phoxim and chlorphoxim; with these larvicides, the Ephemeroptera are the most affected non-target insects. With permethrin and carbosulfan, in contrast, Trichoptera and Chironomidae are the non-target insects most affected.

Long-term impact

Given the complexity of bioecological factors (competition, predation, larval life span, resistance or habituation), the long-term impact of larvicides cannot be regarded as an accumulation of short-term impacts; the impact of larvicides on the benthic fauna diminishes in the long term, although the classification of insecticides in accordance with their short-term toxicity (see above) is confirmed in the long term. For example, pretreatment and treatment period data on the impact of *B. thuringiensis* H-14 or temephos are very similar, but quite different from the data on treatment periods for carbosulfan or permethrin (*45*). There is a reduction in the density of most benthic organisms in the long term, and changes in the structure of populations. Nevertheless, on watercourses treated only

with organophosphorus compounds, it has been noted that, only a year after treatment has ceased, the situation reverts almost to the state existing before treatment.

10.3.2 *Impact on fish*

Short-term impact
In general, the larvicides listed in Table 7 do not kill river fish if used at the prescribed rates. For example, the estimated median lethal concentrations for some African species of fish are 10-100 times the operational doses of the products (*46*). Furthermore, the cerebral enzyme activity of fish which, in the laboratory, is reduced by some 25% after exposure to temephos (*47*) is not changed at all under natural conditions (*48*).

Long-term impact
Observation of the watercourses over almost 20 years of treatment in West Africa has shown no loss of species, though there are fluctuations in the numbers of fish in the environment, mainly for hydrological reasons (*49*). Nevertheless, the condition of the main species of fish is satisfactorily stable, which suggests that there is enough food for them.

10.4 Environmental management

Dams constructed for purposes of power generation or large-scale irrigation schemes can reduce the current speed of water for long distances, and this can prevent the breeding of *S. damnosum* s.l.

The construction of small hillside dams, causeways, irrigation channels, etc., by providing breeding places for vectors close to human populations, constitutes a real threat and contributes to the spread of onchocerciasis. Such artificial breeding sites should be removed or broken up when they are no longer needed.

10.5 Integrated control

The integrated control of onchocerciasis requires the availability of a range of methods, including both medical treatment, in the form of chemotherapy and nodulectomy, and techniques aimed at suppressing the vector. At present, vector control is based entirely on the use of chemical or biological larvicides. In integrated vector control, all appropriate technological and management techniques are used to suppress vector populations in a cost-effective manner.

The development of effective macrofilaricidal and microfilaricidal drugs suitable for the large-scale treatment of onchocerciasis and better formulations of chemical and biological larvicides for *Simulium* species would allow the broad integration of control techniques and resources.

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11. Control through chemotherapy

11.1 Introduction

Ivermectin as a microfilaricide for the treatment of human onchocerciasis proved to be both highly effective and well tolerated in clinical and community trials, leading to its registration for human use in 1987. Its efficacy and the decision of Merck and Co., Inc. to donate the drug for the global treatment of onchocerciasis (see below) have resulted in the initiation of large-scale drug distribution programmes in endemic countries both within and outside the OCP area, in addition to the larviciding activities hitherto carried out.

11.2 Organizations and groups stimulating and supporting the distribution of ivermectin

In addition to the OCP three other bodies play a significant role in the stimulation and support of ivermectin distribution.

The Mectizan Donation Program
In 1987, Merck and Co., Inc. decided to donate Mectizan (the formulation of ivermectin approved for human use) for the global treatment of onchocerciasis "for as long as necessary to as many as necessary". In early 1988, an independent Mectizan Expert Committee, including representatives from WHO and the Centers for Disease Control and Prevention in the United States, was established at the Carter Center in Atlanta, GA, to review and approve applications for the use of Mectizan and to stimulate and increase its distribution.

In mid-1993, the Carter Center established the Mectizan Donation Program to (i) expand the activities of the Mectizan Expert Committee in support of nongovernmental agencies involved in ivermectin distribution; (ii) create regional coalitions of individuals and organizations distributing ivermectin; (iii) generate resources to support distribution; and (iv) review methods and strategies designed to sustain distribution. The Committee now serves as an advisory body to the Donation Program while retaining responsibility for the review of applications for Mectizan use.

Ivermectin for use in the treatment of onchocerciasis may be approved by one of the following three methods: (i) via the Mectizan Expert Committee for ivermectin intended for use in community-based programmes; (ii) via the Merck Humanitarian Program office in Paris for limited quantities for use in individuals or small isolated populations; and (iii) through Merck and Co., Inc. for use in research.

The number of treatments provided annually continues to grow at a dramatic rate: 1.4 million in 1990, 2.8 million in 1991, 5.3 million in 1992 and 9.2 million in 1993. It is important to note that the figure of

9.2 million treatments in 1993, impressive in its own right, actually represents the coverage of a relatively small proportion of the 100 million people at risk from the disease.

NGO Coordination Group for Ivermectin Distribution
The NGO Coordination Group for Invermectin Distribution is an open-ended group whose membership currently consists of Africare, Christoffel-Blindenmission, Helen Keller International Inc., the International Eye Foundation, Organisation pour la Prévention de la Cécité, the River Blindness Foundation and Sight Savers (formerly the Royal Common-wealth Society for the Blind), working in collaboration with the Mectizan Donation Program and WHO.

The Group was established in December 1992 and aims to promote worldwide interest in, and support for, the use of ivermectin in the treatment of onchocerciasis in endemic countries, and to assist interested countries or groups of countries in planning, implementing and evaluating ivermectin distribution programmes. It seeks to mobilize the needed resources, and supports operational research on large-scale ivermectin distribution. The Group is already active in most endemic African countries outside the OCP area, and is associated with the Onchocerciasis Elimination Program in the Americas (see below). It was responsible for the treatment of over 3 million individuals with ivermectin in 1993.

Onchocerciasis Elimination Program in the Americas (OEPA)
Since mid-1990, a concerted effort has been made to improve the coordination of ivermectin distribution activities in the six Latin American countries where the disease is endemic. Following the Inter-American Conference on Onchocerciasis, held in 1991, it was agreed that a regional elimination strategy was feasible. In September 1991, the XXXV Directing Council of the Pan American Health Organization adopted resolution XIV recommending that Members should promote a Multinational Strategic Plan of Action toward Onchocerciasis Elimination in the Americas, as part of a larger resolution calling for the elimination of several diseases. In this way the Onchocerciasis Elimination Program in the Americas (OEPA) was created. The goal of this multinational, multiagency and multidonor initiative is to eliminate severe pathological manifestations of the disease and to reduce morbidity in the Americas through the mass distribution of ivermectin. OEPA offers financial, technical and management support for the implementation of national onchocerciasis elimination programmes in Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela, within the framework of a larger regional strategy. A special Program Coordination Committee has been established to guide OEPA, review national plans, recommend financial support from a special OEPA trust fund and provide technical assistance. OEPA also employs technical staff who work with the six national programmes and coordinate their efforts.

11.3 Methods of distribution

Chemotherapy of onchocerciasis can be effected by means of:

- community-based distribution, where the village leader appoints some-one to be trained as a community-based distributor to carry out the yearly treatment within the village;
- active treatment campaigns, where organized teams travel to the endemic communities to treat people;
- passive treatment campaigns, where drugs are left at fixed health posts within the community, and patients are encouraged to visit such posts.

Each of these methods has its advantages and disadvantages.

11.3.1 *Chemotherapy in countries participating in the OCP*

Ivermectin distribution is carried out at varying levels in all 11 countries participating in the OCP, but mostly in those in the western and southern extensions; in the original Programme area it is carried out in specific foci only. The extent of the distribution was markedly increased in 1992 and over 1.7 million individuals were treated in 1993. Community acceptability has been good and coverage of the target population has increased over the years.

11.3.2 *Chemotherapy in African countries outside the OCP area*

Large-scale ivermectin distribution is carried out by ministries of health with the support of various NGOs in 12 of the 16 endemic countries outside the Programme area, and small-scale distribution in the remaining four. There has been a considerable increase in activities in recent years, for example in Nigeria, where 18 out of 30 states are distributing ivermectin to treat over 1.5 million persons, and in Uganda, where some 700 000 persons are under treatment. In countries where distribution was started only recently, it is expected to expand rapidly. Community acceptance has been excellent, and the demand for treatment generally exceeds the rate of expansion, which has been limited by resources.

Data on the numbers of people treated with ivermectin in Africa and the Arabian peninsula, by country, during 1993 are given in Table 8, while those for Latin American countries are given in Table 9. The figures given in Tables 8 and 9 are the numbers of persons in onchocerciasis-endemic communities reported (from sources deemed by the present Expert Committee to be reliable) to have been treated during 1993 in large-scale ivermectin distribution programmes. However, many of the programmes providing figures for these tables were, by the end of 1993, still in the early stages of implementation and had not yet achieved full coverage. The possible increase in numbers of treatments in 1994 is indicated by the fact that ivermectin tablets sufficient for 9.2 million

Table 8
Ivermectin treatment through the Mectizan Donation Program in Africa and the Arabian peninsula: estimates of number of people under treatment in 1993

Country	No. of people under treatment
Angola	0[a]
Benin[b]	183 000
Burkina Faso[b]	10 000
Burundi	50 000
Cameroon	130 000
Central African Republic	60 000
Chad	60 000
Congo	25 000
Côte d'Ivoire[b]	240 000
Equatorial Guinea	40 000
Ethiopia	0[a]
Gabon	1 000
Ghana[b]	70 000
Guinea[b]	180 000
Guinea-Bissau[b]	40 000
Liberia	0[a]
Malawi	100 000
Mali[b]	320 000
Niger[b]	32
Nigeria	1 500 000
Senegal[b]	45 000
Sierra Leone[b]	480 000
Sudan	35 000
Togo[b]	270 000
Uganda	700 000
United Republic of Tanzania	100 000
Yemen	3 000
Zaire	80 000
Total	4 722 032

[a] Small numbers of people being treated under the Merck Humanitarian Program.
[b] Participates in the OCP.

treatments approved by the Mectizan Expert Committee were shipped by Merck and Co., Inc. in 1993 for use worldwide in distribution programmes. It is important to note that only about half of those treated actually have onchocerciasis, so that the number of infected people receiving ivermectin treatment represents a relatively small proportion of those who need it.

11.3.3 *Chemotherapy in the Americas*

The epidemiological characteristics of onchocerciasis in the Americas (small and geographically confirmed foci in large forest areas), as well as the dedication of local health workers and commitment of donors, have allowed the organization of the Multinational Strategic Plan of Action toward Onchocerciasis Elimination in the Americas (see section 11.2 above).

The individual characteristics of national plans are determined by the local and regional characteristics of the disease and the way that it is perceived by the community, as well as the structure of the health systems, within the framework of the larger regional strategy. In Guatemala and Mexico, the plans are aimed at controlling morbidity and eventually interrupting transmission by giving ivermectin treatments twice a year. In Brazil, Colombia, Ecuador and Venezuela, the aim is to control morbidity, treatments being given once or twice a year. An important characteristic of these plans is the integration of large-scale ivermectin distribution for onchocerciasis control with other measures (e.g. hepatitis B vaccination of children) that target the most important health problems in the endemic areas, through the organization of primary health care workers.

Table 9

Ivermectin treatment through the Mectizan Donation Program in the Americas: estimates of number of people under treatment in 1993

Country	No. of people under treatment
Brazil	0[a]
Colombia	0[a]
Ecuador	11 700
Guatemala	62 500
Mexico	97 000
Venezuela	2 700
Total	173 900

[a] Treatment programmes recently started.

11.4 Identification of priority areas for large-scale ivermectin treatment

In the course of the development of a national plan for ivermectin-based control, the overall endemicity of onchocerciasis in the country has first to be mapped. In the extension areas of the OCP in West Africa, epidemiological mapping revealed the detailed distribution of the prevalence and intensity of infection, and provided reliable estimates of the number of people infected and blind. However, this mapping exercise was based on an abundance of epidemiological and entomological data and detailed geographical information collected during helicopter surveys. Such detailed information is not available in the countries not participating in the Programme; a new, rapid technique for mapping the endemicity of onchocerciasis in known or potentially endemic areas has therefore been developed. Its ultimate aim is to help to determine which communities have a sufficiently high level of endemicity to merit active mass treatment with ivermectin and which other communities, having lower levels of endemicity or only sporadic cases of onchocerciasis, should be provided with clinic-based (or "passive") treatment.

11.4.1 *Rapid epidemiological mapping of onchocerciasis*

When the extent of potentially endemic areas is to be assessed on a country-wide basis, the first step is to exclude both the urban centres of population and those rural areas, e.g. swampy areas, high mountains, very dry or desert areas, and large game reserves, where for various reasons there is almost no human population.

Where the remaining potentially or actually endemic area is extensive, the problem arises how to select indicator communities, where endemicity can be assessed by means of the technique known as rapid epidemiological assessment (see below) in the most cost-effective manner. Rapid though this method may be, under field conditions in rural areas that depend on subsistence and/or cash-crop farming, it is feasible for a single examination team to assemble and examine on average only two communities per working day. Given the usual shortage of trained personnel, it may therefore take an unacceptably long time to cover every community in a large endemic area, even by means of the rapid technique. Rapid epidemiological mapping is based, therefore, on the selection of a very small sample of communities to be surveyed, from which the results can be extrapolated to a large number of other communities.

The best method of selecting such indicator communities is by consensus among a team of three persons, consisting of an epidemiologist, an entomologist with experience of onchocerciasis, and a geographer. The country or area concerned is first divided into major bioclimatic zones, some of which may be excluded from further consideration; further subdivisions of the potentially endemic areas are then made on the basis of river basins. Within each of these, indicator communities are selected

after a study of the geography, hydrography and geology on maps on a scale of 1:200000–1:50000, and after drawing on all available local epidemiological and entomological data, published documents and the expertise of local health workers. If possible, small, light aircraft should be used for aerial surveys.

The rapid epidemiological mapping technique has recently been tested with considerable success in Cameroon. The ratio of selected indicator communities in which rapid epidemiological assessment was carried out to the total number of communities in the areas surveyed was in the range 1:20–1:50. The results were encouraging and appeared to predict reliably those communities in forest areas with hyperendemic onchocerciasis. In woodland, savanna and forest mosaic areas, rapid epidemiological mapping was reliably predictive of "first-line" villages, but will need fine-tuning by additional assessment surveys (perhaps at a community ratio of 1:5 or 1:10) if the borders of the area requiring active mass treatment are to be determined. Guidelines on rapid epidemiological mapping have been prepared by WHO (50).

11.4.2 Rapid epidemiological assessment

Classically, endemicity levels have been assessed by making qualitative assessments or quantitative measurements of the numbers of microfilariae in skin snips to determine the prevalence and intensity of onchocerciasis in a community. Intensity is often recorded as the community microfilarial load. Unfortunately, skin snipping is costly and time-consuming and requires skilled personnel and facilities for transport and microscopy. It is also somewhat unpopular with examinees, and incurs the risk of transmitting human immunodeficiency and hepatitis viruses.

Simpler methods of rapid epidemiological assessment have recently been developed which depend on determining the prevalence of nodules in a specific age/sex group or, with less sensitivity and specificity, the prevalence of leopard skin or the rate of blindness.

In almost all environments, determining the prevalence of onchocercal nodules is the simplest, most acceptable method of rapid epidemiological assessment that is both non-invasive and reasonably reliable. It involves determining the prevalence of such nodules in a random sample of 30–50 men over 20 years of age who have been resident in the community concerned for at least 5–10 years and are engaged in rural occupations. Males are chosen because they are generally more likely to be heavily infected than females, and are more amenable to physical examination. However, in some environments it may be desirable to include women or to increase the sample size.

The personnel employed require only the minimum training necessary to enable them to ascertain whether the patient knows where he has a nodule of O. volvulus, to examine all likely sites (including iliac crests, greater

trochanters, knees, coccyx, rib cage, scapulae and head), and to find and recognize nodules, distinguishing them from lymph nodes (especially those in the groin, which may give rise to a false-positive diagnosis), lipomata, sebaceous cysts, ganglia, etc.

The overall prevalence of onchocercal infection in the sample may be taken to be about twice the prevalence of nodule carriers in the group. As a simple rule of thumb, the onchocerciasis prevalence in males and females in the entire community is approximately 1.5 times the proportion of nodule carriers in the sample.

Use of the prevalence of leopard skin, particularly on the shins, gives less accurate results, since it may be confused with the effects of previous trauma, yaws, vitiligo and leprosy. In addition, owing to the much lower prevalence of such lesions, this method is less sensitive than the nodule method described above. Nevertheless, looking at the shins of passers-by to see whether leopard skin is present is often a rapid method of detecting whether onchocerciasis is endemic in a community and, particularly in Nigeria, has been used for rapid epidemiological assessment.

Determination of the overall blindness rate in communities is not generally a satisfactory method of assessment except in areas where onchocerciasis is at its worst. Without a thorough, expensive, skilled and time-consuming ophthalmic survey, estimates of blindness rates depend largely on hearsay figures obtained from community leaders. Moreover, the overall baseline prevalence of non-onchocercal blindness is about 1% in rural communities in tropical areas, so that it is only where blindness rates exceed 2–3% and where the sample is large that it is possible to be reasonably certain that onchocerciasis is the main cause.

These new methods of rapid epidemiological assessment have now largely replaced the use of skin snips for assessing the level of onchocerciasis endemicity in communities as a basis for intervention, the most important being that based on the prevalence of nodules, as described above.

11.4.3 Threshold for active mass distribution

In large-scale ivermectin distribution programmes, individual diagnosis and treatment are not practical. A more efficient approach is to specify that, above a certain preselected threshold of endemicity (usually determined by rapid epidemiological assessment), all persons in the community who are eligible to receive ivermectin (i.e. those not covered by the manufacturer's exclusion criteria, see section 8.2.1) should be treated. In communities where the endemicity level is below this threshold, arrangements should be made for individual clinic-based treatment to be offered at all suitable health centres in the area.

The ideal threshold for active mass treatment is the prevalence below which onchocerciasis is sporadic, which has been defined by various authors as somewhere between 15% and 30% in the total population. However, in

many instances, especially at the start of a drug distribution campaign, logistic and financial considerations make it necessary to concentrate first on communities with a prevalence of 60% or more, roughly equivalent to a 40% prevalence of nodule carriers in the sample used for rapid epidemiological assessment. Later, as the worst-affected communities come under treatment, coverage may be extended progressively to communities of lower prevalence until the ideal threshold is reached.

11.5 Suggestion for further study

- Comparative studies are required on current methods of ivermectin distribution to determine the most cost-effective and sustainable methods of ivermectin delivery.

12. Monitoring and evaluation of control

12.1 Monitoring large-scale chemotherapy

Monitoring is a way of supervising programme activities and ensuring that they are correctly carried out. Supervision of staff should be an integral part of an ivermectin distribution programme.

Record forms have been designed for use in recording the various activities involved in large-scale ivermectin distribution so that field staff's activities can be verified and monitoring facilitated. In addition, spot checks are regularly made in a small number of randomly selected communities to ensure that the performance of field staff is adequate. Checklists provide standard measures for judging performance and help to make field staff realize what is expected of them. A supervisor monitoring the activities of field staff should encourage open discussion with them so as to instil the confidence that is needed to ensure effective programme implementation.

Monitoring should be carried out at different levels and should therefore cover activities related to ivermectin distribution, the treatment of adverse reactions, the performance of field teams, the adequacy of logistics (for example use of motorcycles, inventory of supplies) to meet the evolving needs of the programme, its articulation with the primary health care system, and the development of the programme activities towards self-sustainability.

A typical checklist which could be used to monitor the activities of a community-based worker might include the following questions:

- Is there anyone in the community who is not satisfied with, or refuses to take, ivermectin?
- Were some people in the community not offered ivermectin?

– Are there any people in the community who had a bad reaction after taking ivermectin, and were not taken care of appropriately?

12.2 Entomological evaluation of the impact of vector control

Surveys of blackfly larvae in the appropriate aquatic habitats provide an immediate and direct means of checking the effectiveness of larviciding. The capture and dissection of adult flies can be used as a means of following the dynamics of *Simulium* populations and vector infectivity, and hence the level of potential transmission of the parasite.

12.2.1 *Surveys of blackfly larvae*

Larval surveys are carried out at sites selected 24–48 hours after the insecticide has been sprayed, to establish whether the preimaginal stages (larva and pupa) of the vector are present.

When a positive result is obtained, larvae may be collected for cyto-taxonomic study, and newly emerged adults obtained from pupae. Larval chromosomes and the morphology of adult flies are then examined to identify the species present. Data collected during these surveys are recorded on standardized forms and then used to evaluate the impact of larviciding operations.

12.2.2 *Surveys of adult blackflies*

Biting females are still collected on human bait in the absence of an effective technique for trapping host-seeking flies.

Catching points are selected in the light of the particular epidemiological situation and of their accessibility. These points should preferably be sited within the immediate flight range of the adult female from suspected larval habitats. They should also be located in places where transmission is likely to occur near indicator villages (see section on population and location, page 81), as this makes it easier to evaluate the impact of larvicidal operations.

In circumtropical locations, catching is carried out from 07:00 to 18:00 (i.e. 11 hours a day), the vector collectors working alternate hours. Results are recorded on special forms for computer entry.

12.2.3 *Identification and dissection of adult female blackflies*

The captured flies are identified and dissected so that their physiological age (parous or nulliparous) can be determined and developmental stages of *O. volvulus* detected. A high proportion of nulliparous females indicates incomplete control, probably resulting from shortcomings in larviciding or the colonization of untreated tributaries. A high proportion of parous

females indicates aging of the local blackfly populations, which reflects either successful larviciding or the presence of migratory female flies.

Both third-stage larvae detected during dissection and infective flies may be preserved and sent to a laboratory for identification by means of DNA probes. Where such a system operates in the OCP area, the identification of infective-stage larvae is usually carried out every week as a matter of routine. DNA probes are not yet used operationally to identify adult flies, although several are available and others are being developed (see section 7.4). Dissection results are recorded on forms and then stored on computer by means of epidemiological software.

12.2.4 *Transmission indices*

The identification and dissection of adults provide a method of determining parity, infection and infectivity rates at a given catching site.

The fly density and the level of transmission of onchocerciasis at a given location are quantified by two entomological indices, namely the annual biting rate and the annual transmission potential, which are calculated from the data collected by the entomological evaluation network.

The annual biting rate is the theoretical total number of bites that would be received in one year by a person stationed at a capture point for 11 hours a day. It is calculated by adding together the monthly biting rates established for each capture point.

The annual transmission potential is the theoretical total number of infective larvae (third-stage larvae in the heads of the blackflies) that would be received in 1 year by an individual stationed at a capture point for 11 hours a day. It is calculated by adding together the monthly transmission potentials.

These are good comparative indicators of the entomological situation. In the savanna areas of West Africa, entomological results are considered satisfactory when the first is less than 1000 and the second less than 100.

12.3 Evaluation of control

By means of epidemiological evaluation, progress towards programme objectives can be measured and the improvements needed to meet those objectives identified. Regular evaluation of the activities of an onchocerciasis control programme is necessary if it is to be successfully implemented and a satisfactory outcome achieved. Clear objectives need to be set and indicators defined whereby progress towards these objectives can be regularly measured and assessed. Three main indicators are of general importance in the evaluation of control programmes, namely impact, output and management indicators. These indicators generally need to be measured regularly, although it may often not be easy to measure all of them.

12.3.1 *Evaluation of impact*

The methods of epidemiological evaluation used for measuring the impact of different strategies employed in onchocerciasis control are summarized in Table 10. Further details are given below.

Population and location
The indicator villages selected for the evaluation are, as far as possible, those nearest to a productive breeding site; they are normally "first-line" villages.

In any long-term longitudinal epidemiological evaluation, the choice of village should take into consideration the mobility and size of the population to be evaluated. A population size of about 300 inhabitants has been considered ideal.

Parasitological examination
Evaluation of the impact of onchocerciasis control has been based on the assessment of trends in community microfilarial load and in the prevalence of infection which provide a measure of the regression of the reservoir of infection. Another indicator used is the incidence of infection, which reflects the level of transmission of infection. However, this last indicator is unsuitable for use in adults because of the inability of any parasitological test to distinguish between old and new infections; infection rates in children born after control has been started are therefore used. A comparison between the observed rate and the expected rate of incidence in the absence of onchocerciasis control then provides a measure of the reduction in onchocerciasis transmission.

Alternatively, the incidence of infection can be estimated from the changes in the prevalence (measured by skin snip) of the disease in children qualifying for ivermectin treatment for the first time each year.

Ophthalmological examination
Detailed ophthalmological examinations may be carried out in selected groups of villages to determine both microfilarial counts in the eye and trends in community microfilarial loads in the eye, which reflect the intensity of infection. Changes in the typical onchocercal eye lesions can also be demonstrated.

The main limitations of ophthalmological examinations are the need for specialized equipment and highly trained personnel and the high cost involved. To avoid problems with observer variation, it is recommended that eye lesions should also be photographed.

Clinical examination
Changes in the skin lesions occurring in a defined population may be assessed using a standardized method of classification in conjunction with photography.

Table 10
Epidemiological evaluation of the impact of onchocerciasis control

Control strategy and objectives	Objectives of epidemiological evaluation	Current methods		Preferred method
		Approach used	Measurements	Limitations	
Ivermectin treatment for morbidity control	Assessment of the impact on ocular and skin disease	Ophthalmological and clinical examination	Longitudinal follow-up of eye and skin changes with photographic records	Expensive Difficulty of inter- and intra-observer variation Time-consuming	Ophthalmology (currently available)
Elimination of the parasite reservoir by vector control and/or ivermectin treatment	Assessment of the impact on transmission	Parasitological examination using the skin-snip method	Measures of incidence in non-infected, non-treated individuals	Low sensitivity of skin snips in early and light infections	Serology (at operational testing stage)
Recrudescence control	Detection of new infections	Parasitological examination using the skin-snip method	Measures of incidence of new infection	Low sensitivity in early and light infections Inability to detect prepatent infections	Serology (at operational testing stage)

Other methods

Two potentially useful methods for the epidemiological evaluation of onchocerciasis control are:

– immunodiagnostic methods (see section 7.5) to detect early and prepatent infection (*32*); and
– the use of the polymerase chain reaction to detect parasite DNA in vectors (see section 7.4).

12.3.2 *Evaluation of output*

Evaluation of output may be very important; for example, evaluation of the output of a large-scale chemotherapy programme may serve as an indirect measurement of the programme's impact where baseline data based on skin snips do not exist, as in some endemic countries outside the OCP area.

Output indicators may include the percentage coverage of the target population to be treated, the correctness of execution of ivermectin distribution, the results of monitoring adverse reactions, and the degree of success of health education in the communities concerned. These measures, which show the extent to which the targets of the programme are attained, provide a measure of its success and give an indirect indication of the progress made towards the attainment of the overall objective, e.g. the prevention of onchocercal blindness, onchocercal skin lesions or lymphatic disease.

12.3.3 *Evaluation of management*

Evaluation of the management of a programme is also crucial to its successful outcome. Possible indicators include matters related to planning and decision-making, health management and information systems, supervision and monitoring of programme activities, and progress towards the full integration of programmes into the primary health care system and sustainability.

12.4 Suggestions for further study

- Traps for female flies searching for a blood-meal should be developed.
- DNA probes need to be perfected for field use in distinguishing different members of *Simulium* species complexes, particularly at the adult stage.
- Methods should be developed for the mass screening of blackfly populations with DNA probes to identify *O. volvulus* infective larvae, together with the mathematical techniques needed to transform data derived from the use of such probes into transmission indices useful in establishing and monitoring control programmes.

13. Sustainability of ivermectin distribution programmes

13.1 Introduction

Donor organizations and ministries of health throughout the developing countries have, over the past decade, become increasingly committed to health services delivery programmes that are sustainable, cost-effective and integrated horizontally within the overall health care system. Ivermectin distribution programmes are no exception, but present a number of unique issues that must be addressed if the goal of sustainability is to be realized, as follows:

- Ivermectin is provided free of charge by the manufacturers, Merck and Co., Inc., through the Mectizan Donation Program for active mass distribution or through the Merck Humanitarian Program for the treatment of individuals and small isolated populations. While these donations have served as a catalyst for increased ivermectin delivery, the actual resources needed for delivering the drug to people must still be found.
- Initially, the major costs of drug distribution were borne by a variety of external donors, but mainly by NGOs. The commitment of NGOs has been crucial to the dramatic expansion of ivermectin distribution, but is unlikely to continue indefinitely.
- Above a certain level of endemicity, active mass distribution of the drug to eligible persons (with due regard for the exclusion criteria) must be carried out at least once a year for 10 years or more. This requirement for regular, long-term distribution of the drug makes it even more important that ivermectin programmes meet the criteria of cost-effective sustainability.

13.2 The parties concerned

A number of constraints on the sustainability of ivermectin distribution programmes stem from the conditions imposed by the various parties concerned, namely:

- the supplier of the drug, Merck and Co., Inc., and its advisory body, the Mectizan Expert Committee;
- the donors providing financial support for distribution programmes;
- ministries of health and the different levels of health systems;
- the afflicted populations themselves, in terms of their accessibility and their compliance with the treatment regimen.

13.2.1 The manufacturers

The manufacturers are concerned that the exclusion criteria for ivermectin treatment (see section 8.2.1) are observed, that there is adequate provision to deal with severe adverse reactions, and that drug stocks are properly managed and controlled. In more remote endemic areas, it is often difficult

to comply rigidly with these conditions, but more than 19 million doses of ivermectin have now been given to treat onchocerciasis without a single serious, life-threatening mishap. It has therefore proved to be such a safe drug that strict observance of some of the exclusion criteria and the initial requirements for intensive monitoring for adverse reactions may eventually become less important. Already, the Mectizan Expert Committee, and through it Merck and Co., Inc., have shown increasing willingness to accommodate methods of simplifying field distribution (e.g. through measurement of body height instead of body weight).

13.2.2 *The donors*

Donors have generally sought, as early as possible, to establish a secure long-term financial and managerial base for ivermectin distribution programmes, *inter alia*, by specific provision for ivermectin distribution and onchocerciasis control in the central or regional budgets of the health services.

Donors also want to establish effective health education and information programmes so as to create and maintain a demand for treatment. Such health education must be directed not only at communities, either directly or via their leaders, but also at teachers, school attenders and health workers at all levels. Public information campaigns are also needed.

13.2.3 *The ministries of health and the health services*

Ministries of health are constrained by shortage of funds and of trained personnel; they face a multitude of health problems, all competing for limited resources. In general, they do not favour vertical programmes of health care delivery which are liable to founder when donor interest declines. One possible alternative is to develop self-sustaining horizontal programmes, integrated with the primary health care systems or other health care delivery programmes.

13.2.4 *The inhabitants of the infected communities*

The recipients of ivermectin often have little understanding of onchocerciasis. The significance and benefits of treatment must therefore be emphasized so as to ensure that regular annual treatment comes to be regarded as traditional and a demand for its continuation is thereby created.

13.3 Establishment of sustainable programmes

The prerequisites for the creation of sustainable ivermectin distribution programmes are as follows:

- Ministries of health must be involved in the earliest stages of programme design and implementation. There must be a clear agreement between

donors and governments about the strategy and the timetable for full assumption of financial and administrative responsibilities by the government.

- The public health and socioeconomic importance of onchocerciasis in the country concerned must be adequately assessed and perceived as a priority.
- A national plan for the control of onchocerciasis should be drafted and should include provision for epidemiological mapping, using the new rapid assessment techniques, and for different methods of distribution.
- Agreements with appropriate agencies and NGOs for the initiation of ivermectin distribution programmes need to be drawn up.
- Surveys of knowledge, attitudes and perceptions should be undertaken in affected communities. These will serve to determine the degree of understanding of onchocerciasis in affected communities, to guide the development of health education programmes, and to assist in creating a tradition of, and a demand for, annual treatment.
- Health education and training programmes, particularly at the village level, must be instituted. This will involve the establishment of village health committees and the training of community-based distributors of ivermectin.
- The mechanisms, conditions and the lag-time involved in applying for ivermectin supplies through the Mectizan Expert Committee need to be understood.
- The commitment of ministries of finance to facilitating the importation of ivermectin free of duty is crucial.
- Ivermectin distribution programmes must be integrated within the primary health care system or with other systems of health care delivery.
- Ivermectin distribution programmes must be cost-effective and should include the establishment of acceptable cost-recovery systems; it must be emphasized that payment covers only the distribution costs and not the cost of the drug itself.

13.4 Cost-effectiveness

Countries in which onchocerciasis is endemic typically have limited resources available for health services delivery. In addition, because of the nature of the onchocercal parasite, ivermectin may need to be given annually for many years. A primary determinant of an ivermectin programme's sustainability, therefore, is its cost-effectiveness. As a result, ministries of health, NGOs, donors and others continue to focus carefully on cost-effectiveness analysis. This, however, is not simple to perform, as demonstrated by the wide range of results obtained from studies of the cost of existing ivermectin distribution programmes, which suggest that the cost per year per person treated may be as low as US$ 0.10 or as high as US$ 5.00.

This wide range of cost estimates is a direct reflection of the lack of consistent, comparable budgets for different ivermectin distribution programmes and the absence of a uniform formula for cost per treatment. Factors that can contribute significantly to variability include capital expenditures, start-up cost versus long-term running costs, salary, travel expenses, etc. for outside experts, and the cost of reaching different target populations. Ivermectin programme budgets and the formula for assessing cost per treatment need to be standardized so as to ensure that cost analyses are both comparable and reliable.

If ivermectin distribution programmes are to be sustained, ministries of health, donors, NGOs and others must have consistent, reliable and comparable financial data in order to make decisions about the allocation of resources. In addition, operational research designed to evaluate the relative cost-effectiveness of different delivery strategies needs to be increased; such research also requires uniform budgeting and reporting methods.

Initiatives are currently under way in WHO, the Mectizan Donation Program, and elsewhere to address this problem.

14. Training

As regards training in onchocerciasis control, WHO has up to now emphasized the training of young scientists in developing countries; in particular, those in the field of medical entomology at the MSc level have been supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. In Africa and the Americas, certain universities have been identified as training centres and supported by the provision of both resource persons and training materials; several continue to receive such support.

Human resource development has traditionally played a key role in most activities designed to control vector-borne disease so as to ensure that staff are capable of fully carrying out their responsibilities, and onchocerciasis control is no exception. In the OCP, for example, more than 400 fellow-ships have been awarded since 1974 and approximately 45% of the recipients have received specialized training in medical entomology and related areas. The trainees have for the most part been employed in ministries of health and have continued to work in their areas of expertise.

In countries outside the OCP area, the emphasis in onchocerciasis control is no longer on vector control but on chemotherapy. Capacity building and human resource development must be an integral part of programmes in such endemic countries if sustainability is to be achieved.

Public health workers should be the target of training activities, emphasis being placed on applied epidemiology and health service management, especially at the district level. Centres in endemic countries should be identified and provided with training and health education materials

suitable for short courses or workshops aimed at developing local expertise, e.g. by training trainers. Consultants from national, regional and international bodies, and having a broad range of experience, can run such courses. On the successful completion of training, staff will be responsible for planning, organizing, supervising, or monitoring and evaluating large-scale chemotherapy for the control of onchocerciasis.

Training should be aimed at developing the capacity for sustainable control. It should cover all the disciplines required in control programmes, including epidemiology, mapping, biostatistics, medical entomology, clinical chemotherapy and social science. In addition, since new techniques, involving immunological assays in humans and parasite DNA detection in blackflies are likely to be used in the future for monitoring the effectiveness of control programmes, the training of some individuals in the basic laboratory skills needed in using these techniques will be necessary.

14.1 Types of training

The various types of training required include: continuing education; in-service training; courses for community health workers, district-level medical personnel and administrators; and degree-level and postgraduate education.

The need for continuing education and training at all levels is particularly important in the light of the increasing attention being given to environmental health issues, human behavioural, social and cultural factors, changing patterns of epidemiology, community participation in drug distribution, insecticide monitoring and resistance, rotation of insecticides, expanded disease and vector surveillance, threats of vector reinvasion, and other important topics.

14.1.1 In-service training

Training can sometimes be provided within programmes for certain types of specialist whose work is not highly technical but who would benefit from greater exposure to programme activities on a broader range of subjects. Such training can be provided in a series of in-service training seminars in which use can be made of specific training information, manuals and audiovisual aids, such as slides, graphs, videos and interactive educational programmes.

14.1.2 Community health workers

Health personnel at the community level should be trained to distribute ivermectin correctly to eligible communities, manage any adverse reactions which may occur, and keep records of their activities. They should also be trained to explain why regular drug treatment is necessary and make people aware of its benefits.

14.1.3 *District-level medical personnel*

Nurses may be trained to supervise the activities of village health workers, check records, provide the necessary support and, if necessary, manage adverse drug reactions. Where applicable, district medical officers should be trained to supervise ivermectin distribution.

14.1.4 *Health administrators*

More specialized training for health administrators can be provided through short courses or at postgraduate level. Such training may require financial support from donor countries or NGOs and should be carried out at existing training institutions on a country, intercountry or regional basis.

A vital aspect of continuing education is the creation of career structures at the country level for staff who have been trained in this way so as to provide them with the possibility of promotion and thus retain them in their countries of origin after their training. The necessary courses can be organized on a subregional basis, so that individuals from several national programmes can participate in them. Training modules, protocols and associated materials can be developed in conjunction with the OCP and with national and regional programmes. The usefulness of such training can be measured by the number of staff who, following training, return to their countries of origin and continue working in their chosen field.

14.2 Training materials

The development of training aids, including manuals, audiovisual aids and interactive educational programmes, should be a priority in each country and regional onchocerciasis control programme, as well as of the OCP, with the emphasis on locally applicable materials and those which can be adapted to specific training needs. Some training materials prepared for use in existing disease control programmes but capable of being modified and adapted, as necessary, for onchocerciasis control, may be suitable in this context.

14.3 Implications of devolution in the OCP area

OCP will cease operations by the year 2000, with devolution of responsibility for onchocerciasis control to the individual participating countries. It has become clear that most staff released from central OCP activities and returning to their home countries wish to continue working in their specialized field. It is important, therefore, that such staff should be trained in broader subject areas of public health in order to improve their qualifications and ensure the utilization of the much-needed health-related skills that they have developed.

15. Conclusions

1. Never have more tools, expertise and resources been available for the control of onchocerciasis. Control programmes based on ivermectin distribution have been established in many regions where no programmes existed before. It is important to ensure that the current momentum is not lost but is instead sustained or increased to take advantage of the unique window of opportunity for the control of this disease.

2. The advent of ivermectin, the initiation of the Mectizan Donation Program, and the participation of ministries of health, NGOs, WHO and other collaborating agencies in ivermectin distribution programmes have led for the first time to effective large-scale campaigns for the control of onchocerciasis morbidity.

3. The availability of ivermectin has also stimulated the development of rapid epidemiological assessment and mapping methods for onchocerciasis, which are now being used outside the OCP area to determine more accurately the distribution of the disease and to identify communities that would benefit from mass treatment.

4. In the sub-Saharan savanna outside the OCP area, onchocerciasis continues to be a major cause of blindness and of great socioeconomic importance. Several of the countries concerned – Cameroon, Central African Republic, Chad and Nigeria – have undertaken large-scale ivermectin distribution programmes requiring considerable external support, an effort that must be sustained. In other countries, no such programmes are in place, although they are urgently needed and should be appropriately supported.

5. It is becoming increasingly clear that, in many areas in which onchocerciasis is present, aspects of the clinical disease itself, for instance onchocercal dermatitis, can provoke important psychosocial responses. These findings require further definition.

6. The prevalence of infection and blindness has declined dramatically in the original OCP area. On the other hand, in several countries, notably Equatorial Guinea and Uganda, recent surveys undertaken in preparation for ivermectin-based control programmes have revealed a much higher prevalence of onchocerciasis than was previously thought to exist.

7. Recent research studies supported by OCP, the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, and others have resulted in significantly greater understanding of the biology of *O. volvulus*, its dynamics within the host, its response to chemotherapeutic agents, and the genetic differences between strains of different pathogenic potential.

8. As it enters its final phase, OCP continues to advance towards its original goal by maintaining effective vector control (for the

interruption of transmission) and integrating ivermectin treatment (for morbidity control) into its overall control strategy. With devolution now in progress, the ultimate success of the OCP will depend on the ability of participating countries to maintain and consolidate its past achievements.

9. The creation in the Americas of the Multinational Strategic Plan of Action toward Onchocerciasis Elimination has led to the establishment of a multinational, multiagency and multidonor coalition, the Onchocerciasis Elimination Program in the Americas, to support and coordinate national onchocerciasis control plans in the six countries of Latin America in which the disease is endemic, with the aim of eliminating onchocerciasis as a public health problem.

10. Ivermectin distribution programmes, to be sustainable, must be cost-effective and, wherever possible, integrated into the primary health care system.

11. Ivermectin programme budgets and the formulae for assessing cost per treatment must be standardized so as to ensure that cost analyses are both comparable and reliable.

16. Recommendations

1. Endemic countries in which knowledge of the distribution and severity of onchocerciasis is still insufficient should give priority to rapid epidemiological assessment and mapping in order to facilitate the planning of national control programmes.

2. All endemic countries should undertake ivermectin distribution programmes for onchocerciasis control and integrate them into primary health care; these programmes should include a built-in evaluation component from the outset so as to assure sustainability on a cost-effective basis.

3. Further research is urgently needed to determine the psychosocial and economic impact of onchocercal dermatitis and lymphatic disease, especially in areas where there is little onchocercal blindness but where these other conditions are common.

4. Research on the development of a safe, effective macrofilaricidal drug for onchocerciasis should be intensified.

5. Further research should be conducted, in the context of existing control programmes, on the long-term impact of repeated ivermectin treatment on *O. volvulus*, its transmission, and associated morbidity and immune responses.

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Annex
A clinical classification and grading system for recording the cutaneous changes of onchocerciasis[1]

Notes on using the classification scheme

(i) Absolute criteria for recording the presence of each clinical category are given in boxes in bold type. The absolute criteria are summarized again at the end of each clinical section.

(ii) For activity grading, excoriations are defined as scratch marks with breach of the surface of the skin (loss of epidermis +/- dermis) resulting in current or previous bleeding or loss of serous fluid. Superficial scaling alone is not recorded.

(iii) For distribution grading, the following may each be considered as individual anatomical sites (see Fig. A1):

1.	one or both shoulders;	8.	right leg;
2.	back;	9.	left leg;
3	one or both buttocks;	10.	right groin;
4.	anterior chest;	11.	left groin;
5.	abdomen;	12.	head and neck;
6.	right arm;	13.	perineum.
7.	left arm;		

If desired, the anatomical sites involved may be specified by allowing separate computer fields for each of them.

I. Acute papular onchodermatitis (APOD)

General description. Acute papular onchodermatitis consists of small, widely scattered pruritic papules which progress to vesicles and pustules in more severe cases. Erythema and oedema of the skin may also be present, affecting a single limb or area of the trunk or face. Oedema of a limb with the papular eruption accentuated on that limb may be seen. A similar clinical pattern is seen post-dosing with antimicrofilarial drugs such as diethylcarbamazine or ivermectin. APOD may also develop in an individual from an area non-endemic for onchocerciasis after visiting an

Figure A1

Body map showing anatomical sites for use in distribution grading of cutaneous changes of onchocerciasis (see notes on using the classification scheme)
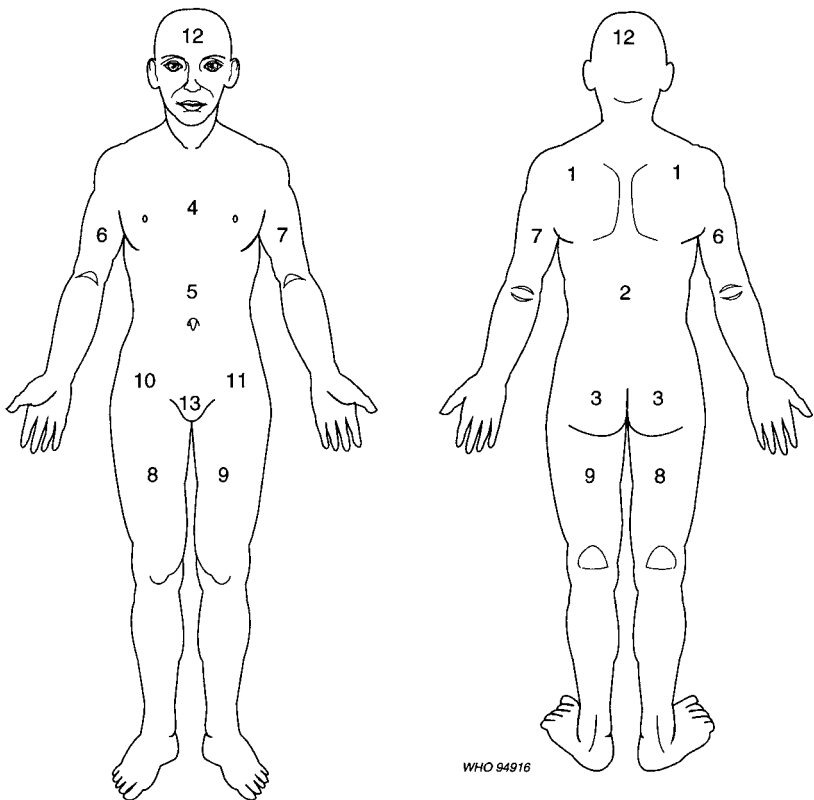
endemic area. In this situation, oedema of a limb or area on the trunk may be found alone or in association with a subtle, urticated papular eruption.

Sites of predilection: shoulders, arms, trunk or elsewhere.

Grade	Clinical features
Severity grading	(Key features in boxes)
0	APOD absent
1	APOD present

> **(a) small 1–3-mm-diameter solid scattered papules**
>   ***and***
> **(b) lesions itchy**

+/– (c) accompanying diffuse oedema obliterating normal skin creases

2

<div style="border:1px solid">

a + b (as above) plus additional sign:
(d) small 1–3-mm-diameter vesicles or pustules at apex of papules

</div>

+/– (c) as above

Activity
grading
    0   No itching
    1   Itching but no excoriations
    2   Excoriations present

Distribution
grading
    0   APOD absent
    1   Only one anatomical site involved (e.g. shoulders)
    2   More than one anatomical site involved (e.g. shoulders and buttocks)

Absolute criteria for APOD = (a + b) or (a + b + d)

II.   Chronic papular onchodermatitis (CPOD)

General description. The skin lesions are scattered flat-topped papules which vary greatly in size (from approximately 3 to 9 mm in diameter) and height above the skin surface (some lesions are almost macular, others are elevated up to 5 mm). Itching occurs in some lesions but is not a constant feature. Post-inflammatory hyperpigmentation is characteristic. Individuals with this type of skin disease may also have acute lesions and other changes due to onchocerciasis.

Sites of predilection: buttocks, waist area, shoulders or elsewhere.

Severity
grading
    0   CPOD absent
    1   CPOD present

<div style="border:1px solid">

(a) papules larger than those in APOD but variable in size and height and often flat-topped *and*
(b) lesions itchy (except in late resolving stage) *and*
(c) eruption hyperpigmented compared with surrounding skin and macular areas of post-inflammatory hyperpigmentation common

</div>

Activity
grading
    0   No itching
    1   Itching but no excoriations
    2   Excoriations present

Distribution
grading
    0   CPOD absent
    1   Only one anatomical site involved (e.g. buttocks)
    2   More than one anatomical site involved (e.g. buttocks and shoulders)

Absolute criteria for CPOD = (a + (b) + c)

III. Lichenified onchodermatitis (LOD)

General features. Lichenified onchodermatitis tends to be a regular feature of onchocerciasis in certain geographical areas such as Sudan and Yemen although it is seen less frequently elsewhere. Teenagers and young adults are typically affected. The main characteristics are pruritic, hyperpigmented, hyperkeratotic plaques. With increasing severity the plaques become more confluent. The distribution is usually asymmetrical and may involve one limb (sowda). The draining lymph nodes are often enlarged. In later stages the skin is grossly lichenified, but in some patients this may revert to a normal (though hyperpigmented) or atrophic skin over a number of years, with or without treatment. Itching is very intense in the acute stage. Acute or chronic papular onchodermatitis may coexist with lichenified onchodermatitis.

Sites of predilection: one or both legs, sometimes elsewhere.

Severity
grading
    0   LOD absent
    1   LOD present

> **(a) raised, discrete papulonodules or plaques of thickened skin *and***
> **(b) skin noticeably darker than surrounding skin (unless surrounding skin is itself intensely pigmented)**

+/- (c) one side may be more severely affected than the other (as in sowda)
+/- (d) active lymphadenopathy of draining lymph nodes may be present

    2

> **(a) + (b) (as above) plus additional sign:**
> **(e) plaques of thickened skin are partially confluent**

+/- c, +/- d as above

3

> (a)+(b) (as above) plus additional sign:
> (f) plaques have become confluent over large areas giving the appearance of grossly thickened skin

+/- (c), +/- (d) as above

Activity
grading
    0   No itching
    1   Itching but no excoriations
    2   Excoriations present

Distribution
grading
    0   LOD absent
    1   Only one site affected
    2   More than one site affected

Absolute criteria for LOD = (a+b) or
(a+b+e) or
(a+b+f)

IV. Atrophy (ATR)

General description. Atrophic skin adopts many of the characteristics of aging, such as loss of elasticity and contours, and the skin appears excessively wrinkled. Hairs may be lost and sweating in affected areas is reduced. In order to avoid confusion with senile atrophy, ATR is only scored as a significant abnormality in individuals aged less than 50 years.

Sites of predilection: buttocks, less commonly limbs.

Atrophy is recorded as present or absent.

Severity
grading
    0   ATR absent
    1   ATR present

> (a) skin appears wrinkled and dry *and*
> (b) when the edge of a finger is pushed firmly along the skin, many additional fine wrinkles appear on the surface

(c) skin is easily lifted in certain sites between the thumb and forefinger; it returns to the normal position slowly on release
(d) there is usually no itching
(e) small wounds and cuts may bleed for a long time and heal slowly
(f) the skin appears prematurely aged in younger persons

Distribution
grading
    0   ATR absent
    1   Only one anatomical site involved (e.g. buttocks)
    2   More than one anatomical site involved (e.g. buttocks and legs)

Absolute criteria for ATR = (a + b)

V. Depigmentation (DPM)

General description. Onchocercal depigmentation is often described as "leopard skin". Patches of complete pigment loss are seen, with islands or "spots" of normally pigmented skin centred around hair follicles. The surrounding areas of skin may be normal or hyperpigmented. Lesions are rarely itchy and are flat or slightly depressed. Sometimes the skin is not fully depigmented and is seen as yellow-brown areas on black skin. Such lesions may represent early or incomplete depigmentation.

Sites of predilection: shins, less commonly lateral groins, lower abdomen.

Severity
grading
    0   DPM absent
    1   DPM present

> **(a) areas of incomplete pigment loss with islands or "spots" of normally pigmented skin centred around hair follicles**

    2

> **(b) areas of complete pigment loss with islands or "spots" of normally pigmented skin centred around hair follicles**

          (c) absence of itching

Distribution
grading
    0   DPM absent
    1   Only one anatomical site involved (e.g. one shin)
    2   More than one anatomical site involved (e.g. both shins)

Absolute criterion for DPM = (a) or (b)

The following changes associated with onchocercal skin disease may also be recorded simply as follows:

VI. Palpable onchocercal nodules

0	Nodules absent
1	Nodules present

N.B. The site of the nodules may be documented on a diagram, with each point representing a single nodule or single cluster of adjoining nodules. If desired, the location of nodules may be recorded for computer entry by noting the number of discrete nodules or discrete nodule masses for each of the following anatomical sites: head, neck, right arm, left arm, upper trunk (above umbilicus), right axilla, left axilla, lower trunk (below umbilicus), right iliac crest, left iliac crest, right trochanter, left trochanter, right groin, left groin, right buttock, left buttock, sacrum, right knee, left knee, right ankle, left ankle, right foot and left foot.

VII. Lymphadenopathy

0	Lymph nodes not greater than 1 cm diameter
1	Lymph nodes greater than 1 cm diameter, non-tender
2	Lymph nodes greater than 1 cm diameter, tender

N.B. The site of lymphadenopathy may be specified if desired.

VIII. Hanging groin (HG)

Hanging groin(s) are unilateral or bilateral folds of skin present in the inguinal region. These are inelastic and may contain enlarged lymph nodes.

0	HG absent
1	Early HG with inguinal or femoral lymph nodes grossly protuberant
2	HG present, with loose, redundant folds of atrophic skin +/– palpable inguinal or femoral lymph nodes

IX. Lymphoedema (LYM)

0	LYM absent
1	LYM of limb present
2	LYM of the external genitalia present

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