THE EPIDEMIOLOGY AND CONTROL OF ONCHOCERCIASIS IN WEST AFRICA

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THE EPIDEMIOLOGY AND CONTROL OF ONCHOCERCIASIS IN WEST-AFRICA

De epidemiologie en bestrijding van onchocerciasis in West Afrika

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Aan mijn ouders

Aan: Marge
Wande
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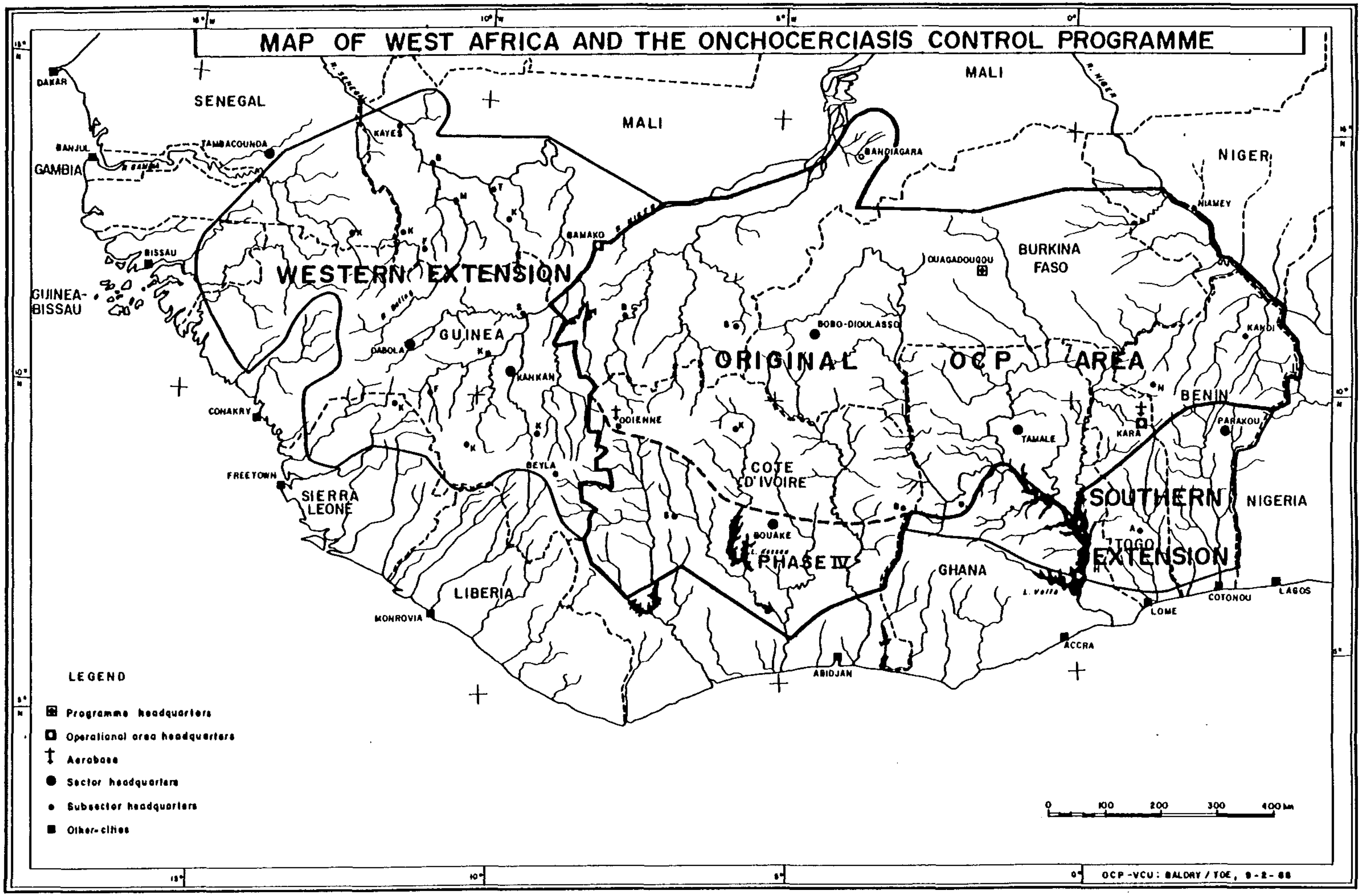
List of abbreviations and specific terms used in onchocerciasis epidemiology

ABR	Annual Biting Rate: estimated number of *Simulium* bites a person at a catching point would receive per year
ATP	Annual Transmission Potential: estimated number of L3 which would have been transmitted to a person at a catching point per year
choroido-retinitis	inflammation of the choroid and retina of the eye
CMFL	Community Microfilarial Load, i.e. the geometric mean mf/s among persons aged 20 years or more.
CMFL/AC	the geometric mean MFAC among persons aged 20 years or more.
CMFL/C	the geometric mean DMFC among persons aged 20 years or more.
DMFC	dead mf in the cornea
force-of-infection	the probability of (super)infection per unit of time
holo-endemic	community with a CMFL > 40 mf/s
hyper-endemic	community with a prevalence of skin snip positives > 60%
host-parasite model	an epidemiological model which describes the dynamics of the parasite and its reproduction in a human host population
infective flies	flies harbouring infective (L3) *O.volvulus* larvae
iridocyclitis	inflammation of the iris and the ciliary body of the eye
ivermectin	new microfilaricide registered in 1987 under the proprietary name Mectizan™ for the treatment of human onchocerciasis
L1	larval stage of *O.volvulus* in the vector before the first moult
L2	larval stage of *O.volvulus* between first and second moult
L3	larval stage of *O.volvulus* following second moult in the vector. This is the infective stage which may be transmitted to man
larvicide	an agent for killing the aquatic larval stages of the vector
LMFC	living mf in the cornea
longevity of an infection	period between inoculation of L3 and death of the last mf due to this onchocerciasis infection
mf	microfilariae, i.e. the offspring of the adult *O.volvulus*
mf/s	mf per skin snip
MFAC	mf in the anterior chamber of the eye
microfilaricide	chemotherapeutic agent which kills microfilariae
nodulectomy	surgical removal of subcutaneous nodules containing adult *O.volvulus*
OCP	Onchocerciasis Control Programme in West Africa
Onchocerca volvulus	the filarial nematode which causes onchocerciasis
(an) onchocerciasis infection	inoculation of L3 larva and the subsequent development of one adult fertilized female worm which produces mf
optic atrophy	degeneration of the optic nerve
pre-patent period	period between inoculation of L3 and first appearance of mf in the skin due to this onchocerciasis infection
reinvasion	long distance migration of vectors, which are often highly infective, into a controlled area
sclerosing keratitis	opacification of the cornea following corneal inflammation
Simulium damnosum s.l.	the vector of onchocerciasis in West Africa (the blackfly) consisting of several sibling species. The most important are the savanna vectors *S.damnosum* s.s. and *S.sirbanum*, and the forest vectors *S.soubrense*, *S.sanctipauli*, *S.yahense* and *S.squamosum*.
skin snip	skin biopsy for microscopic examination for presence of mf
SSPH	Severe Symptomatic Postural Hypotension
superinfection	a new onchocerciasis infection in a person who already is harbouring at least one onchocerciasis infection



MAP OF WEST AFRICA AND THE ONCHOCERCIASIS CONTROL PROGRAMME

Chapter 1

Introduction and Study Objectives

INTRODUCTION

Onchocerciasis is a major parasitic disease which is endemic in large parts of Africa and in isolated foci in Central and South America and in Yemen. It has been estimated that as many as 18 million people are infected with the parasite, the filarial nematode *Onchocerca volvulus*, and more than 99% of all infected people live in Africa. The adult worm produces millions of microfilariae which migrate into the skin of the human host. The parasite is transmitted by blackflies (Diptera, Simuliidae), which ingest microfilariae during a bloodmeal on man. In the flies, some of these microfilariae develop into infective larvae which can be transmitted to another person during a subsequent bloodmeal to develop into new adult worms. The microfilariae are the main cause of the clinical manifestations of the disease which include dermal, lymphatic and systemic complications. However, the most severe complications are onchocercal lesions of the eye which may ultimately lead to total blindness. The World Health Organization estimates that some 340,000 people are blind as a result of onchocerciasis. The majority of the onchocercal blind are found in the West and Central African savanna belt where the disease is most severe. There, onchocerciasis is not only a major public health problem, but often also an obstacle to socio-economic development. Fear of the disease has led to the depopulation of relatively fertile river valleys where the vector of the disease, *Simulium damnosum* s.l., has its breeding sites and where transmission is most intense.

The possibilities for onchocerciasis control are limited. Until recently chemotherapy was not an option because the existing drugs for the treatment of onchocerciasis produced very serious adverse reactions which prevented their utilization on a mass scale. The only alternative was vector control through the application of larvicides to the rivers where the breeding sites of the vector are found. During the 1950s vector control was applied successfully in certain isolated foci in East Africa where the vector *Simulium neavei* s.s. was completely eliminated. But experiences in West Africa had shown that isolated vector control was not appropriate because of the wide distribution of the infection and the active migratory behaviour of the West African savanna vectors of the *Simulium damnosum* complex. The only possible approach was larviciding of all breeding sites over an extensive area and during a long period of time. This was the approach chosen for the Onchocerciasis Control Programme in West Africa (OCP) when it was launched in 1975 in the Volta river basin area which, at that time, was the most severely affected region in the world.

The strategy of the OCP is to interrupt transmission by vector control for a period in excess of the maximum duration of onchocerciasis infection in the human host. The vector is kept at bay until the parasite reservoir in the human hosts has died out naturally. Based on very limited information from the East African control programmes on the longevity of onchocerciasis infection in man, the Programme was initially planned to last for a period of 20 years. The long term objective of the OCP is "to control onchocerciasis as a disease of public health and socio-economic importance and to ensure that there will be no recrudescence of the disease thereafter".

During the first 8 years of larviciding from 1975 to 1983, vector control was quite successful in most of the Programme area according to the results of the entomological evaluation. The major problem was reinvasion of the border areas by infective vectors from outside the OCP and it became clear that the capacity for long distance migration of the savanna vectors *S.damnosum* s.s. and *S.sirbanum* had been greatly underestimated. The implication was that the Programme had to be extended and preparatory studies for extensions were started.

In 1983 the Programme faced two major unresolved epidemiological questions which were of utmost importance for both the short and long term planning of onchocerciasis control in the OCP.

The first question concerned the geographical distribution of different epidemiological patterns of ocular onchocerciasis in West-Africa. It had long been recognised that extreme onchocercal blindness rates in excess of 5% were found only in hyperendemic savanna areas but never in the forest. The most generally accepted explanation was that the parasites in these zones belonged to different strains with different pathogenicity. For large parts of the pre-forest and forest zones, however, it was not clear if the lesser severity of ocular disease was due to a forest form of onchocerciasis or if it concerned the 'blinding' savanna form of the disease but at a low level of endemicity. Since the mandate of the OCP was limited to the control of the severe 'blinding' form of onchocerciasis, the solution of this problem was of direct operational importance because it would determine which areas were to be included in the vector control operations. A decision was most urgently needed on the boundary of larviciding operations in southern Ivory Coast where the main vectors, which belonged to the *S.soubrense/sanctipauli* subcomplex and which bred in the large forest rivers, had become resistant to the larvicide of choice, temephos. Their control throughout southern Ivory Coast using alternative larvicides would be an extremely expensive undertaking, if at all it was possible.

The second question concerned the epidemiological impact of vector control. Epidemiological surveys had been undertaken at intervals of 3-4 years in more than 150 indicator villages which represented all the major river basins in the original Programme area. Each survey had included skin snip examinations for the presence and intensity of *O.volvulus* microfilariae. However, the routine analysis of these data had, after 8 years of control, not yet provided clear evidence of interruption of transmission and had shown no important decline in the parasite reservoir. No children below the age of 5 years were found to be infected, but not many infections would have been expected in this age group even if there had been no control. The standardized prevalence of microfilariae in the skin snip, which was at that time the current epidemiological index, had shown only a limited decline during the first eight years of control. To most observers these results appeared to be unsatisfactory and the question was raised if vector control really had interrupted transmission and if reinfection was not still occurring at an undetected but nevertheless significant level. Others, who were willing to take the entomological evaluation data as evidence of interruption of transmission, were worried about the slow decline in infection levels and became concerned about the required duration of vector control and the cumulative costs involved in the expensive aerial larviciding operations. For long term planning and financing of the Programme it was therefore urgent to arrive at a better understanding of the epidemiological impact of vector control and to make credible predictions of the expected trends in onchocerciasis infection during the remaining control period.

In the mean time, in 1982, a promising development in the field of chemotherapy of onchocerciasis occurred when Aziz and his collaborators reported from a small clinical trial that ivermectin was an effective microfilaricide which was much better tolerated than the previous microfilaricide of choice, diethylcarbamazine (DEC). Though this report was initially received with skepticism, subsequent clinical trials confirmed the conclusion and the manufacturer of the drug informed the OCP in 1986 that it had started procedures for registration of ivermectin for the treatment of human onchocerciasis. At that stage it became urgent for the Programme to decide if it was going to use ivermectin in the control of onchocerciasis, and if so, how.

The answer to this question was not straightforward. Only a limited number of patients had been treated in the clinical trials in a hospital environment and there existed great uncertainty concerning the safety of the drug for mass treatment. Secondly, the OCP was a time limited programme which was achieving its objective through the interruption of transmission by vector control exclusively. A question of major operational importance, therefore, was to what extent ivermectin mass treatment could contribute to transmission control. Thirdly, the clinical trials had only demonstrated the microfilaricidal effect of the drug but not yet its effect on the prevention of onchocercal disease, in particular ocular disease. It was therefore obvious that further operationally oriented research was required before ivermectin mass treatment could be incorporated in the OCP strategy for onchocerciasis control.

STUDY OBJECTIVES

The present thesis deals with research which has been undertaken since 1983 with the aim of finding answers to the three main epidemiological questions which have been discussed above, i.e.

1.-What are the epidemiological patterns of ocular onchocerciasis in West Africa and what is the geographical boundary of the blinding, savanna, form of onchocerciasis

2.-What has been the epidemiological impact of vector control in the OCP and what are the predicted epidemiological trends for the remainder of the vector control period.

3.-What is the potential of ivermectin as a tool for onchocerciasis control.

Following a review of onchocerciasis in West-Africa in chapter 2, the research on ocular onchocerciasis patterns in different bioclimatic zones is discussed in chapter 3. Chapter 4 deals with the epidemiological evaluation of vector control, including the development and use of epidemiological models and research on the reproductive lifespan of *O.volvulus*. In chapter 5 the results of community trials of ivermectin are presented. Chapter 6 gives the general conclusions with reference to their practical implications for onchocerciasis control. Finally, a summary in English and in Dutch is provided in chapter 7.

GENERAL REFERENCES:

Merck, Sharp and Dohme. *Mectizan™, Product monograph.* Merck & Co. Inc. Rahway N.J. (1988)

WHO, UNDP, FAO and IBRD. Onchocerciasis control in the Volta River Basin Area. Report of the preparatory assistance mission to the governments of Dahomey, Ghana, Ivory Coast, Mali, Niger, Togo and Upper Volta. World Health Organization, Geneva, WHO/OCP/73.1 (1973) unpublished mimeographed document.

World Health Organization. WHO Independent Commission on the Long-term aspects of the Onchocerciasis Control Programme: Final report. OCP, Ouagadougou (1981) unpublished mimeographed document.

World Health Organization. *WHO Expert Committee on Onchocerciasis: third report.* WHO Technical report Series, No. 752 (1987)

Chapter 2

Onchocerciasis in West Africa: a Review

INTRODUCTION

The following article gives a review of onchocerciasis in West-Africa, with special emphasis on the demographic aspects of its epidemiology and control, and on the socio-economic importance of the disease. It is primarily included in this thesis to provide a background for the discussion of the three major research questions in the subsequent chapters. The review of vector-parasite complexes, blindness patterns and differences between bioclimatic zones is of direct relevance to chapter 3, while the sections on intensity of transmission and man-vector contact provide a basis for discussions on age specific epidemiological trends, epidemiological modelling and the impact of ivermectin treatment on transmission. The article contains also a description of the Onchocerciasis Control Programme in West-Africa.

Even though it concerns mainly a review, the article does include original epidemiological data for the pre-control period as well as epidemiological results of 12 years of vector control which complement the findings in chapter 4. Previously unpublished data on resettlement of the abandoned river valleys after 12 years of vector control are also presented and the article is concluded with a discussion of questions relating to the cessation of larviciding.

Chapter 2.1

Demographic aspects of the epidemiology and control of onchocerciasis in West Africa

In: Demography and Vector-borne diseases. (Ed.M.Service)
CRC Press Inc, Boca Raton Fl, 1989, Ch.24

INTRODUCTION.

Demography plays an important role in the epidemiology of onchocerciasis. Demographic factors influence the degree of man-vector contact and determine to a large extent the intensity of transmission and the severity of onchocerciasis in the community, while extreme blindness rates and excess mortality in the blind are important demographic consequences of the disease. A very specific characteristic of onchocerciasis is the way it affects human migration and settlement patterns and the disease has been directly responsible for serious underpopulation and underutilization of the land in many river valleys in the West African savanna.

Since these river valleys contain some of the most fertile soil in the savanna belt, onchocerciasis has been recognized to be not only a serious public health problem but also a major obstacle to socio-economic development. It was for these reasons that a large scale vector control programme was launched in 1975 in the savanna area of seven West African countries. The control programme has been extremely successful during the first 12 years of its operations. Not only has the disease been brought under full control in 90% of the original programme area, but the population has started to move into most of the initially underpopulated zones in the river valleys.

In this chapter on the demographic aspects of onchocerciasis, we shortly review the epidemiology of the disease, with special emphasis on factors influencing man-vector contact, and discuss onchocerciasis-related population movement and settlement patterns in the West African savanna during the pre-control period. Following a short description of the Onchocerciasis Control Programme (OCP) we give an overview of the epidemiological impact of the first 12 years of control, and present some of the latest results on migration and land utilization in the valleys where onchocerciasis was previously endemic.

DISEASE AND TRANSMISSION

The Parasite.

Onchocerciasis is caused by infection with the filarial worm *Onchocerca volvulus* for which man is the only known reservoir. The adult worms are usually found in subcutaneous nodules and have an average longevity which is presently estimated to be around 11-12 years (Karam et al 1987). The adult female worm produces millions of microfilariae which migrate to the skin of the host. The diagnosis of infection is usually based on the microscopic examination of skin snips for the presence and density of microfilariae. Though the skin snip method lacks some sensitivity in very light infections, it has been an invaluable tool in onchocerciasis epidemiology because of its highly specific results while it also provides a measure of the intensity of infection.

Clinical manifestations.

The microfilariae are the main cause of the clinical manifestations of the disease. These include dermatitis, resulting in severe itching, depigmentation and atrophy of the skin, and lymphadenitis which may lead to hanging groin and elephantiasis of the genitals (Buck 1976). However, the most severe complications of onchocerciasis are irreversible ocular lesions of both the anterior and posterior segment of the eye, resulting in impaired vision and finally in total blindness. The severity of the disease is closely related to the intensity and the duration of infection (WHO 1976). Occasional infections rarely result in demonstrable clinical signs and the incidence of severe pathology depends on the degree of superinfection, and on the corresponding increase in the density of microfilariae in the skin and in the eye. The risk of (super)infection, or force-of-infection, is a function of the intensity of transmission in the area concerned (Remme et al 1986). Hence, the severity of the disease and the intensity of transmission are closely related.

The Vector.

The parasite is transmitted by a blackfly, *Simulium damnosum* s.l., which ingests microfilariae during a bloodmeal on man. In the fly, some of these microfilariae develop into infective larvae which can be transmitted to another person during a subsequent bloodmeal and develop into new adult worms. The life-cycle of *O. volvulus* cannot be completed without this passage through the vector. The blackfly breeds in rapids in fast flowing water and consequently the transmission is most intense, and the disease most severe, in the river valleys. In West Africa *S. damnosum* s.l. consists of at least nine species of which six are common and widespread, all of which occupy different bioclimatic zones (Philippon 1977). *S. sirbanum* and *S. damnosum* s.s. are found throughout the West African savanna and are capable of long distance, wind-assisted migration over distances up to 400 km. *S. yahense* and *S. squamosum* breed in small streams in dense forest, but in addition *S. squamosum* can breed in medium-sized streams in forest and savanna areas: neither species migrates far. *S. sanctipauli* and *S. soubrense* are found predominantly along the large rivers in the forest areas, but *S. soubrense* also shows a limited distribution in the lower ranges of the savanna, the so-called intermediate zone or preforest zone. The members of the first pair, *sirbanum* and *damnosum* s.s., are usually referred to as savanna vectors and the flies of the other two subcomplexes as forest vectors.

Vector-parasite complexes.

For several decades it has been recognized that the epidemiological pattern of onchocerciasis, and in particular the severity of ocular disease, varies considerably between geographical zones (Duke et al 1966). The most striking is the difference in ocular pathology between the West African savanna and forest areas (Prost 1980). While onchocercal blindness can be rampant in hyper endemic communities in the savanna, virtually no blindness is found in forest villages with a comparable intensity of infection (Dadzie et al 1989). It is presently believed that the explanation lies in the existence of various *O. volvulus* strains of different pathogenicity. This hypothesis is supported by the results of recent studies, which have demonstrated genetic differences between parasite populations from a savanna and a forest focus (Cianchi et al 1985), and of older studies of the pathogenicity of microfilariae which had been injected into the rabbit eye (Duke and Anderson 1972). The geographical distribution of the "blinding" type of onchocerciasis coincides with the distribution of the two savanna vectors, *S. damnosum* s.s. and *S. sirbanum*, while no severe ocular onchocerciasis has been demonstrated in highly endemic villages in the Ivory Coast where *S. yahense* is the sole vector (Dadzie et al 1989). Crossed transmission experiments in which vectors from one bioclimatic zone were allowed to feed on patients from another zone, have demonstrated that the probability of larval development for these "foreign" parasites was significantly reduced compared to the results obtained with patients coming from the same area as the vector (Philippon 1977). Based on these results, it is now generally accepted that onchocerciasis in West Africa involves several vector-parasite complexes, with parasite populations which vary considerably in their pathogenicity.

Endemicity levels and blindness in the savanna.

The vector-parasite complex in the West African savanna is responsible for the most severe form of onchocerciasis in the world. Blindness can affect over 10% of the population in the most affected villages, which are located in the river valleys where the breeding sites of the vector are found, thus earning the disease the infamous name of river blindness. However, even within those river valleys there exists, between the various communities, a considerable variation in the severity of the disease and in the level of infection. Attempts have been made to characterize those variations by defining levels of endemicity of onchocerciasis in the community (Prost et al 1979), and the most commonly used index has been the age and sex standardized prevalence of infection, as measured by the results of skin snip examinations.

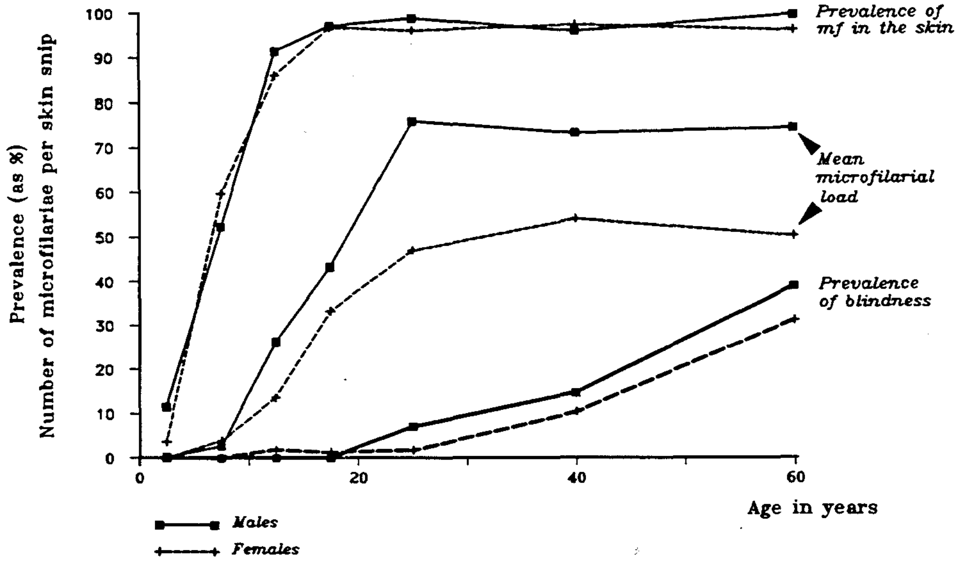
It has been demonstrated that onchocerciasis is socially inapparent when the prevalence of microfilariae (mf) in the skin snip remains below 35%, and that severe blindness rates are only found in so-called hyper endemic villages, i.e. villages which have a mfs prevalence of 60% or above. However, even within this latter group, the prevalence of blindness ranges from 0% to 15%, and a better index of endemicity is the Community Microfilarial Load (CMFL, Remme et al 1986), because the prevalence of onchocercal eye lesions and blindness are linearly related to this index. Onchocerciasis becomes an important public health problem when the CMFL reaches 15-20 mf per skin snip (mf/s), and blindness will affect more than 5% of the population when the CMFL exceeds 40 mf/s (Remme et al 1989). With such high blindness rates, the disease becomes insupportable and will threaten the survival of the village itself (Prost et al 1979).

Blindness patterns and excess mortality.

An example of the extremely high levels of blindness which may result from onchocerciasis, is given in Figure 1 which gives age- and sex-specific epidemiological results for nine savanna villages combined. Each village is from a different river basin and has been selected from among the villages with the highest intensity of infection and with a CMFL for males greater than 50 mf/s. Figure 1 shows that, even though nearly everybody above the age of 10 years is already infected in these highly endemic villages, there is virtually no blindness among the younger age groups. The intensity of infection rises sharply between the age of 10 to 20 years but it takes at least another 10 years till the cumulative effect of high intensities of infection result in a significant increase in the prevalence of blindness. However, from the age of 30 years onward, blindness becomes a very serious problem and above the age of 50 years it affects more than 30% of the female population and close to 40% of the males.

Fig.1: Onchocerciasis infection and blindness

Combined results for nine hyperendemic villages



Dramatic as these cross-sectional figures are, they still underestimate the extent of the blindness problem in these communities because of the significant excess mortality among the blind. It has been estimated that the life-expectancy of a person, who is already blind at the age of 30 years, is reduced by 13 years compared to others of his age group (Prost and Vaugelaude 1981). On average the mortality among the blind may be about three to four times higher than among non-blind of the same age and the incidence of blindness must, therefore, be considerably higher than is reflected by the prevalence. It has been estimated that in hyperendemic communities with a prevalence of blindness of about 4 to 6%, as many as 46% of the males and 35% of the females will become blind before they die (Prost and Vaugelaude 1981). These estimates are not very different from the observed prevalences of blindness in the oldest age-group in Figure 1. However, it should be noted that this graph shows the results for nine selected villages, which represent the upper range of hyper endemicity and had an average prevalence of blindness equal to 7.6%. It is quite possible that in these villages more than half the population will loose their sight during their lifetime.

When blindness reaches such extreme levels as described above, onchocerciasis becomes not only the dominant public health problem, with direct demographic consequences, such as excess mortality in a significant portion of the population, but it will have also severe repercussions on the economic performance of the village. Blindness incapacitates an important part of the working population and reduces them to dependents instead. The result is less production of food for the family of the afflicted persons and ultimately less food for the total village. In hyper endemic villages with a high intensity of infection, blindness is, therefore, not only an individual problem for the patients concerned, but of major concern to the community as a whole.

INTENSITY OF TRANSMISSION AND MAN-VECTOR CONTACT

Factors which determine the intensity of transmission.

As has been mentioned before, the severity of onchocerciasis in a particular area depends to a large extent on the local intensity of transmission. The intensity of transmission varies according to two groups of factors: (1) intrinsic factors of the intermediate and the definite host, which govern the chances of the parasite to develop after entering the host, into a stage which can be transmitted, and (2) factors which determine the interaction between the two host populations. It is the second group of factors which are of major interest in this chapter on the demographic aspects of onchocerciasis, and, therefore, only the most important intrinsic host factors are reviewed.

Though it is known that only a minor proportion of *O. volvulus* larvae, which are inoculated in man, develop into adult worms, extremely little information is available about the quantitative aspects of the actual process, and to what extent host-protective immunity plays a role. The factors involved vary probably significantly between individuals, but they are not believed to be responsible for major differences between geographical areas. On the other hand, the factors which determine the chances of larval development in the vector are quite well understood and their relative importance differs greatly between vector species. The two most important factors are the formation of a peritrophic membrane around the bloodmeal and the survival rate of the vector. Microfilariae which are entrapped in the peritrophic membrane are prevented from developing into infective larvae and the West African savanna vectors are very efficient in the formation of a strong membrane (Philippon 1977). Only few microfilariae can escape and parasite loads are, therefore, relatively low in the savanna. Forest flies are far less efficient in the formation of a solid membrane and are as such better vectors. However, this factor is compensated by the fact that savanna vectors have a much higher survival rate which allows a significant proportion of flies to survive long enough for the parasites to complete their development and for the flies to become infective to man.

Man-vector contact.

Intrinsic host factors determine the chances of parasite development in the human host and in the vector. But, within a geographical zone with a given vector species, the variation in the intensity of transmission depends solely on differences in the density of the human and the vector population and on their degree of interaction. Demographic and behavioural factors come, therefore, into play and the various aspects of man-vector contact are discussed in more detail.

Vectorial aspects.

The vector density shows seasonal and annual variations which are directly related to hydrological conditions which determine the availability and productivity of the breeding sites. The rivers in the forest are usually perennial and the vector is present throughout the year. In the savanna most of the rivers flow only during the rainy season and transmission is limited to a period of a few months when immigrant flies have reestablished a new fly population at the local breeding site. Certain rivers may not flow, or only very shortly, during years of drought and the annual variation in the intensity of transmission can be extreme.

The dispersal of the fly from the breeding site is another important determinant of man-vector contact. The shade provided by the dense vegetation in the forest allows active dispersion of the vector in all directions, but in the savanna the fly stays relatively close to the river and the gallery forest (Le Berre 1966). Also the savanna vector ventures farther away from the river during cloudy days in the rainy season, thus increasing the chances of contact with the farmers who are actively engaged in their field during this period. The tendency to disperse depends on the age of the flies, with nulliparous flies dispersing further and the parous ones generally staying closer to the river banks. Since only multiparous flies can be infective, it follows that not only the biting rate, but also the probability that a biting vector is infective, are greatest in the proximity of the breeding sites.

A very different type of vector displacement affects those areas which are subjected to a significant amount of reinvasion by infective vectors from distant breeding sites. The extent and importance of wind-assisted, long distance migration has only recently been recognized in the context of the vector control operations in the OCP, but it has also been learned that these reinvading flies disperse little upon arrival and that they are mainly a risk factor close to the breeding sites (WHO 1985).

Host preference is of course another crucial factor in *O. volvulus* transmission. Certain populations of *S. sirbanum* play no role in transmission during all, or part, of the year when they are completely zoophilic. However, these populations are exceptions and the savanna vectors are in general highly anthropophilic. The forest vectors *S. soubrense* and *S. sanctipauli* are less anthropophilic, which contributes to the relatively low infection rates in this vector pair, even in hyper endemic areas.

Human population density.

The first demographic factor to be taken into account in the discussion of man-vector contact is the density of the human population in a given area. This factor is not only important because it gives an indication of the availability of the human host, but also because a high human population density may directly limit the intensity of transmission. The size of the vector population cannot exceed a certain maximum which depends on the capacity of the breeding sites. A substantial increase in the human population would, in theory, give a much lower fly-to-man ratio and this should result in a significant dilution of transmission with a much lower force of infection and less severe disease. On the contrary, a major fall in the human population density will intensify transmission and aggravate the severity of disease and the level of blindness.

Various observations in hyperendemic areas in the savanna seem to be consistent with this hypothesis. High onchocercal blindness rates of over 5% are generally only found in small, isolated communities (WHO 1973, WHO 1976) and Hervouët (1978) has shown for the valleys of the Red and White Volta rivers that severe blindness was rarely found above a certain population density which he set at 50 persons per km^2. In his study, onchocerciasis was only a serious public health problem for villages which had a population density of less than 35 persons per km^2. However, a low population density can also be a result of onchocerciasis and several other factors also have to be taken into account in addition to the population density.

Location of human population.

A major determinant is the location of a village in relation to the nearest breeding site. It is not just the distance to the breeding site, as it is also quite important if the zone between the village and the breeding site contains other settlements. If this zone is uninhabited the village is a so-called first line village, and in maximum contact with the flies, while second and third line villages benefit from a certain protective effect from the buffer provided by the first line villages. Onchocerciasis is therefore most severe in first line villages, even if these are located at a fair distance from the river (WHO 1976).

In addition to the location of the village, the pattern of habitation and land utilization contributes also to variations in the intensity of onchocerciasis transmission. Where people work the land in groups and work land located close to the village this reduces the chances of man-vector contact, especially if the land around the village is largely cleared from vegetation which would otherwise provide the shade which *S. damnosum* s.l. prefers to use during its flights in search for a bloodmeal. Villages where the population practices extended cultivation by individual farmers, far from the village on scattered fields close to the river banks, are usually much more severely affected (Prost and Paris 1983).

Individual differences.

Within the village, there are great variations in the intensity of infection between individuals because of differences in man-vector contact. The group which has the least contact with the vector are the youngest children who stay in the village compound most of the time where the vector is only rarely found. When they grow older, the children increasingly get more in contact with the vector such as when they start playing outside the compounds and begin to help their parents with their daily activities; from the age of about 10 years onward both male and female children become as fully exposed to the bites of *S. damnosum* s.l. as their parents (Remme et al 1986). This changing pattern of man-vector contact by age is always clearly reflected in age-specific data on the prevalence and intensity of *O. volvulus* infection in the savanna, and Figure 1 may serve as an example even though it represents only nine of the most endemic villages. Below the age of 10 years, the prevalence of mf/s, and in particular the intensity of infection, are still low. From the age of 10 years onward the children are fully exposed, and the intensity of infection rises sharply during the next 10-12 years, a period equal to the estimated average productive lifespan of *O. volvulus*. The intensity of infection remains approximately constant from the age of about 20 years onward, when the rate at which new adult *O. volvulus* are added to the host, has become balanced by the rate of dying adult worms (Remme et al 1986).

The intensity of infection in adults males is usually significantly higher than in adult females. Adult males are most exposed to the bites of the vector while working for long periods on their fields. The women also assist in this work, but for shorter periods because they have to return to their chores in the family compound. Some typical responsibilities of females, such as collection of water, bring them briefly to the river banks during the early morning or in the evening hours. Though the difference between the sexes can be quite pronounced for the lower range of hyper endemicity, the blindness patterns in Figure 1 show that in the villages with the highest endemicity onchocerciasis becomes a similarly dramatic health problem for both sexes.

Certain occupational groups, such as fishermen and ferrymen, have to spend most of their day close to the breeding sites and are obviously high risk groups. Well known is the special case of the fisherman who works on the river and camps on its banks, and this group is often very highly infected. Also the contribution to transmission varies considerably between individuals. A high intensity of infection is a result, as well as an indication, of a high contact rate between the vector and an infective host, and it is quite likely that heavily infected persons are responsible for a major contribution to the transmission of the parasite. On the other hand, persons with a low intensity of infection are not only less in contact with the vector, but preliminary results of recent fly-feeding experiments on volunteers with different levels of infection indicate that the probability that the fly will take up microfilariae, is significantly reduced if the fly feeds on a person with a light intensity of infection. It is, therefore, not just the prevalence but the distribution of the intensity of infection in the community which determines the intensity of transmission in a given area.

Differences between bioclimatic zones.

Man-vector contact can, in the forest zones, occur over a rather wide area on both sides of the river and, though annual variations in vector densities do occur, the pattern is generally quite stable over time. The vector can be a terrible nuisance, with biting rates at the worst points reaching 300,000 bites per year, and the itching and skin lesions caused by onchocerciasis are a major concern for the population. But it is never sufficient reason to abandon the village and migrate away. Quite the contrary, many villages can be found which are situated on the river banks themselves, virtually on top of the breeding sites. This is another major difference between the forest and the savanna. Most river valleys in the savanna, where onchocerciasis is hyper endemic, are severely underpopulated while several areas, close to the river side, are completely uninhabited. A major question has always been if, and to what extent, onchocerciasis has been the cause of this underpopulation, and we will address these questions in some more detail.

POPULATION DENSITY AND POPULATION MOVEMENT IN THE VOLTA RIVER BASIN BEFORE THE START OF CONTROL.

In the early 1970s, many of the river valleys in the savanna, where onchocerciasis was endemic, were severely underpopulated and the available land was greatly underutilized (Bradley 1976, Hervouët 1978). It has been estimated that as much as 41,000 km^2 of land in the river valleys in Burkina Faso, i.e. an area which represents about 15% of the total territory of the country, was virtually uninhabited and uncultivated. The extent of underpopulation has been well documented for several stretches and affluents of the Black Volta, the Sassandra and the Comoé and it has been described in particular detail for the basins of the Red Volta river and the White Volta river, upstream from their confluence (Hervouët 1978, Rolland and Balay 1985).

Underpopulation and abandoned settlements along the Red and White Volta.

Two wide bands of uninhabited land clearly mark the location of the Red and White Volta rivers on maps of the distribution of the population density in Burkina Faso and Northern Ghana before 1975. However, beyond a certain distance from the river banks, the population was present in high numbers and the interfluvial plateau had a population density of over 100 persons per km^2 with large areas being overpopulated (Hervouët et al 1984). Exceptions did exist, such as in the area around Niaogho (Rolland and Balay 1985), where the population density was relatively high and part of the population still lived close to the river. But the analysis of aerial photographs, which were taken in 1972, revealed that no more than 20 to 30% of the valleys was utilized and that only 7.4% of the land was cultivated (see Table 1). The greater part of the valleys was, therefore, completely uninhabited and unutilized terrain.

Table 1: Changes in land utilization and cultivation in the White and Red Volta river basin in Burkina Faso before the start of vector control operations

		Utilized land					Cultivated land				
River basin study area	Available land in hectares	Total in hectares		As % of available land		Annual increase	Total in hectares		As % of available land		Annual increase
		1956	1972	1956	1972	(%)	1956	1972	1956	1972	(%)
White Volta, central zone (10°30'N - 12°N)											
Bissa	28512	6690	8030	23.5	28.2	1.1	1615	2298	5.7	8.1	2.2
Mossi Kaibo	14240	6023	5678	42.3	39.9	-0.4	613	369	4.3	2.6	-3.1
Yeriba	9750	1940	2738	19.9	28.1	2.2	536	1172	5.5	12.0	5.0
Subtotals	52502	14653	16446	27.9	31.3	0.7	2764	3839	5.3	7.3	2.1
Red Volta, north of 11°N											
Left bank	13975	2901	3852	20.8	27.6	1.8	1529	1838	10.9	13.2	1.2
Right bank	20302	4669	2697	23.0	13.3	-3.4	1555	772	7.7	3.8	-4.3
Subtotals	34277	7570	6549	22.1	19.1	-0.9	3084	2610	9.0	7.6	-1.0

This has apparently not always been the case. In the traditional state of Nangodi along the White Volta in Ghana, all the available land was utilized around the beginning of the century (Hunter 1986). Valleys closer to the river sources in Burkina Faso have probably never seen such a level of land occupation, and several areas may not have had any previous human settlement. However, there have been many attempts at resettlement in the empty valleys, initially through a gradual forward movement by the population living on the overcrowded interfluvial plateau. The pattern of resettlement changed and accelerated between 1910 and 1940 when many small independent villages were established deep in the uninhabited zones, in an attempt of the population to escape the influence of the colonial powers, and its forced labour policy, or the power and exactions of certain local chiefs (Hervouët 1978). Between 1945 and 1975 there was a stagnation in this establishment of new and independent villages while the regular forward movement of the frontline of human habitation from the plateau toward the river banks had come to a standstill. Table 1 shows that between 1956 and 1972 there has been virtually no change in the overall percentage of land utilized. During the same period, there had been a modest increase in the amount of cultivated land in the White Volta basin, which was mainly due to the achievements of the Yeriba tribe and the Bissa population around Niaogho, but these limited gains were nearly cancelled out by the losses on the right bank of the Red Volta.

In the meantime, nearly all the previously established settlements in the valleys had been abandoned by the population. The river valleys were, therefore, not only virtually uninhabited by the year 1975, but they contained also the ruins of hundreds of villages as the evidence that many attempts at settlement had been made during this century but all of them had been doomed to failure.

Depopulation of valleys because of onchocerciasis.

Onchocerciasis is usually quoted as the main cause of the abandonment of villages, which have been established in the proximity of breeding sites of the savanna species of *S. damnosum* s.l., and of the subsequent depopulation of the river valley as a whole. The role of onchocerciasis in this respect is classically described as follows:

Abandonment of villages.

When a new village is established near a breeding site by a group of families which come from an area of low endemicity, such as the nearest villages on the interfluvial plateau, the infection is present in the population but the disease is still socially inapparent. Even in the very unlikely case that all immigrants are free of infection, it will only take a few years before several adults have acquired the infection locally. Because of the new, and very high level of man-vector contact, there will be a progressive increase in the prevalence and intensity of infection. When a certain level of endemicity is reached, the disease becomes a serious public health problem. Blindness afflicts several adults and begins to frighten the population. The village begins to loose its original attractiveness and the young adults, particularly the males between 15 and 30 years, move increasingly away to find work elsewhere, often in the coastal areas. Girls from other settlements refuse to marry into the village and some first families leave and move to other villages in the hinterland.

Because of the reduction in the population size, their will be an increase in the fly-to-man ratio, resulting in a higher intensity of infection and a further deterioration of the severity of the disease, which may cause still others to leave. Life for the remaining population will become increasingly difficult because of the severely unbalanced age structure, the very high dependency ratio, and the declining levels of food production. The situation will continue to worsen till it finally becomes untenable and the last families, including the family of the chief, decide en bloc to abandon the village.

This decision will have both epidemiological and psychological consequences for neighbouring villages and will have an accelerating effect on their decline toward abandonment. The final consequence would be the total desertion of all first line villages and the creation of an empty corridor on both sides of the river. The result of this would be an increased man-vector contact in the next line of villages, for which the abandoned villages had been a buffer between themselves and the breeding site. It will now be in those villages that the epidemiological situation will start to deteriorate till it finally results in the abandonment of this line of villages. In this way the population may be gradually forced back from the river to new lines of retreat, till a distance has been reached where the vector density is so low that onchocerciasis can no longer maintain itself as a severe public health problem (Rolland and Balay 1985, Hunter 1986).

New attempts at settlement.

As has been mentioned before, isolated attempts at resettlement have always been made, even though their frequency has varied considerably over the decades. However, it was exactly this isolation, in combination with a small population size, that made many of these attempts fail within a relatively short period. Notorious is the case of the village of St.Pierre (Burkina Faso, 130 km north of Bobo-Dioulasso) where ocular onchocerciasis became rampant within a decade. Philippon (1977) has also reported the collapse within periods of one to two decades of several small, isolated villages along the Leraba river (border Burkina Faso and Ivory Coast).

Some massive, and temporarily successful, attempts at resettlement may in the past have taken place in certain areas. It has for example been reported that large scale famine around the year 1890 forced the population in Northern Ghana into the river valleys where they occupied all available land and cleared much of the local forest (Hunter 1986). The new occupants did not only come from the interfluvial plateau, but included many strangers from distant clans. Onchocerciasis was, therefore, initially probably only of low endemicity, but blindness started to become a problem after two decades and the population began to retreat along the lines described above. In the early 1960s, as much as 60% of the land in the traditional state of Nangodi had been abandoned. Hunter (1986) estimates that similar migrations have taken place in the preceding decades and he has advanced the hypothesis of a cyclic advance and retreat of total population, with famine pushing the population into the valleys and onchocerciasis gradually forcing them to leave.

Other factors leading to abandonment.

Others, who have investigated the historical migration and settlement patterns in the Red Volta and White Volta river basins in Burkina Faso, have concluded that it has not been just onchocerciasis, but rather a combination of factors, which has caused the depopulation of the river valleys in this area. Several factors, such as wars during the last century and flight from the colonial powers, caused important reductions in the population of plateau and valley alike, while trypanosomiasis epidemics took a heavy toll during the first half of this century and caused considerable emigration from the valleys. But onchocerciasis was the factor which completed the depopulation by slowly destroying the remaining isolated settlements with a low population density.

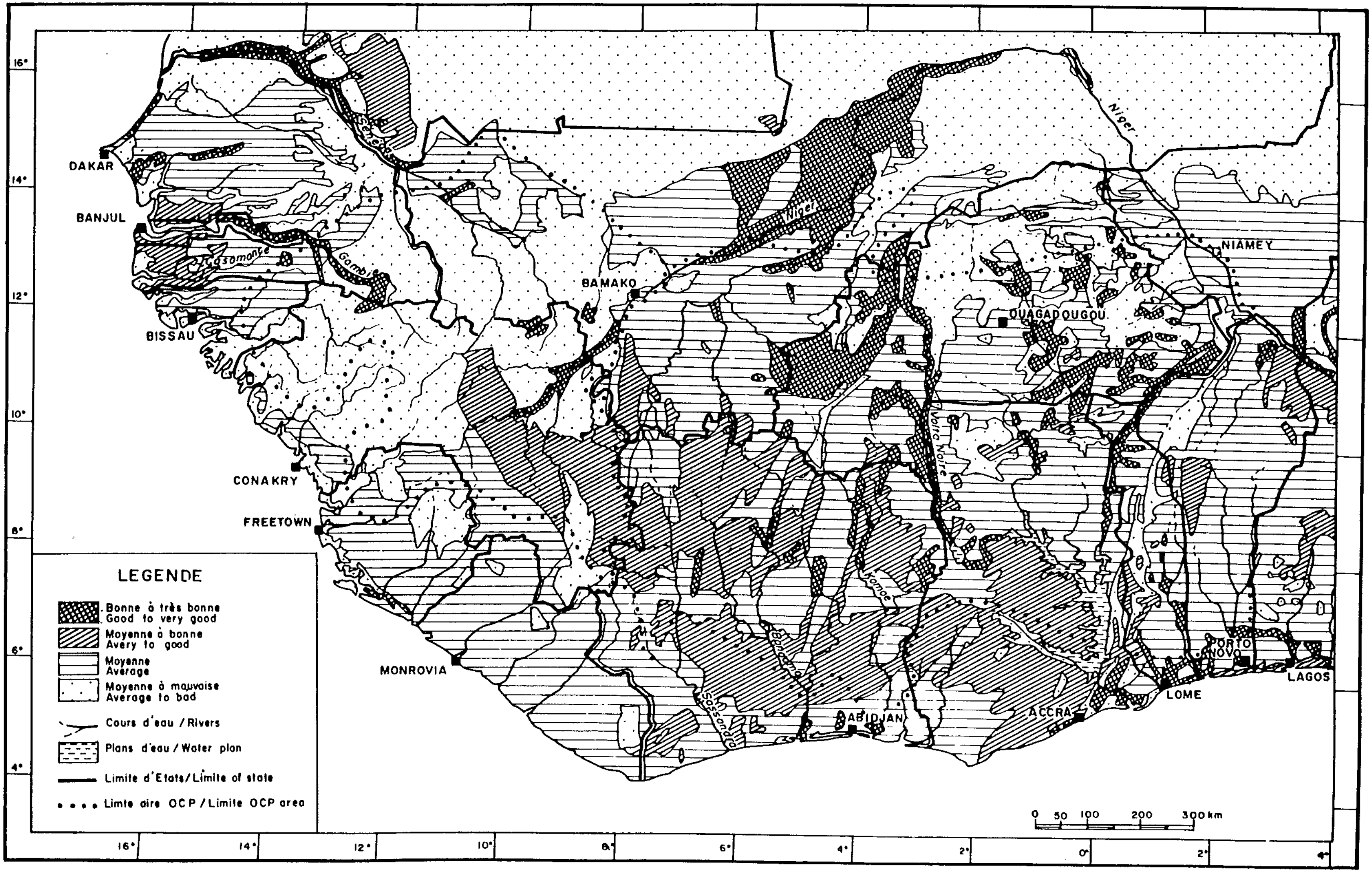
Another finding, which may raise some doubts about the predominance of onchocerciasis among the factors which lead to the abandonment of villages in the river valleys, is that the people who used to live in such abandoned villages, rarely mention onchocerciasis as being the main reason for them to leave (Bradley 1976, Rolland and Balay 1985). Instead they always gave more acute reasons for leaving, such as the nuisance of wild animals or the fear of compulsory recruitment by the colonial government (Rolland and Balay 1985). But most respondents mentioned also that the area "was not good", that "people were killed by the bush", " died one by one before reaching old age" and that "if you go there, you will loose your eyes". These answers would be consistent with a gradual deterioration as a result of onchocerciasis and which may very well have been the underlying reason for making the village no longer viable.

Onchocerciasis as an obstacle to socio-economic development.

Since the valleys remained severely underpopulated, it was equally important to find out which factors prevented their repopulation, and there exists little doubt about the predominant role of onchocerciasis in this respect. The population of the hinterlands always mention onchocerciasis as the overriding factor for not moving into the valleys in spite of such attractions as more fertile land and better accessibility to water. The consistency of this finding between studies by various investigators in the savanna area of different countries (Bradley 1976, Hervouët 1978, WHO 1981, Rolland and Balay 1985) is quite remarkable. Therefore, though the extent to which onchocerciasis has contributed to the depopulation of the valleys is still being debated, there exists a full consensus among all the investigators that the disease has been the single most important obstacle to the repopulation of the abandoned valleys.

The river valleys contain some of the most fertile land in the West African savanna. Figure 2 shows the agricultural value of the soil in the West African region to the west of Nigeria. It can be seen that the soil with the best agricultural value is nearly exclusively found in the valleys of the major rivers, and a comparison with the available epidemiological data shows that onchocerciasis was endemic in nearly all of these areas. Onchocerciasis is, therefore, not

Fig. 2. MAP OF AGRICULTURAL VALUE OF THE SOILS



only a major public health problem but also a major socio-economic problem for the countries involved who were already suffering from severe droughts and of erosion of the soil in the overpopulated interfluvial plateaus. The problem was particularly serious in the Volta river basin and this was an important justification for the large scale control programme which was launched in the year 1975.

THE ONCHOCERCIASIS CONTROL PROGRAMME (OCP).

When the OCP was launched in 1974, it covered the savanna area of seven West African countries where an estimated total of 1 to 1.5 million people were infected, 35,000 were blind, and at least as many severely vision impaired. The strategy of the OCP has been to interrupt transmission through vector control by larviciding for a sufficiently long period to allow the parasite reservoir in man to die out naturally, and the Programme was initially planned to last for a period of 20 years. Control operations have exclusively been based on the aerial application of larvicides to the rivers which contain the breeding sites of *S. damnosum* s.l. Larvicides have been applied on a weekly basis wherever required according to the results of an extensive entomological evaluation network. The original programme area covered 764,000 km^2 of the savanna areas in Burkina Faso, Mali, Ivory Coast, Ghana, Togo, Benin and Niger.

Vector control has been quite effective over most of the Programme area but a major problem has been invasion by infective vectors from outside the OCP. This so-called reinvasion affected mainly the western and south-eastern border areas of the Programme. A second problem has been resistance to the larvicide of choice, temephos (Abate), initially among the *S. soubrense/S. sanctipauli* subcomplex, but more recently also among the savanna species of the vector; and the necessary replacement of temephos by more expensive larvicides has had serious financial repercussions for the Programme.

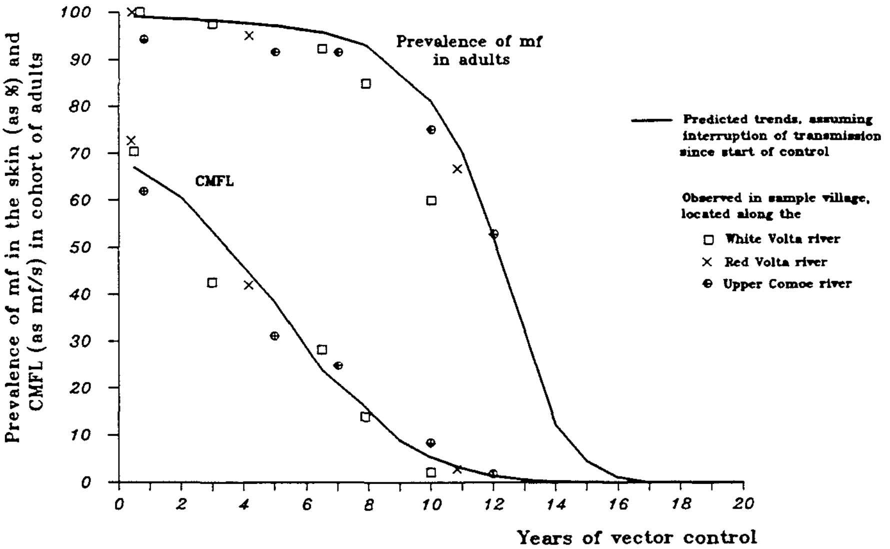
The success of the first 12 years of vector control is clearly reflected in the results of the epidemiological evaluation, which involves the regular examination, at intervals of 3 to 4 years, of the population of 184 indicator villages. At each examination, skin snips are taken and examined for microfilariae in order to determine the presence and intensity of infection. The results can be summarized by three geographic zones with different degrees of control, i.e. the non-reinvaded central zone, the intermediate zone and the reinvaded areas (Remme et al 1986b).

The non-reinvaded zone covers 90% of the initial OCP area where, with the exception of four small and circumscribed foci, the epidemiological results have been excellent. Out of the 9109 examined children, who were born since the start of control in the 124 indicator villages in this zone, only 9 children were found infected against an expected number of over 800 infected children had there been no control. Eight of the infected children came from the small problem foci mentioned above, and no infected children were detected in 120 of the villages.

The trend in the CMFL gives a good reflection of the changing epidemiological situation during the control period (Remme et al 1986a). Soon after the start of control the CMFL started to decline in a linear fashion and after 11 to 12 years of control it had dropped by more than 95%. A typical example of this trend is given in Figure 3. In the central OCP area, the intensity of infection is now so low that onchocerciasis probably constitutes no longer a public health problem. Detailed ophthalmological examinations in a sample of hyper-endemic villages after 7 to 8 years of control and again after 10 years of control appear to confirm this conclusion - virtually no microfilariae are found anymore in the eye, the incidence of anterior segment lesions had been arrested, the prevalence of ocular lesions and blindness has already fallen by 50%, and the annual incidence of onchocercal blindness had been less than 0.15% and exclusively involves cases who had already severe eye lesions in 1975 and for whom control came too late (Dadzie et al 1986, Remme et al 1986b).

Fig.3: Epidemiological trends in the central OCP area

Results for three hyper endemic villages with a similar, and very high intensity of infection before the start of control



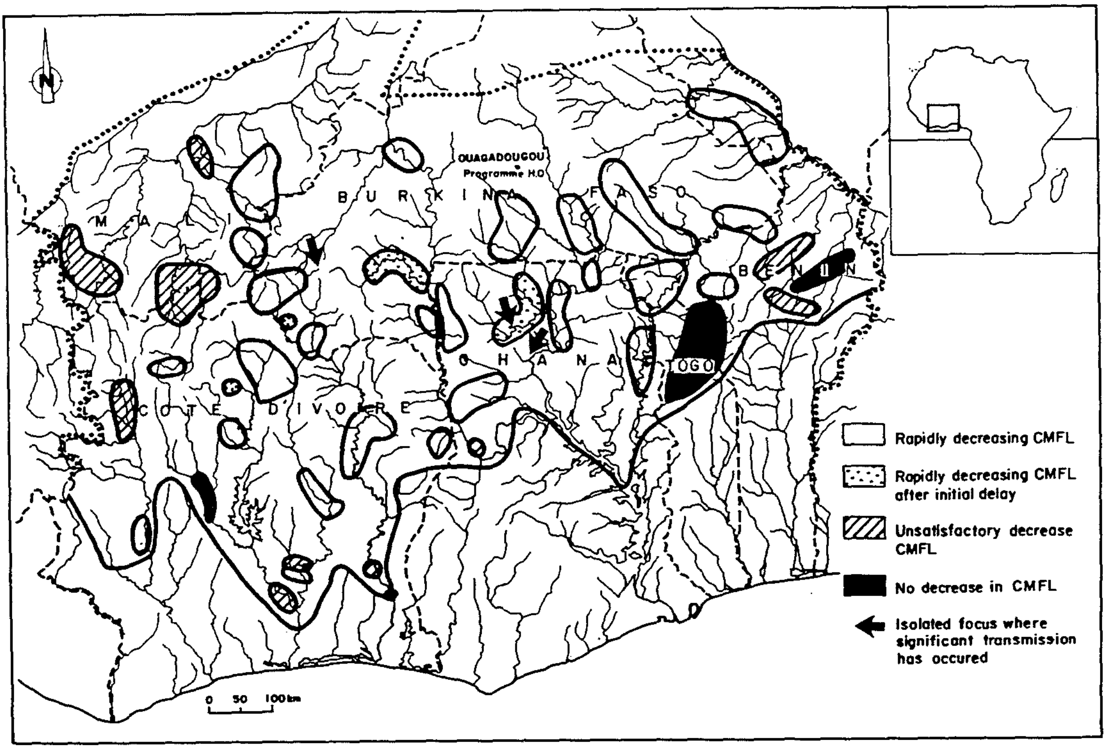
As expected, the prevalence of skin microfilariae started to decline only after a significant delay, but throughout the central area the prevalence is now showing the accelerated fall which had been predicted by mathematical models (see Figure 3). Present projections are that the reservoir of infection will be virtually eliminated after 15 years of control, which is considerably earlier than initially foreseen.

In the intermediate zone the decline in the CMFL was often significantly slower than in the central OCP area. Nevertheless, with the exception of one focus along the Marahoué river, the results were generally much better than expected given the problems with resistance and the fact that the southern boundary of the control operations has never been fixed but has fluctuated considerably over the years.

The epidemiological results for the reinvaded areas are clearly unsatisfactory. As many as 50 infected children were detected against an expected number of 234 had there been no vector control. The reduction in the CMFL was nearly everywhere unsatisfactory and in several villages the CMFL did not show any decrease at all. Transmission has definitely not been interrupted in the reinvaded areas, though elimination of local breeding has usually brought transmission down to much lower levels. However, the remaining transmission is still intolerably high in several foci and associated with high intensities of infection. Control of onchocerciasis can therefore not yet be claimed for the border areas in the west and southeast (see Figure 4).

The available epidemiological evaluation data clearly demonstrate the success of the OCP in controlling onchocerciasis over 90% of the original OCP area. The major challenges facing the Programme today are to consolidate the achievements and to extent control operations to the west and the southeast in order to eliminate the problem of reinvasion and to protect the millions at risk who are living in the extension areas. The total programme area will be increased to 1,320,000 km^2, and four more West-African countries, i.e. Guinea, Guinea-Bissao, Sierra Leone and Senegal, have joined the OCP. The extension of vector control operations started early in 1987.

Fig.4: Location of clusters of indicator villages and classification of the trends in the CMFL (results up to April 1987)



CHANGES IN MIGRATION AND SETTLEMENT PATTERNS AFTER 12 YEARS OF CONTROL.

A large scale evaluation of the socio-economic impact of the first 10 years of control was undertaken by the OCP in 1985 in collaboration with the national onchocerciasis committees of seven participating countries (WHO 1986). Particular attention was given to the evaluation of changes in the pattern of land utilization and cultivation in selected sections of previously hyper endemic valleys of the Volta river basin area. This aspect of the evaluation was nearly exclusively based on comparative analysis of aerial photographs taken during the pre-control period and again shortly before the evaluation upon the initiative of the OCP. The study areas had, therefore, to be chosen from those zones for which such pre-control photographs were available.

The comparative studies have clearly demonstrated that the pre-control trends have been reversed and that there has been a significant repopulation of the valleys in the well-protected zones. However, the observed trends vary considerably between valleys, and range from maximum increases in land utilization in some of the larger river basins, to situations where virtually nothing has changed over the last 10 years.

Changes in the Red and White Volta basin.

An important example of an area where there has been a significant expansion in the amount of utilized and cultivated land is the Red Volta basin, and, even more so, the White Volta basin. Table 2 shows that there has been a dramatic increase of 9-11% per year in the percentage of utilized land throughout the area, and along the White Volta there are no more empty lands where man is not active in one way or another. There has been a similar annual increase of about 10% in the amount of cultivated land, and in several areas the cultivation of the land is even approaching a saturation point. More to the south, and close to the border with Ghana, the farms and the settlements on the right bank of the White Volta have already reached the river itself while the left bank is densely populated by herdsmen who also practice semi-intensive small scale farming. Even the right bank of the Red Volta, where still more than 60% of the land was not utilized in 1983, shows similar dynamics of repopulation as reflected by the rate of increase of 9% in both utilized and cultivated land. All these results are completely different from those, which were given in Table 1 for the pre-control period, and they clearly demonstrate the radical changes which have taken place since the start of the OCP.

Table 2: Changes in land utilization and cultivation in the White and Red Volta river basin in Burkina Faso since the start of vector control operations

		Utilised land					Cultivated land				
River basin study area	Available land in hectares	Total in hectares		As % of available land		Annual increase	Total in hectares		As % of available land		Annual increase
		1956	1972	1956	1972	(%)	1956	1972	1956	1972	(%)
White Volta, north of 12°N											
Right bank	64759	24020	64700	37.1	99.9	9.4	919	4879	1.4	7.5	16.4
Left bank	112440	37595	112440	33.4	100.0	9.6	16220	51578	14.4	45.9	10.1
Subtotals	177199	61615	177140	34.8	100.0	9.2	17139	56457	9.7	31.9	10.8
White Volta, central zone (10°30'N - 12°N)											
Bissa	28512	8030	28500	28.2	100.0	12.2	2298	5623	8.1	19.7	8.5
Mossi Kaibo	14240	5678	13500	39.9	94.8	8.2	369	3006	2.6	21.1	21.0
Yeriba	9750	2738	9675	28.1	99.2	12.2	1170	4134	12.0	42.4	12.2
AVV							69	2429			38.2
Subtotals	52502	16446	51675	31.3	98.4	11.0	3937	12763	7.3	24.3	11.5
Red Volta, north of 11°N											
Left bank	13975	3852	10130	27.6	72.5	9.2	1838	4862	13.2	34.8	9.2
Right bank	20302	2697	7500	13.3	36.9	9.7	772	2100	3.8	10.3	9.5
Subtotals	34277	6549	17630	19.1	51.4	9.4	2610	6962	7.6	20.3	9.3

Examples from other study areas.

Quite contrasting are the results from the comparative studies of aerial photographs taken from the Bougouriba valley, where there has been virtually no change and where more than half of the available land remains unutilized. There has been a little increase in cultivated land as a result of the creation of new fields near the river by members of the Dagara and Birifor tribes, who continue to live in their villages in the overpopulated hinterland. But the rest of the Bougouriba valley has remained stagnant. Other sections of the Black Volta have shown much more dynamism: in 1952 only 3% of the Samandeni region was cultivated, but this percentage had risen to 16% in 1981 and was as high as 31.8% in 1985. The same percentages for the region of St.Pierre were 4.1%, 25% and 34.6%, respectively. Similar extremes are also found along the Leraba: the area downstream from the bridge remains still empty land, but important dynamism and land occupation is found in the rest of the valley.

A significant increase in land utilization has also been observed in some reinvaded areas for which the epidemiological data have indicated that the risk of infection, though considerably reduced since the start of control, is still unacceptably high according to epidemiological criteria. An example of such a development is the Borotou sugar plantation in the upper Sassandra basin in Ivory Coast, which plays a pioneering role in this severely underpopulated zone where the population density was below five inhabitants per km^2. There have been other instances where resettlement has occurred before the reinvasion by infective blackflies had been controlled, but where the impact of local control had greatly reduced the biting rates.

Organized and spontaneous settlement.

Some of the participating countries have created special projects for the organized settlement of new populations in the valleys, where the risk of onchocerciasis transmission had been eliminated. The largest of these projects was the Volta Valleys Development Authority (AVV) in Burkina Faso, which provided the immigrants with extension services and brought an important development of the local infrastructure. From 1974 to 1982, the AVV constructed 300 km of "dirt" roads, founded 58 villages with 152 pump-driven wells, and built several dispensaries, schools and stores. But the organized settlements accounted in 1985 for only 10 to 20% of the newly cultivated land, most of the increase in cultivated area being a result of spontaneous, non-organized, migrations into the valleys.

Several different groups of people were involved in the repopulation of the valleys. Many of the AVV settlers came from distant places on the overpopulated Mossi plateau to the valleys, often only to find that the original population, which had abandoned the valley in the past, had not abandoned their claim upon the land. The establishment of new AVV settlements was in many places even a reason for the population from the interfluvial plateaus to accelerate their forward movement into the valleys, and to increase their cultivated lands as much as possible in defense of what they considered to be their rightful land. Spontaneous settlers also benefited from the new infrastructure, and spontaneous settlement has, therefore, often taken place in close correlation with the increase in organized settlement.

Problems associated with the rapid repopulation.

The rapid repopulation of many river valleys has also introduced a number of ecological problems. Most of the spontaneous settlers use extensive farming methods in which the land is first cleared, then cultivated for 2 to 5 years and subsequently left fallow for a much longer period to allow the regeneration of the soil. However, the new population density is already too high in many valleys to allow such an inefficient utilization of the land, and it is feared that this will result in a major reduction in the fallow period which will lead to the degradation of the soil in the long term. This problem is aggravated by the destruction of the gallery forest by the new occupants in order to meet their firewood requirements. The recent droughts have further worsened the ecological situation and all these factors together pose a very serious danger of desertification of the valleys.

CESSATION OF LARVICIDING AND SOME RELATED DEMOGRAPHIC QUESTIONS.

Vector control has been extremely successful during the first 12 years of operations, but the aerial application of larvicides over an extensive area as in the OCP is a costly affair and the annual budget for 1987 and 1988 approached $ 30 million per year. This level of expenditure can presently be justified by the protection provided to the hundreds of thousand who would otherwise be at risk of infection, but this justification will no longer be valid when the reservoir of the parasite has dropped to insignificant levels as it is expected to do during the next few years. At that moment, the vector could theoretically be allowed to repopulate the breeding sites without causing a resurgence of transmission and recrudescence of the disease. Much attention is presently being given to the study of the residual potential of transmission in the context of the declining levels of infection in the population, and attempts are being made to define the epidemiological threshold when vector control can reasonably safely be interrupted. Several field experiments, such as experimental interruptions of larviciding in foci where the epidemiological trends are most advanced, have recently started.

Density and location of the human population.

The future risk of transmission after cessation of vector control will also depend on demographic factors such as the density and location of the population, and the extent of immigration from non-controlled areas. The considerable increase of the population in most of the river valleys should, in theory, limit the probability of effective transmission because it should significantly lower the fly-to-man ratio. However, many newcomers have settled very close to the river banks and the breeding sites, thus greatly increasing the future chances of man-vector contact. Some settlements have even been established so close to potentially highly productive breeding sites that it is questionable whether the population will be able to sustain the severe biting nuisance which the blackflies will cause once larviciding is interrupted. The residual prevalence and intensity of infection in those new settlements comprising the first line villages will to a large extent determine the risk of resurgence of transmission, and the decision to interrupt larviciding will, therefore, have to be guided by the results from epidemiological surveys in those first line villages in particular.

Immigration and the risk of importation of the parasite.

Though the parasite reservoir is rapidly dying out in the central OCP area, the epidemiological situation has remained essentially unchanged in the endemic areas beyond the Programme boundaries to the west, to the east, and to the south. It has long been recognized that immigrants from these areas may be responsible for importation of the parasite into the OCP. Two types of migration should be differentiated in this respect: (1) migration within the savanna belt and (2) south-north migration from the forest to the savanna areas.

Immigration from non-controlled endemic onchocerciasis foci in the savanna may result in the importation of the blinding savanna strain of *O. volvulus*, and is, therefore, of most concern. However, the chances of importation of the parasite from the west and southeast will progressively reduce with the duration of the recently started extensions of vector control in the extension areas, and should be negligible within 15 years. Much more frequent may be the importation of the parasite when migrants who originate from the savanna, return to their home villages after having worked for several years in the richer areas in the south along the West African coast. Many of these migrants go to work on the coffee and cocoa plantations in the forest where they are heavily exposed to infection by *O. volvulus*. However, the parasite involved is probably only the more benign forest strain, and introduction of this strain into a typical savanna area may be of little importance because of the incompatibility which has been demonstrated between the savanna vectors and forest strains of the parasite from certain foci (Philippon 1977). Nevertheless, the available data are still limited, especially for areas where *S. soubrense* predominates (Prodhon et al 1982), and definite conclusions will have to await the results of further experiments and the development of specific tools for the diagnosis of parasite strains.

In spite of all the attention which is being given to this question of importation of the parasite through migration, it is not at all clear what the epidemiological importance of this phenomenon could be and what prevalence of infection might be attributed to importation alone. But the rapidly falling levels of infection in the central OCP area make it more and more feasible to study this question seriously and several studies are presently underway.

REFERENCES

Bradley,A.K.. Effects of onchocerciasis on settlement in the middle Hawal valley, Nigeria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 70 (1976) 225-229.

Buck,A., Onchocerciasis, in *Epidemiology and Community Health in Warm Climate Countries*, Cruickshank,R., K.L.Standard, H.B.L.Russell, Eds., Churchill Livingstone, London (1976) 263-229.

Cianchi,R., M.Karam, M.C.Henry, F.Villani, S.Kumlien, L.Bullini. Preliminary data on the genetic differentiation of *Onchocerca volvulus* in Africa (Nematoda:Filarioidea), *Acta Tropica*, 42 (1985) 341-351.

Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna. *Tropical Medicine and Parasitology*, 37 (1986) 263-270.

Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. II. West African rainforest foci of *Simulium yahense*. *Tropical Medicine and Parasitology*, 40 (1989) 348-354

Duke,B.O.L., D.J,Lewis, P.J.Moore. *Onchocerca-simulium* complexes I - Transmission of forest and Sudan-savanna strains of *Onchocerca volvulus* from Cameroon, by *Simulium damnosum* from various West African bioclimatic zones. *Annals of Tropical Medicine and Parasitology*, 60 (1966) 318-336.

Duke,B.O.L., J.Anderson. A comparison of the lesions produced in the cornea of the rabbit eye by microfilariae from the forest and Sudan-savanna strains of *Onchocerca volvulus* from Cameroon. I. The clinical picture. *Tropical Medicine and Parasitology*, 23 (1972) 354-368.

Hervouet,J.P.. La mise en valeur des vallées des Volta Blanche et Rouge: un accident historique. *Cahier ORSTOM, Série Sciences Humaines*, 15 (1978) 81-97

Hervouet,J.P., J.C.Clanet, F.Paris, H.Some. Settlement of the valleys protected from onchocerciasis after ten years of vector control in Burkina Faso. OCP/GVA/84.5, Geneva. 1984 (unpublished mimeographed document).

Hunter,J.M. Personal communication (1986)

Karam,M., H.Schultz-Key, J.Remme. The population dynamics of *Onchocerca volvulus* after 8 years of vector control in West-Africa. *Acta Tropica*, 44 (1987) 445-457.

Le Berre,R., Contribution à l'étude biologique et écologique de *Simulium damnosum* Theobald, 1903 (Diptera, Simuliidae). *Mémoires ORSTOM*, 17 (1966)

Philippon,B., Etude de la transmission d'*Onchocerca volvulus* (Leukart, 1983) par *Simulium damnosum* Theobald 1903, en Afrique Tropicale, *Travaux et Documents de l'ORSTOM*, 63 (1977).

Prod'hon,J., J.M.Jestin, Y.Sechan, G.Hébrard, J.Prud'hom, D.Quillévéré. Influence des migrations humaines ou vectorielles sur la stratégie du programme de lutte contre l'onchocercose dans la région du Bassin de la Volta. *Cahier ORSTOM, Série Entomologie Médicale et Parasitologie*, 20 (1982) 285-298

Prost,A., J.P.Hervouet, B.Thylefors. Les niveaux d'endémicité dans l'onchocercose. *Bulletin of the World Health Organization*, 57 (1979) 655-662.

Prost,A. Le polymorphisme des onchocercoses humaines ouest-africaines. *Annales de Parasitologie Humaine Comparée*. 2 (1980) 239-245.

Prost,A., J.Vaugelaude. La surmortalité des aveugles en zone de savane ouest-africaine. *Bulletin of the World Health Organization*, 59 (1981) 773-776.

Prost,A., F.Paris. L'incidence de la cécité et ses aspects épidémiologiques dans une région rurale de l'Afrique de l'Ouest. *Bulletin of the World Health Organization*, 61 (1983) 491-499.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Remme,J., K.Y.Dadzie, M.Karam, B.Philippon, G.Zerbo. The effects of 11 years of *Simulium* control in the OCP on ABRs, ATPs, prevalence and intensity of *O.volvulus* infection and on the incidence and prevalence of eye lesions. Working paper for WHO Expert Committee on Onchocerciasis. WHO/ONCHO/EC/WP/86.4, Geneva (1986) unpublished mimeographed document.

Remme,J., K.Y.Dadzie, A.Rolland and B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. I. West African savanna. *Tropical Medicine and Parasitology*, 40, No.3 (1989) 340-347.

Rolland,A., G.Balay. L'Onchocercose dans le foyer Bissa. O.C.C.G.E. Centre Muraz. Technical Report no.111/ONCHO. Unpublished mimeographed document, translation in English by OCP, Ouagadougou (1986)

WHO, UNDP, FAO and IBRD. Onchocerciasis control in the Volta River Basin Area. Report of the preparatory assistance mission to the governments of Dahomey, Ghana, Ivory Coast, Mali, Niger, Togo and Upper Volta. World Health Organization, Geneva, WHO/OCP/73.1 (1973) unpublished mimeographed document.

World Health Organization. *Epidemiology of onchocerciasis:* report of a WHO Expert Committee. WHO Technical Report Series, No. 597 (1976)

World Health Organization. Senegambia project, Onchocerciasis control in Guinea, Guinea-Bissau, Mali, Senegal and Sierra Leone. Report of a feasibility study. OCP/JPC/2.8. Geneva (1981) unpublished mimeographed document.

World Health Organization. Ten years of onchocerciasis control in West Africa, OCP/GVA/85.1B, Geneva (1985) unpublished mimeographed document.

World Health Organization. Report on the evaluation of the socio-economic impact of the onchocerciasis control programme. OCP/JPC/7.2, Geneva (1986) unpublished mimeographed document.

Chapter 3

Epidemiological Patterns of Ocular Onchocerciasis in West Africa

INTRODUCTION

The mandate of the OCP is the control of the severe 'blinding' form of onchocerciasis which is responsible for the devastating blindness rates and underpopulation of many river valleys in the West African savanna. However, the southern boundary of this 'blinding' form of onchocerciasis was not clearly demarcated. For large parts of the pre-forest and forest zones it was not clear if the lesser severity of ocular disease was due to a more benign forest form of onchocerciasis or if it concerned the 'blinding' savanna form of the disease at a low level of endemicity. The solution of this problem would determine which areas were to be included in the vector control operations. In the early 1980s a decision was most urgently needed on the boundary of larviciding operations in southern Ivory Coast and the OCP undertook, therefore, in 1983 and 1984 a series of ophthalmological surveys in the pre-forest and forest zones of the Ivory Coast in order to clarify the epidemiological patterns of ocular onchocerciasis in this area. The interpretation of the findings, and their comparison with the epidemiological patterns of the savanna, necessitated the re-analysis of ophthalmological data from pre-control surveys in savanna villages in order to describe the savanna patterns of ocular onchocerciasis in relation to the intensity of infection in the community. This relationship would be the basis for a comparative analysis of community patterns of ocular onchocerciasis in other bioclimatic zones.

The analytical methodology is developed in chapter 3.1 which provides operational definitions of ocular lesions, their separation in early and advanced lesions, and the classification of blindness with respect to the likelihood of onchocerciasis being the cause. Community patterns of ocular microfilarial loads, ocular lesions and blindness are related to the Community Microfilarial Load (CMFL) which is the index of intensity of infection in the community as measured by the results of simple skin snip examinations. The concept of endemicity of onchocerciasis is reviewed and a measure of the public health importance of onchocerciasis in the savanna is introduced.

In chapter 3.2 the methodology is applied to the data from typical forest zones where *S.yahense* is the sole vector. The pattern of ocular onchocerciasis is compared with that of the savanna after correction for the differences in endemicity levels, and a new explanation for the differences between savanna and forest onchocerciasis is arrived at. In an addendum to this chapter a summary is provided of similar studies which have been completed or which are still ongoing in other bioclimatic zones in West Africa. The addendum provides also an overview of how the results on the epidemiological pattern of ocular onchocerciasis in the savanna are utilized in the epidemiological mapping of the extension areas and in the identification of priority villages for mass treatment with ivermectin.

Chapter 3.1

Ocular onchocerciasis and intensity of infection in the community

I. West African savanna

Tropical Medicine and Parasitology, 40 (1989) 340-347

INTRODUCTION

It has often been noted that the severity of onchocerciasis, and in particular it's ocular manifestations, varies greatly from one endemic region of the world to the other and from one bioclimatic zone within the same region to the next. Extreme differences between bioclimatic zones exist in West Africa, especially, where little blindness is found in the southern forest zones on the one hand, but rampant blindness occurs in the northern savanna zones on the other, (Budden 1963, Monjusiau 1965, Anderson and Fuglsang 1974, Prost 1980). It is generally believed that these differences can be explained by the existence of different parasite strains with varying degrees of pathogenicity (Duke et al,1981).

In the dry northern savanna zone of West Africa, onchocerciasis was not only a major public health concern, but it was also an important socio-economic problem which led to the depopulation of the relatively fertile river valleys. This situation gave birth in 1974 to the Onchocerciasis Control Programme of West Africa (OCP), to control the severe, blinding onchocerciasis in the Volta river basin area and in several neighbouring river basins. An important operational problem which arose was to delineate the boundaries of the area to be covered and this clearly necessitated epidemiological mapping of ocular onchocerciasis patterns. The severity of ocular onchocerciasis is known to be related to the intensity of infection (Anderson et al 1976, Thylefors et Brinkmann 1977). However, the level of infection varies greatly between communities and it is therefore necessary to correct for the confounding effect of the intensity of infection in the community when comparing patterns of ocular onchocerciasis between different zones. A recently advocated statistic, the Community Microfilarial Load or CMFL (Remme et al, 1986) is a good index of the community level of infection and appears to be an appropriate tool for use in such analysis.

The different relationships between the severity of ocular onchocerciasis and the intensity of infection in the community, which may be found in different bioclimatic zones in the OCP area, will be presented in a series of three papers. In this first paper, the relation between community indices of ocular onchocerciasis and the CMFL in the savanna will be described in detail. This will serve as reference for subsequent papers on the epidemiological patterns in other bioclimatic zones in West Africa.

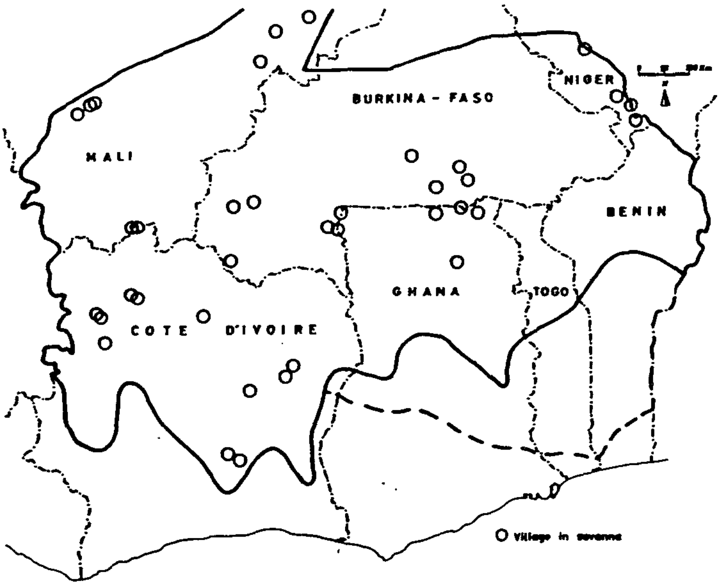
MATERIALS AND METHODS

Village selection

Only the central savanna zone of the OCP area, where the vectors responsible for transmission of infection were predominantly the savanna pair of *Simulium damnosum s.s.* and *Simulium sirbanum*, was considered for the present study and the OCP area to the east in Togo and Benin where a mixture of savanna and forest vectors occur in different proportions at different seasons of the year, was excluded. A total of 33 villages was selected for the study and these represent all villages from the central savanna zone, where the OCP has undertaken a standard ophthalmological survey shortly before or after the start of vector control (see Fig.1). Four of these do in fact represent the pooled results for pairs of very small villages which were located close to each other and which had a similar value of the CMFL.

Population size : The total census population in the 33 villages was 10870. Of these, 4484 males and 4487 females, who were present at the village and gave their consent, underwent the OCP standardised parasitological examination in the form of skin snips at both iliac crests, using the Holth's sclerocorneal punch (Prost et Prod'hon 1978). In the present study only the microfilarial count made after 30 minutes incubation of the skin snip in distilled water was considered. 6884 subjects, 3400 male and 3484 female aged 5 years and over were examined ophthalmologically using the standardised OCP protocol described elsewhere (Dadzie et al 1986).

Fig.1 Location of the study villages in the area of the Onchocerciasis Control Programme



Analytical indices used.

For the purpose of this analysis, the village populations were divided into a male and female subpopulation because of the well-known difference in the intensity of infection between the sexes (Remme et al, 1986) while this intensity is one of the main variables under consideration in the present paper. For each male and female subpopulation the values for parasitological and ophthalmological indices as defined below were determined.

Parasitological indices.

The results of the parasitological examinations from the villages, i.e. the skin snip count, were transformed into the index CMFL, the community microfilarial load, which is the geometric mean number of microfilariae per skin snip (mf/s) among adults aged 20 years and over in the community, including those with negative count. The geometric mean was calculated using the log(x+1) transformation.

Ophthalmological indices.

Three groups of ophthalmological indices were used for the analysis: community indices of ocular microfilarial loads, of ocular lesions and of blindness. Only the results of the ophthalmological examination of the right eye were used for the calculation of the indices for ocular parasite loads and ocular lesions.

A. Community indices of ocular microfilarial loads: The following mean microfilarial loads were calculated:

i. CMFL/AC, which is the community microfilarial load in the anterior chamber of the eye, was estimated by calculating the geometric mean value of microfilarial count in the anterior chamber of the right eyes of adults aged 20 years and above in the community, including those with negative counts. Since ocular microfilarial counts are recorded in coded groups (Thylefors and Brinkman, 1977), the geometric midpoints of the groups was used in the calculations and a log(x+1) transformation was applied in the calculation of the geometric mean.

ii. CMFL/C, the community load of dead microfilariae in the cornea, was estimated similarly. Living microfilariae, which are recorded separately and are also coded in groups, were not taken into account because it was considered that the addition of two group midpoints, rather than the actual values, would introduce too much variability, especially as living microfilariae are much less common.

B. Community indices of ocular lesions: These were given by the standardised prevalence of each of the four main onchocercal ocular lesions in the community viz sclerosing keratitis, iridocyclitis, choroido-retinitis and optic atrophy. These lesions were classified into the early stage and the advanced stage, when the lesion had progressed further, and were defined as follows:

i. Sclerosing keratitis.

a) An early sclerosing keratitis was a corneal opacity limited to the nasal or temporal periphery.
b) An advanced sclerosing keratitis was a corneal opacity more extensive than the former, presenting as an inferior semi-lunar opacity but which could extend to cover the pupil area.

ii. Iridocyclitis

a) An early iridocyclitis, in the acute or chronic stage, was characterised by flare, often associated with corneal precipitates, but without synechiae.
b) An advanced iridocyclitis is the same condition, but with either anterior or posterior synechiae.

iii. Choroido-retinitis

a) An early choroido-retinitis was the beginning retinal pigment epithelial atrophy, typically located temporal to the macular area.
b) Advanced choroido-retinitis is present when atrophy of chorio-capillaris, choroido-retinal scarring or sub-retinal fibrosis can be seen in addition to the atrophy of retinal pigment epithelium.

iv. Optic atrophy

a) An early optic atrophy was the early pallor of the disc or acute or chronic optic neuritis.
b) An advanced optic atrophy was the frank optic atrophy, presenting as post-neuritic optic atrophy, often associated with sheathing of the central retinal vessels and increased peri-papillary pigmentation. Primary optic atrophy was considered not to be related to onchocerciasis and was therefore excluded from the analysis.

C. Community indices of blindness: Blindness was defined according to the standard definition of the WHO as the inability to count fingers at 3 meters with the better eye (WHO 1977). Severe visual field constriction to less than 10°, estimated by fundus examination and from the patient's behaviour, was recorded as blindness and was included in this group. The forms of 410 blind, 258 males and 152 females were reviewed and an attempt was made to separate blindness due to onchocerciasis from blindness which was unrelated to it. In this exercise three main categories of blindness were identified.

1. Blindness due to typical ocular onchocerciasis and blindness very likely to be due to it. 58.5% of all cases, i.e. 161 male and 79 female blind, were classified into this category.

2. Blindness due to causes other than onchocerciasis, such as cataract, trachoma, trauma, congenital anomalies and infection and blindness unlikely to be due to ocular onchocerciasis. 52 male and 41 female blind, representing 22.7% of all blind, fell into this category.

3. Blindness whose etiology was uncertain in the sense that no clear signs could be elicited to allow an unequivocal association or not with onchocerciasis. This was the case for the remaining 45 male and 32 female blind (18.8% of all cases) and this group included 19 cases who were blind from bilateral phthisis bulbi and 28 patients reported by the village community to be blind but who were not present to be examined by the ophthalmologist for various reasons.

As a result of this exercise therefore, three indices of blindness were defined for use in the analysis, i.e.

a) The standardized prevalence of all blindness (i.e. all the above three groups)
b) The standardized prevalence of blindness definitely due to onchocerciasis (which is group 1 only)
c) The standardized prevalence of "blindness excluding definite non-onchocercal causes" (defined to include groups 1 and 3).

Statistical analysis.

The relationship between the above indices of ocular onchocerciasis and the CMFL was analyzed for each sex using a univariate regression analysis without weighting for the population size. F-statistics were calculated to test the significance of the difference in slopes between the sexes and a standard Analysis of Covariance was used to compare the relative position of the regression lines under the assumption of equal slopes (Armitage, 1971). All standardized prevalences were calculated using the direct method and the OCP standard population which consists of the first 22041 persons examined by the epidemiological evaluation teams of the OCP (see Table 1).

Table 1: OCP standard population by age and sex

Age in years	Male	Female	Total
0-4	1,401	1,353	2,754
5-9	1,769	1,507	3,276
10-14	1,739	1,465	3,204
15-19	1,085	921	2,006
20-29	1,409	1,738	3,147
30-49	2,388	2,821	5,209
50+	1,208	1,237	2,445
Total	10,999	11,042	22,041

RESULTS

Table 2 gives the correlation coefficients for the relationship between the various community indices of ocular onchocerciasis and the CMFL, and provides a good general overview of the main findings of the present study. As can be seen, there exists a high level of correlation between the mean ocular microfilarial loads and the CMFL, and equally high correlation coefficients were obtained for the prevalence of advanced lesions of the anterior segment of the eye and for the prevalence of the various definitions of blindness. The level of correlation is much lower, though still statistically significant, for the advanced lesions of the posterior segment of the eye. Among the early lesions it is only sclerosing keratitis which shows a distinctly significant correlation with the intensity of infection in the community.

Table 2. Coefficients of correlation between indices of ocular onchocerciasis and the CMFL

	Coefficient of correlation with the CMFL		
Indices of ocular onchocerciasis	Male populations only	Female populations only	Both male and female populations
Ocular microfilarial loads			
CMFL/AC	0.72^{***}	0.72^{***}	0.74^{***}
CMFL/C	0.76^{***}	0.74^{***}	0.77^{***}
Prevalence of early lesion			
Sclerosing keratitis	0.67^{***}	0.49^{**}	0.64^{***}
Iridocyclitis	0.33	0.38^{*}	0.41^{*}
Optic Disk	0.29	0.23	0.35^{**}
Choroido-retinitis	0.21	0.36^{*}	0.34^{*}
Prevalence of advanced lesion			
Sclerosing keratitis	0.67^{***}	0.70^{***}	0.71^{***}
Iridocyclitis	0.68^{***}	0.53^{**}	0.65^{***}
Optic Disk	0.63^{**}	0.36^{*}	0.60^{***}
Choroido-retinitis	0.45^{*}	0.34	0.49^{***}
Prevalence of blindness			
Total blindness	0.64^{***}	0.68^{***}	0.68^{***}
Excl. non-onchocercal causes	0.63^{***}	0.74^{***}	0.70^{***}
Definite onchocercal blindness	0.66^{***}	0.62^{***}	0.67^{***}

*:$P<0.05$; **:$P<0.01$; ***:$P<0.001$

The relationship between the two indices of ocular microfilarial loads and the CMFL is demonstrated in detail in Fig.2a and Fig.2b. As can be seen, there exists a clear linear relationship between the mean microfilarial loads in the eye and the mean loads in the skin, and the relationship appears to be approximately equal for both sexes. This conclusion is confirmed by a formal statistical comparison of the regression lines for the two sexes for which the results are shown in Table 3, together with the values of the various regression coefficients. There exists between the two sexes no statistically significant difference in the slope nor in the location of the regression lines for ocular microfilarial loads. It may be noted that the mean microfilarial loads in the anterior chamber of the eye are generally higher than the mean loads of dead microfilariae in the cornea.

Figure 3 gives two examples of the relationship between the prevalence of early ocular lesions and the CMFL. The prevalence of early sclerosing keratitis shows also a significant relationship with the intensity of infection, even though there is considerable variability, especially for the females (Fig.3a). There is no difference between the linear regression lines for the two sexes, and there is virtually no early sclerosing keratitis in communities with a CMFL of less than 10 mf/s. The other early lesions show a much poorer correlation with the CMFL. The prevalence of early iridocyclitis ranges from 0% to as high as 20%, and, though the general pattern appears to be somewhat similar to that for sclerosing keratitis, the variability is much greater and no clear linear relation with the CMFL can be determined.

Fig.2 Community indices of ocular microfilarial loads in relation to the CMFL (● and solid lines: males; o and broken lines: females)

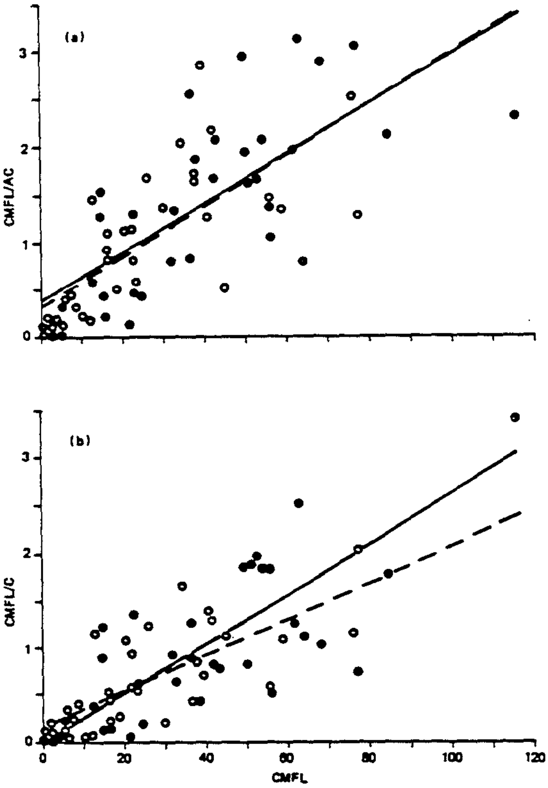
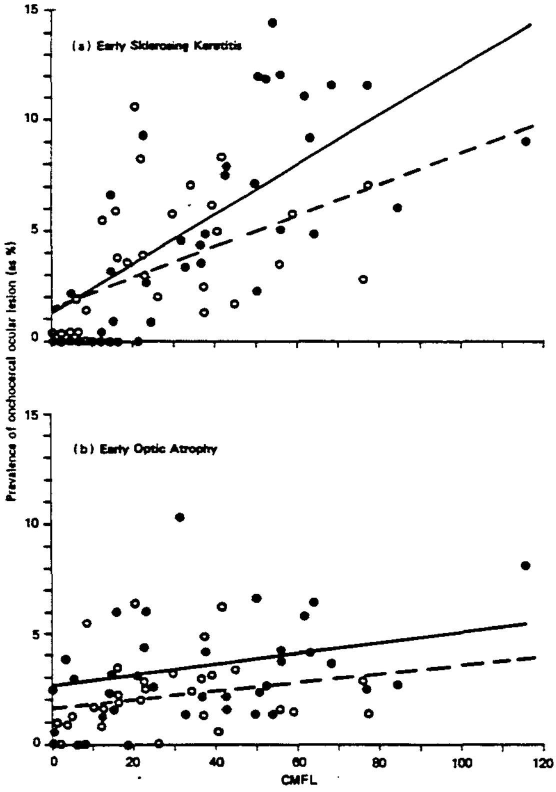


Table 3. Regression coefficients for the linear regression of community indices of ocular onchocerciasis on the CMFL

	Male populations		Female populations		Statistical significance of difference between the two sexes		Male and female populations	
Indices of ocular onchocerciasis	Intercept	Slope	Intercept	Slope	Test on slope	Analysis of covariance	Intercept	Slope
Ocular microfilarial loads								
CMFL/AC	0.38	0.026	0.32	0.027	N.S.	N.S.	0.34	0.026
CMFL/C	-0.02	0.026	0.15	0.019	N.S.	N.S.	0.06	0.024
Prevalence of early lesion								
Sclerosing keratitis	1.25	0.112	1.48	0.070	N.S.	N.S.	1.15	0.103
Iridocyclitis	4.17	0.071	2.65	0.053	N.S.	N.S.	2.97	0.078
Optic Disk	2.63	0.025	1.61	0.019	N.S.	P<0.05	1.87	0.030
Choroido-retinitis	2.30	0.019	0.80	0.037	N.S.	N.S.	1.34	0.032
Prevalence of advanced lesion								
Sclerosing keratitis	0.07	0.083	-0.29	0.070	N.S.	N.S.	-0.27	0.083
Iridocyclitis	0.21	0.079	1.01	0.044	N.S.	N.S.	0.56	0.067
Optic Disk	1.54	0.077	0.83	0.034	N.S.	P<0.001	0.76	0.074
Choroido-retinitis	1.15	0.053	0.53	0.019	N.S.	P<0.01	0.50	0.051
Prevalence of blindness								
Total blindness	1.54	0.099	0.90	0.106	N.S.	N.S.	1.13	0.104
Excl. non-oncho causes	0.95	0.084	-0.08	0.109	N.S.	N.S.	0.37	0.096
Definite oncho blindness	0.42	0.077	0.09	0.076	N.S.	N.S.	0.18	0.079

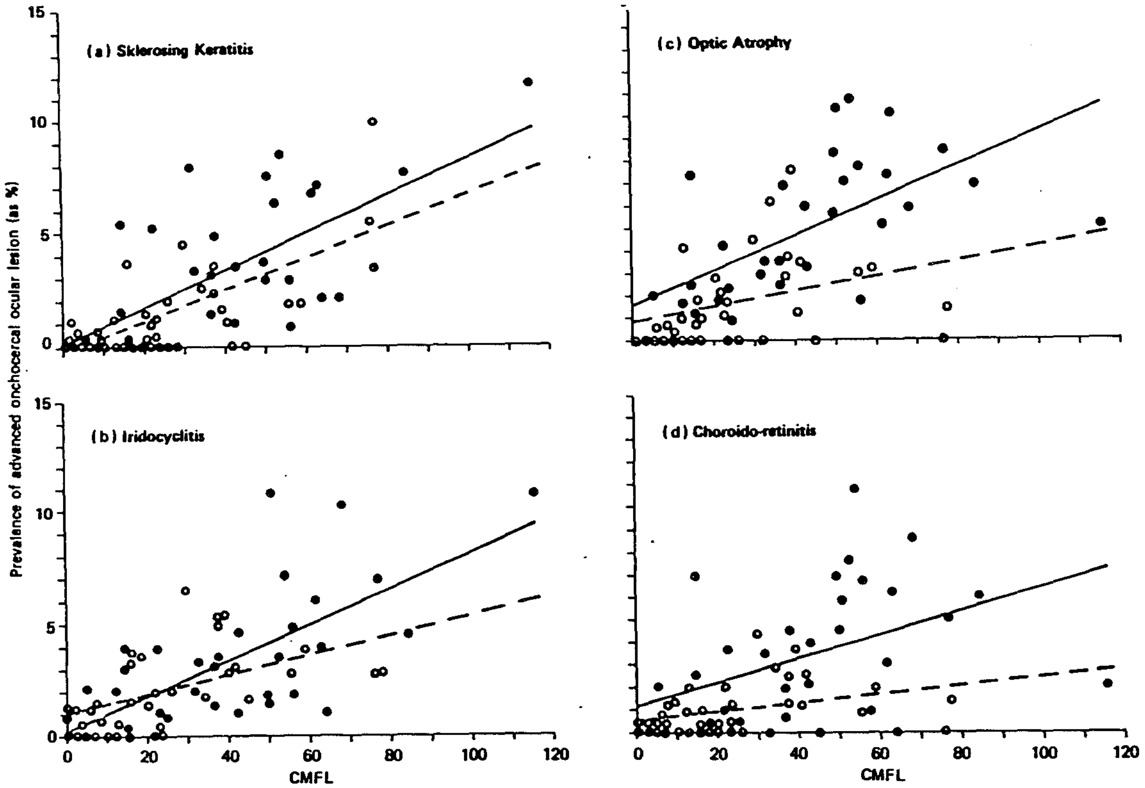
Fig.3 Prevalence of early onchocercal ocular lesions in relation to the CMFL
(● and solid lines : males; o and broken lines: females)



The pattern for the early lesions of the posterior segment of the eye is quite different from those of the anterior segment, as can be seen in Fig.3b for the early lesions of the optic disc. With increasing CMFL there is hardly any increase in the prevalence of early lesions of the optic disc, which appears to be nearly independent of the intensity of infection in the community. The prevalences for males are generally higher than those for females, a finding which is of borderline statistical significance (Table 3). The pattern for the early choroido-retinitis is not very different from those for the optic disc: the correlation is poor and the prevalence does not increase anymore from a CMFL of 20 mf/s upward. However, below a CMFL of about 10 mf/s, virtually no choroido-retinitis is found.

More regular are the results for the advanced eye lesions, and particularly for the lesions of the anterior segment of the eye (Figs.4a and 4b). Both the prevalence of advanced sclerosing keratitis and of advanced iridocyclitis show a clear linear relationship with the CMFL and there is no significant difference between the regression lines for the two sexes. There is even a fair similarity in the pattern for the two types of lesions of the anterior segment of the eye, and the regression lines for males are nearly identical. The main difference between the two lesions is that, with few exceptions, no advanced sclerosing keratitis is found in populations with a CMFL of less than 15-20 mf/s, while advanced iridocyclitis is quite common at these lower endemicity levels.

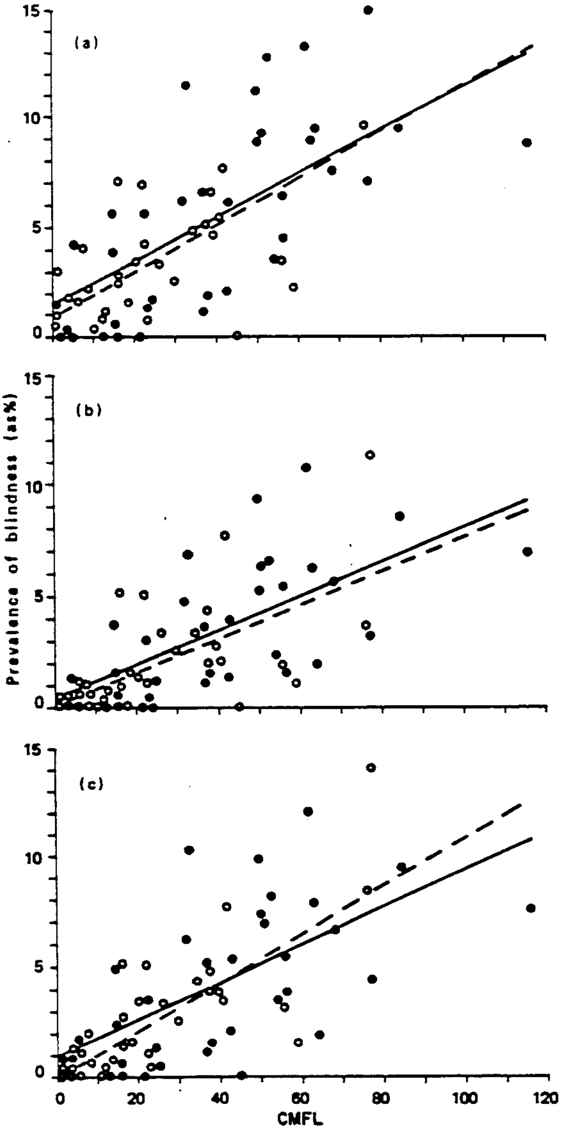
Fig.4 Prevalence of advanced onchocercal ocular lesions in relation to the CMFL (● and solid lines: males; o and broken lines: females)



Also the prevalence of advanced lesions of the posterior segment of the eye, viz optic atrophy and choroido-retinitis (Figs.4c and 4d), is clearly associated with the intensity of infection in the community, albeit that the variability is much greater than for the advanced lesions of the anterior segment. Of all the four advanced lesions, it is the lesion of the optic disc which has the highest prevalence generally, and this is particularly so for the male populations. There exists a remarkable, and a highly significant, difference between the sexes in the prevalence of advanced lesions of the optic disc, with the males being much more affected than the females at all levels of the CMFL. A significant difference between the sexes is also observed for advanced choroido-retinitis though the difference is less pronounced in this case.

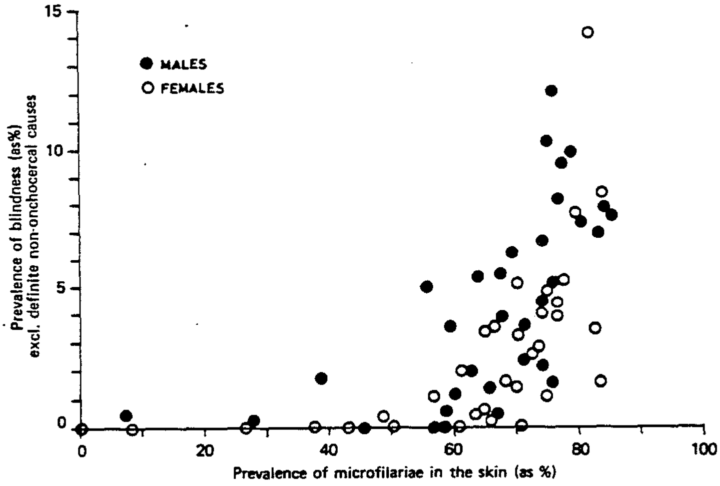
The Figures 5a-5c show the relationship between the prevalence of blindness and the CMFL for the three different classifications of blindness used in the analysis, and it can be seen that the relationship is clearly linear in each case. If all blind cases are included, the level of blindness is already important at low intensities of infection, and the prevalence of blindness exceeds 2% in several populations with a CMFL of less than 10 mf/s. However, the pattern changes considerably if blindness, due to causes other than onchocerciasis, is excluded and Figs. 5b and 5c show that onchocercal blindness was only rarely found in populations with a CMFL of less than 15 mf/s.

Fig.5 Prevalence of different categories of blindness in relation to the CMFL, (a) All blindness, (b) Definite onchocercal blindness only, (c) Blindness excluding definite non-onchocercal causes (● and solid lines: males; o and broken lines: females)



For the purpose of comparison, Fig.6 shows the relationship between the standardized prevalence of "blindness excluding definite non-onchocercal causes" as was also used in Fig.5c, and the standardized prevalence of mf in skin snips. The relationship appears to be an exponential one with a strong variability in the prevalence of blindness for communities with a prevalence of mf in the skin of more than 60%. The level of blindness in females is much lower than in male populations with a comparable prevalence of mf in the skin.

Fig.6 Prevalence of blindness excluding non-onchocercal causes in relation to the prevalence of microfilariae in the skin



DISCUSSION

Though it has long been realized that the severity of ocular onchocerciasis in the West African savanna is closely related to the level of infection in the community (Budden 1957, Rolland 1969), there have been very few attempts to arrive at a quantitative description of this relationship. The most important previous work was done by Prost et al (1979) who used the prevalence of infection, as measured by the presence of microfilariae in skin snips, to define three endemicity levels of onchocerciasis, viz. hypo-endemicity for a prevalence of less than 35%, meso-endemicity for a prevalence between 35% and 60%, and hyper-endemicity for a prevalence of 60% or more. These authors could show that the disease is socially inapparent in hypoendemic communities but that onchocerciasis may become intolerable in hyperendemic villages. The prevalence of infection is therefore a good qualitative tool for the identification of villages where onchocerciasis is not a severe public health problem. However, as will be apparent below, the prevalence is not a very good index of the severity of disease among the hyperendemic communities where there may be little difference in prevalence of infection but large variation in the levels of intensity of infection.

At the individual level, the severity of ocular onchocerciasis is known to be associated with the intensity of infection (Anderson et al 1976, Thylefors and Brinkmann 1977), and it is thus not completely surprising that our analysis has demonstrated a high degree of correlation between the community indices of ocular onchocerciasis and the intensity of infection in the community. Most community indices of the various stages of ocular onchocerciasis, i.e. indices of ocular parasite loads, of ocular lesions and of onchocercal blindness, showed a clear and generally linear relationship with the CMFL, and this index of the intensity of infection appears therefore to be also a good quantitative index of the severity of ocular disease in the community, even though the degree of correlation was low for some of the ocular indices.

The mean microfilarial loads in the anterior chamber of the eye and in the cornea, as measured by the CMFL/AC and CMFL/C respectively, show a very good linear relationship with the CMFL, supporting the view that the level of ocular invasion is a direct function of the general intensity of infection (Anderson et al 1976). It is noteworthy that the relationship appears exactly the same for both males and females.

The correlation between the prevalence of the early ocular lesions and the CMFL is poor, except for early sclerosing keratitis. The diagnosis of the early onchocercal eye lesions is known to be often uncertain and susceptible to considerable observer variation (Dadzie et al 1986), and this may explain much of the observed variability. It would therefore appear that the early lesions are not sufficiently reliable to be used in a comparative analysis of ocular onchocerciasis patterns. However, the diagnosis of an early sclerosing keratitis, viz, a temporal or nasal peripheral opacity of the cornea invaded by microfilariae, is a relatively more definite diagnosis of an early onchocercal eye lesion and this explains the much better correlation between the prevalence of this particular early eye lesion and the CMFL. Because of these findings, we will retain from the four early onchocercal lesions only early sclerosing keratitis for the comparative analysis of ocular onchocerciasis patterns in different bioclimatic zones for which the results will be reported in subsequent papers.

All indices of advanced eye lesions show a significant correlation with the CMFL, but the advanced lesions of the anterior segment of the eye show a better linear correlation, as does also early sclerosing keratitis. This finding, together with the results for ocular microfilarial loads, clearly demonstrates that the severity of sclerosing keratitis and iridocyclitis is a direct function of the intensity of infection and the related level of microfilarial invasion of the anterior segment of the eye. However, it should be remembered that these lesions of the anterior segment of the eye tend to obstruct the view of the fundus which may be harbouring an equally blinding disease in a considerable proportion of cases in communities with very high endemicity levels of infection (Rolland 1974, Rolland et al 1979, Anderson et al 1976), and this may partly explain the lesser degree of correlation for the lesions of the posterior segment of the eye.

Advanced optic atrophy is found more frequent than advanced choroido-retinitis, and the relative importance of optic atrophy in our study is much higher than was observed in the study in the savanna of the Cameroon (Anderson et al 1976). It has been suggested that onchocercal optic atrophy is more likely to result from optic nerve disease than to develop consecutive to retinal disease (Bird et al 1975). It is therefore not impossible that the development of optic atrophy could precede the development of choroido-retinitis and thus be found more frequently. Furthermore, some of the observed optic atrophy may be due to causes other than onchocerciasis, including nutritional and toxic factors, and possibly hereditary disorders. The prevalence of both posterior segment lesions is higher in males than in females and this difference remains statistically significant after correction for the intensity of infection. It is difficult to explain this observation but it may be speculated that intrinsic hormonal factors contribute to this particular difference between the sexes.

The inevitable presence of blindness due to causes other than onchocerciasis in endemic communities complicates the proper description of the pattern of onchocercal blindness. We have tackled this problem by using in our analysis three definitions of the prevalence of blindness which differ in their level of certainty with regard to the cause being attributable to onchocerciasis or not. The first classification of blindness, defined to include all blindness irrespective of cause, is of historic interest and obviously overestimates the level of onchocercal blindness. In communities with a CMFL of less than 10 mf/s, over two-thirds of the blindness is not caused by onchocerciasis, in our study. The second classification of blindness, whose definition limits it to definite onchocercal cause only, is particularly appropriate for these lower endemicity levels. It, however, underestimates the prevalence of blindness in the higher endemicity levels. In such communities with a CMFL of over 40 mf/s, the proportion of blindness not due to onchocerciasis is low. However, there is also a considerable proportion of blindness whose cause cannot be determined with certainty even though the epidemiological situation would suggest that onchocerciasis may be a likely cause. The third classification of blindness, defined to exclude blindness not caused by onchocerciasis but to include blindness of definite onchocercal as well as of uncertain etiology, appears the best compromise for describing the level of onchocercal blindness in relation to endemicity.

Prost et al (1979) have shown for a large number of male populations that the prevalence of all blindness, irrespective of cause, was generally less than 1%-1.5% among hypoendemic populations but that these blindness levels ranged from 0% to 14% in the hyperendemic group. Our results for the relation between the prevalence of blindness, after excluding definite non-onchocercal causes, and the prevalence of microfilariae in the skin in both male and female populations, are consistent with this and suggest, like Prost et al, that onchocercal blindness is only rarely found below a prevalence of infection of 50-60%. Our findings also confirm that there exists, within the hyperendemic group, an extreme variation in blindness rates which range from 0% to 15% and that this wide spectrum of ocular disease cannot be effectively discriminated by the prevalence of infection.

In contrast, there exists a clear linear relationship between the level of blindness and the CMFL, the index of the intensity of infection in the community. It is evident from this finding, as well as from the above results on ocular lesions, that the CMFL is a superior index of endemicity which allows a better prediction of the severity of the disease in the community, and particularly so for populations with a prevalence of infection of more than 60%. Ocular onchocerciasis begins to become an important public health problem from a CMFL of 15-20 microfilariae per snip, it is very serious from 40 microfilariae onward and becomes rampant above 60 microfilariae per snip. New terms may be introduced for this grouping, and the term holo-endemicity has already been used to refer to villages with a CMFL of more than 40 microfilariae per snip. However, we are of the opinion that the creation of a new classification is probably counterproductive and would direct attention away from the introduction of a quantitative measure for the endemicity level which relates directly to the severity of the disease in the community.

The limitation of the prevalence of infection as an index for describing the severity of onchocerciasis is also obvious when comparing the sexes. Given a certain prevalence of infection, females have a much lower prevalence of blindness. This observation can be explained by the much lower intensity of infection among females whilst the relation between the prevalence of blindness and the CMFL is linear and is virtually the same for both sexes. Because of this similarity it would be acceptable to combine the two sexes and calculate the prevalence of blindness and CMFL for the total village. However, it should be noted that in case of a great difference in intensity of infection between the sexes, such a combination would result in a loss of information by lowering the CMFL for the highly infected sex to the village average. It is, especially, for the high CMFLs that the typical pathology of the savanna onchocerciasis can be unequivocally demonstrated.

REFERENCES

Anderson,J., H.Fuglsang, P.J.S.Hamilton, T.F.de C.Marshall. Studies on onchocerciasis in the United Cameroon Republic. II. Comparison of onchocerciasis in rainforest and sudan-savanna. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 68 (1974) 209-222.

Anderson,J., H.Fuglsang, T.F.de C.Marshall. Studies on onchocerciasis in the United Cameroon Republic. III. A four-year follow-up of 6 rainforest and 6 savanna villages. The incidence of ocular lesions. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 70 (1976) 362-373.

Armitage,P. *Statistical methods in medical research*. Blackwell, Oxford (1971).

Budden,F.H. Comparative study of ocular onchocerciasis in savanna and rainforest. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 57 (1963) 64-70.

Budden,F.H. Natural History of Onchocerciasis. *British Journal of Ophthalmology*, 41 (1957) 214-227

Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna. *Tropical Medicine and Parasitology*, 37 (1986) 263-270.

Duke,B.O.L. Geographical aspects of onchocerciasis. *Annales de la Société Belge de Medecine Tropicale*. 61 (1981) 179-186.

Monjusiau,A.G.M., J.Lagraulet, R.d'Haussy, G.W.Goeckel. Aspect ophtalmologiques de l'onchocercose au Guatemala et en Afrique occidentale. *Bulletin of the World Health Organization*, 32 (1965) 339-355

Prost,A., J.Prod'hon. Le diagnostique parasitologique de l'onchocercose, revue critique des méthodes en usage. *Médecine Tropicale*, 38 (1978) 519-532.

Prost,A., J.P.Hervouet, B.Thylefors. Les niveaux d'endémicité dans l'onchocercose. *Bulletin of the World Health Organization*, 57 (1979) 655-662.

Prost,A. Le polymorphisme des onchocercoses humaines ouest-africaines. *Annales de Parasitologie Humaine Comparée*, 2 (1980) 239-245.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Rolland,A., G.Balay. L'Onchocercose dans le foyer Bissa. O.C.C.G.E. Centre Muraz. Technical Report no.111/ONCHO. Unpublished mimeographed document, translation in English by OCP, Ouagadougou (1986)

Rolland,A. Résultats de deux examens oculaires pratiques à 6 ans d'intervalle dans deux villages onchocerquiens de Haute Volta. *Bulletin of the World Health Organization*, 51 (1974) 257-261.

Rolland,A., B.Thylefors, C.Pairault. Evolution sur neuf ans de l'onchocercose oculaire dans une communaute villageoise d'Afrique occidentale. *Bulletin of the World Health Organization*, 56 (1978) 805-810.

Thylefors,B., U.K.Brinkmann. The microfilarial load in the anterior segment of the eye. A parameter of the intensity of infection of onchocerciasis. *Bulletin of the World Health Organization*, 55 (1977) 731-737.

World Health Organization. *International Classification of diseases* Volume I. Geneva (1975).

Chapter 3.2

Ocular onchocerciasis and intensity of infection in the community

II. West African rainforest foci of Simulium yahense

Tropical Medicine and Parasitology, 40 (1989) 348-354

INTRODUCTION

Onchocerciasis in the West African rainforest belt has been known to cause little or no blindness and low prevalence of eye lesions. Comparative studies that have been done in the rainforest and in the savanna in West Africa in the last two decades have confirmed these findings in general, (Budden 1963, Anderson et al 1974, Prost 1980). However, the details in the results of these studies have varied and inconsistencies with regard to the relative frequencies of the different onchocercal eye lesions have been reported. Several reasons may account for the discrepancies in the different reports and these may include regional differences in the epidemiological pattern of ocular onchocerciasis as well as methodological factors. Some of such important factors may be the discrepancy in the definitions of eye lesions by the different authors and the lack of correction for the intensity of infection in the different communities in the method of comparative analysis used by the different authors.

In a companion paper (Remme et al 1989) a quantitative approach for analysing the burden of ocular onchocerciasis in relation to the intensity of infection in the community, was elaborated for the bioclimatic zone of West African Savanna. In this paper, we will apply this method of analysis to describe the pattern of ocular onchocerciasis which is prevalent in an area in the rainforest where the blackfly, *Simulium yahense* is the sole vector. Furthermore, we shall compare the pattern of ocular onchocerciasis existing there with that found in the savanna bioclimatic zone. We shall investigate the factors which could account for any differences found between the two bioclimatic zones and finally, we will attempt to advance explanations for any observed variations in the clinical patterns of ocular onchocerciasis in the two zones.

MATERIALS AND METHODS

Village Selection:

Five villages in south-western Ivory Coast forest where the vector for the transmission of onchocerciasis is exclusively *Simulium yahense*, were selected for the analysis, (Fig. 1). These villages had been surveyed in the course of the epidemiological mapping of onchocerciasis for the Onchocerciasis Control programme in West Africa (OCP).

Population size: 1020 people, 486 males and 534 females of all ages underwent parasitological examination following the OCP standardised methodology as described elsewhere (Prost et Prodhon 1978). 720 subjects, 341 males and 379 females aged 5 years and over were examined ophthalmologically according to OCP protocol (Dadzie et al 1986).

Analytical indices used.

1) *The parasitological index:* This was the CMFL, the community microfilarial load which is the geometric mean number of microfilariae per skin snip (mf/s) among adults aged 20 years and over, including those with negative counts, in the community (Remme et al 1986). Male and female indices were estimated separately.

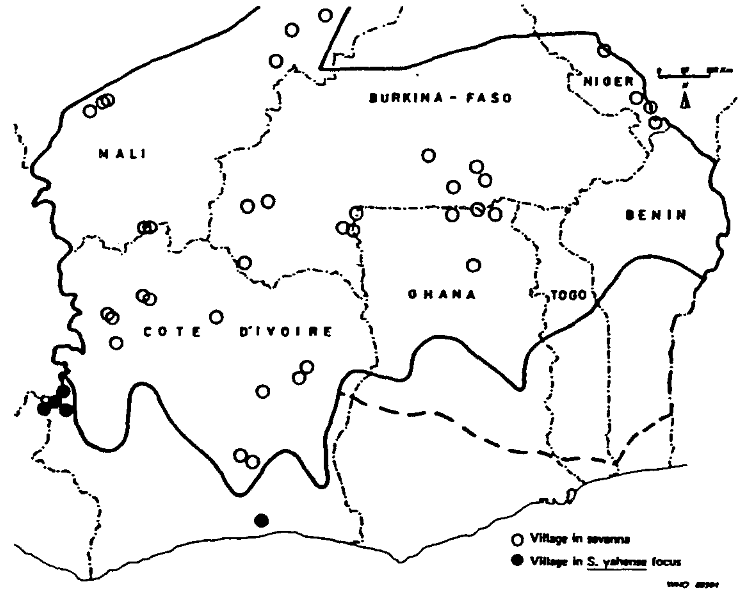
2) *Ophthalmological indices* comprised of:

a) the community indices of ocular microfilarial load, which are:

i. CMFL/AC, the community microfilarial load of the anterior chamber of the eye, being the geometric mean of the microfilarial count of the anterior chamber of the right eye of adults aged 20 years and above including those with negative count.

ii.CMFL/C, the community load of dead microfilariae in the cornea, of the right eye, defined as above.

Fig.1 Location of study villages in Yahense forest areas and in the savanna



b) the standardised prevalences of the four typical onchocercal eye lesions, viz. sclerosing keratitis, iridocyclitis, post-neuritic optic atrophy and choroido-retinitis. These lesions were graded into the early and the advanced stages. Only lesions at the advanced stage and early sclerosing keratitis were considered, following the conclusions from the companion paper that the other early lesions, viz. iridocyclitis, post-neuritic optic atrophy and choroido-retinitis, are not sufficiently reliable and specific for their utilisation in comparative analysis.

c) the standardised prevalence of blindness excluding cases of blindness definitely not caused by onchocerciasis was used in this paper.

The detailed definitions of the eye lesions as well as the classification of blindness into the above category has been reported in the companion paper (Remme et al 1989).

Statistical Analysis.

Because of the considerable difference in the intensity of infection between the sexes in the five rainforest villages, we divided each village population into a male and a female subpopulation in order to enhance the power of the comparative analysis of the epidemiological pattern between the *S.yahense* foci and the savanna. The relationship between the indices of ocular onchocerciasis and the community indices of microfilarial loads in the skin and in the eye was analysed using a univariate regression analysis without weighting for the size of the subpopulation. F-statistics were calculated to test the significance of the difference between the slopes of regression lines for the ten rainforest subpopulations on the one hand and for the sixty-six subpopulations from the savanna, which were introduced from the companion paper, on the other. A standard Analysis of Covariance was used to compare the relative position of the regression lines under the assumption of equal slopes (Armitage 1971). All prevalences were standardised prevalences which had been calculated using the direct method and the OCP standard population.

RESULTS

Indices of ocular onchocerciasis in relation to the CMFL.

The first section of the results deals with the relationship between the various community indices of ocular onchocerciasis and the mean load of microfilariae in the skin as measured by the CMFL. The summary of the results is found in Table 1, which gives the coefficients of correlation between the ocular indices and the CMFL in the *S.yahense* forest foci. Among all the indices of ocular onchocerciasis, only the CMFL/AC and the CMFL/C show a statistically significant correlation with the CMFL. Table 1 gives further the results of significance tests of the difference in the slope and position of the regression lines for the Yahense forest foci compared to the regression lines for the savanna villages. It is obvious that the relationship between the severity of ocular onchocerciasis and the intensity of infection in the Yahense forest foci is completely different from that in the savanna. The difference in the regression lines between the two bioclimatic zones is statistically significant for all the indices of ocular onchocerciasis. It is most marked for early sclerosing keratitis, advanced iridocyclitis and for the prevalence of blindness excluding definite non-onchocercal causes.

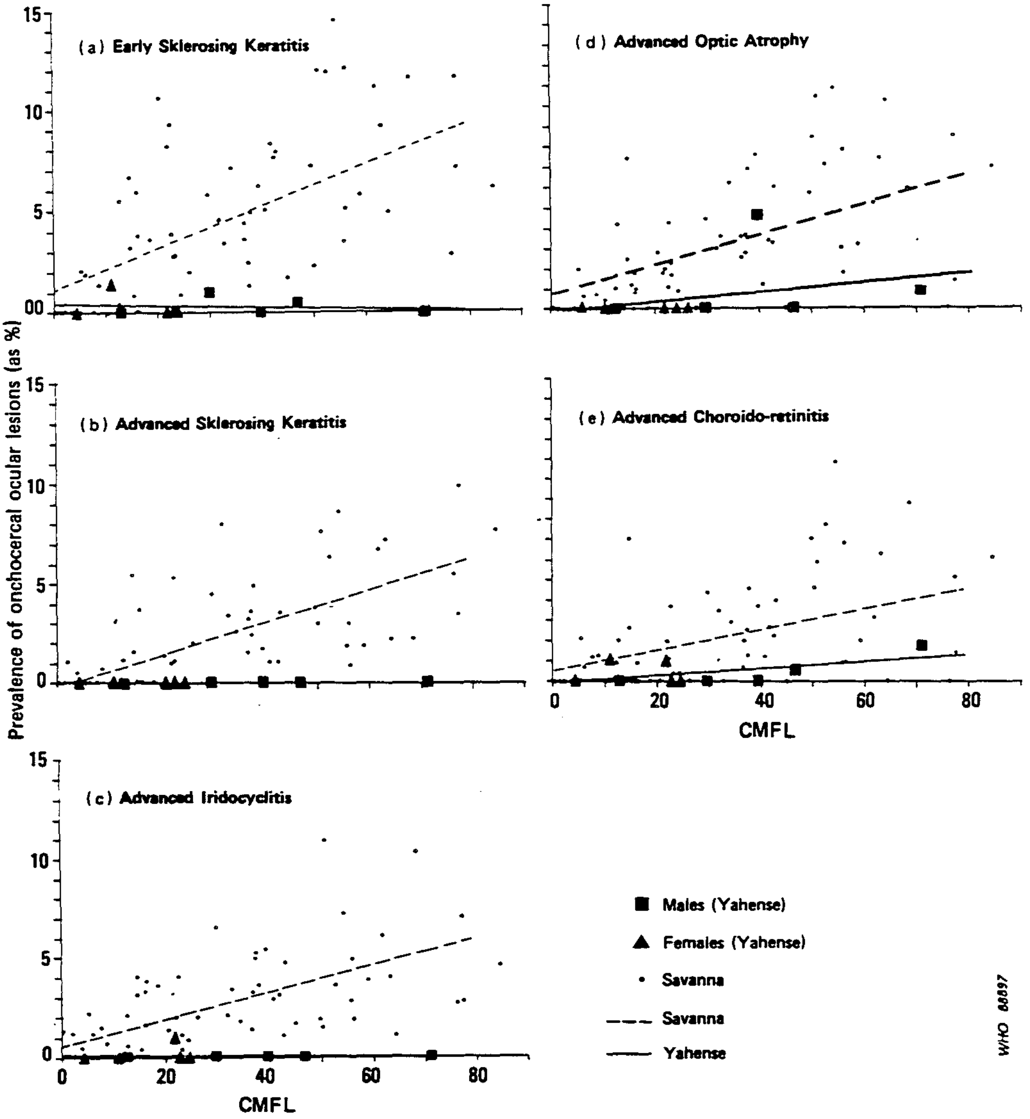
Table 1. Coefficients of correlation between indices of ocular onchocerciasis and the CMFL and a comparison of the regression lines for Yahense foci with the savanna

		Statistical significance of difference between Yahense forest and savanna	
Indices of ocular onchocerciasis	Coefficient of correlation with CMFL in Yahense foci	Test on slope	Analysis of Covariance
Ocular microfilarial loads			
CMFL/AC	0.75*	N.S.	P<0.01
CMFL/C	0.72*	P<0.05	P<0.05
Prevalence of ocular lesion			
Early sclerosing keratitis	-0.16	P<0.05	P<0.001
Advanced Sclerosing keratitis	0.00	P<0.05	P<0.01
Advanced iridocyclitis	-0.12	P<0.05	P<0.001
Advanced optic atrophy	0.33	N.S.	P<0.01
Advanced choroido-retinitis	0.51	N.S.	P<0.05
Prevalence of blindness, excluding definite non-onchocercal causes	-0.29	P<0.05	P<0.001

*: P<0.05

Fig. 2a-2e illustrate in detail the relationship between the standardised prevalence of certain onchocercal eye lesions and the CMFL in the Yahense forest and in the savanna. Whilst the early form of sclerosing keratitis is only very occasionally found in the Yahense foci, not a single advanced sclerosing keratitis and only one case of advanced iridocyclitis has been diagnosed in those villages. The absence of the advanced lesions of the anterior segment of the eye is particularly remarkable for the subpopulations with a CMFL between 40 and 70 mf/s. This pattern contrasts sharply with the results for the savanna where a clear linear relationship between the prevalence of these lesions of the anterior segment of the eye and the CMFL exists, and where a CMFL of 40-70 mf/s goes together with a predicted prevalence of 3-5% for each of the advanced lesions of the anterior segment and of 5-8% for early sclerosing keratitis.

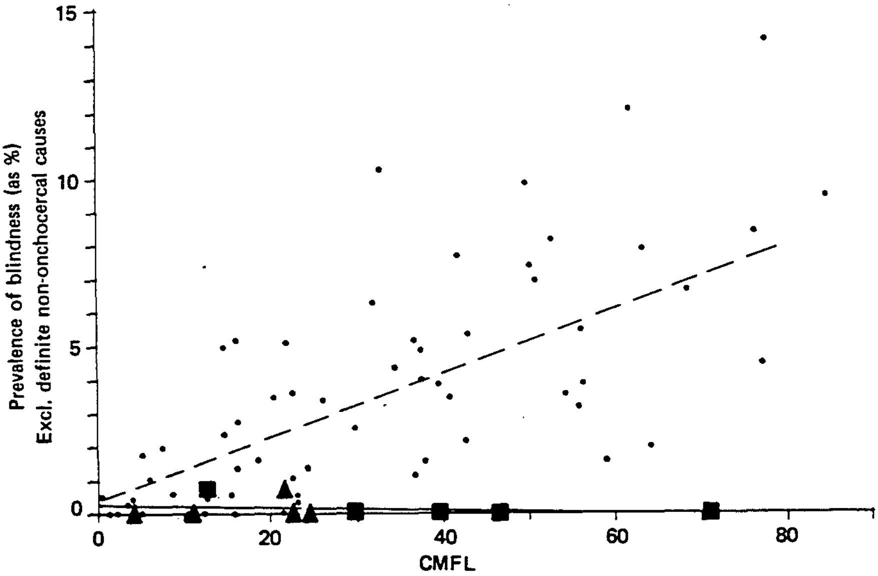
Fig.2 Prevalence of onchocercal ocular lesions in relation to the Community Microfilarial Load (CMFL)



Lesions of the posterior segment of the eye are also rare in the Yahense foci (Fig.2d-2e). Of the only three cases of advanced optic atrophy which were found, two, both males from the same small village were responsible for a rather inflated prevalence of 4.5%, a value which fits more in the pattern for savanna villages. When this outlier is disregarded, clearly, a completely different pattern of optic atrophy in the Yahense foci compared to the savanna is found. The difference in pattern is, however, less marked for advanced choroido-retinitis because of the lower prevalence for this lesion in the savanna as compared to advanced optic atrophy.

Fig.3 shows that the pattern of blindness is also completely different between the Yahense foci and the savanna. The prevalence of "blindness excluding definite non-onchocercal causes" does not increase at all with the CMFL in the Yahense forest in contrast to the deep linear increase observed in the savanna. The total number of blind found in the Yahense villages was four and two were definitely not due to onchocerciasis and these were excluded from the analysis. Of the remaining two, one was not seen by the ophthalmologist and the cause of blindness of the fourth was indeterminate.

Fig.3 Prevalence of blindness excluding non-onchocercal causes in relation to the CMFL



The relationship between the community microfilarial load in the eye and in the skin is shown in Figs.4a and 4b. Both the CMFL/AC and the CMFL/C show a linear relationship with the CMFL for the Yahense villages as well as for the savanna villages. However, the regression lines for the Yahense foci run significantly lower and this implies that for the same load of skin microfilariae, a lower load of microfilariae are found in the eyes of subjects in the Yahense forest than in the savanna.

Prevalence of ocular lesions in relation to the CMFL/AC.

The second section of the analysis deals with the relationship between the prevalence of the various onchocercal ocular lesions and the community microfilarial load of the anterior chamber of the eye, CMFL/AC in both the Yahense forest and the savanna. The results are summarised in Table 2 and the detailed illustrations are found in Fig.5a-5e. This section of the analysis includes not only new results for the Yahense foci but reports also on this type of results for the first time for savanna villages. In the savanna, a high degree of correlation between the prevalence of ocular lesions and the CMFL/AC exists. The correlation coefficients ranging from 0.60 to 0.70 are all highly significant. It is noteworthy that the prevalence for the two advanced lesions of the posterior segment of the eye show a better correlation with the CMFL/AC than with the CMFL.

Fig.4 Community indices of ocular microfilarial loads in relation to the CMFL

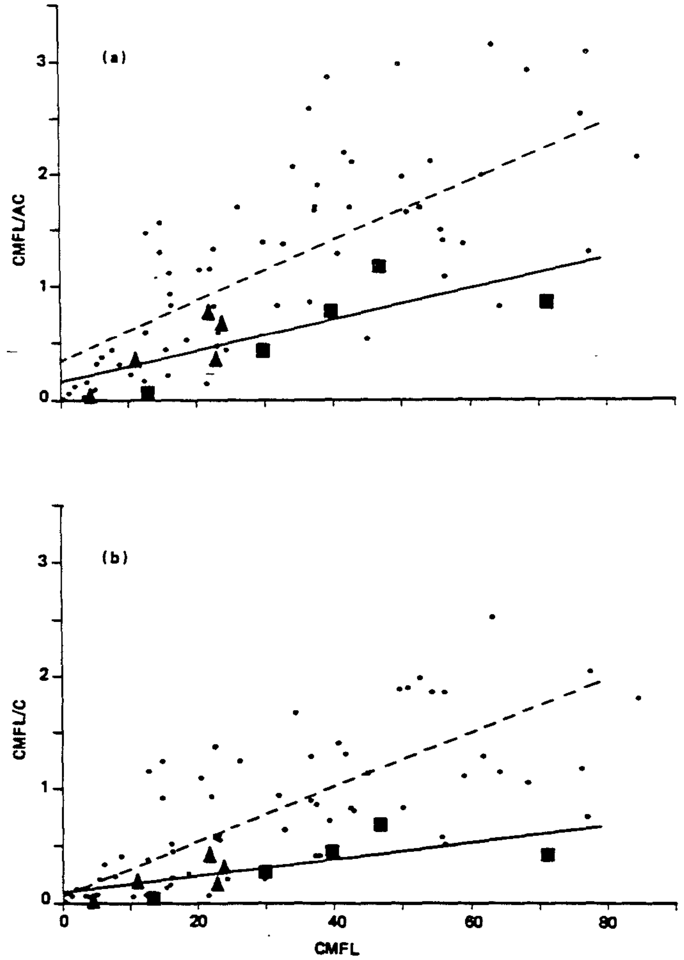
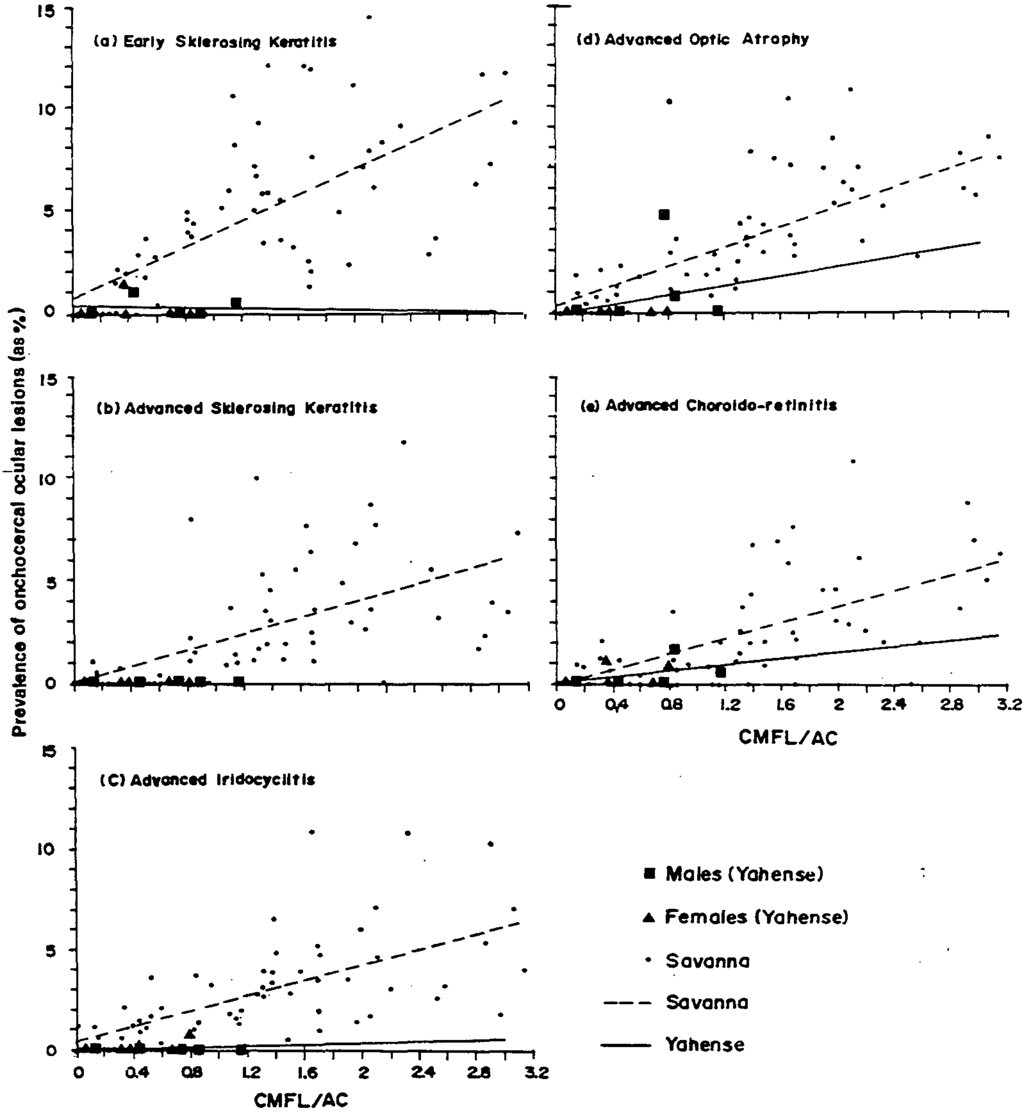


Table 2. Regression coefficients for the linear regression of the prevalence of the different ocular lesions on the CMFL/AC

	Savanna		Yahense Foci		Statistical significance of difference between Yahense and savanna	
	Intercept	Slope	Intercept	Slope	Test on slope	Analysis of covariance
Early sclerosing keratitis	0.72	3.142	0.35	-0.091	N.S.	$P<0.05$
Advanced sclerosing keratitis	0.07	1.964	0.00	0.000	N.S.	N.S.
Advanced iridocyclitis	0.44	1.929	-0.01	0.202	N.S.	$P<0.05$
Advanced optic atrophy	0.33	2.356	-0.06	1.111	N.S.	N.S.
Advanced choroido-retinitis	-0.22	1.967	0.03	0.718	N.S.	N.S.

Fig.5 Prevalence of onchocercal ocular lesions in relation to the Community Microfilarial Load in the anterior chamber of the eye (CMFL/AC)



The range for CMFL/AC in the Yahense foci is small compared to the range for the savanna which is 3 times as large and this limits the discriminating power between the two zones. This limitation is well illustrated by the results for advanced sclerosing keratitis in Fig.5b, showing all but one of the Yahense subpopulations having a CMFL/AC of less than 1. Though no advanced sclerosing keratitis exists in the Yahense foci, very few cases of the lesion are found in communities with these low values of the CMFL/AC in the savanna also. The intensity of ocular microfilariae in the Yahense foci is therefore too low to allow the determination of any difference in the pattern for advanced sclerosing keratitis between the two bioclimatic zones, given a certain level of microfilarial invasion of the eye. However, other figures suggest that such a difference does indeed exist and that, for a given CMFL/AC, the prevalence for certain ocular lesions in the Yahense foci is less, notably for early sclerosing keratitis and advanced iridocyclitis. Table 2 shows that the difference between savanna and forest is of borderline statistical significance for those two onchocercal lesions.

DISCUSSION

Previous comparative studies carried out in the savanna and the forest bioclimatic zones have reported high blindness rates in the savanna and low rates in the rainforest zone (Budden 1963, Monjusiau et al 1965, Anderson et al 1974, Prost 1980). With respect to the pattern of distribution of onchocercal eye lesions, all the studies have been unanimous in reporting the absence of sclerosing keratitis in the rainforest zone. In connection with the three other typical onchocercal eye lesions, some studies have reported the prevalence of iritis, choroido-retinitis and optic atrophy to be less in the rainforest than in the savanna bioclimatic zone, (Budden 1963, Monjusiau et al 1965, Prost 1980). However, one study has reported the prevalence of these lesions to be similar in both the rainforest and the savanna bioclimatic zones, except the prevalence of optic atrophy which was significantly higher in the forest than in the savanna. (Anderson et al 1974). Regional variations in the expression of the disease may be evoked to explain the differences in the various reports. This explanation is in itself acceptable since the studies themselves point out the apparent differences in the pattern of distribution of ocular onchocerciasis in the different areas. Discrepancies in the definitions of eye lesions by different authors may also account for the variations in the results of the studies. Finally the method of analysis which did not correct for the intensity of infection in the community, which is a possible confounding factor, may give erroneous results in the comparative analysis.

The basis of the present study, as set out in the first paper, (Remme et al 1989), are: 1) the clear definitions of onchocercal eye lesions, 2) the selection for this analysis of only those onchocercal eye lesions whose diagnosis is definite, viz., onchocercal eye lesions at the advanced stage and early sclerosing keratitis, 3) the method of analysis applied, which is based on a correction for the intensity of infection in the community, and which allows for the unequivocal comparison of the results of the analysis.

This study confirms previous reports that onchocerciasis in the Yahense forest foci hardly causes blindness and shows also that an increased CMFL is not associated with an increased blindness. In the savanna, however, there is a linear relationship between the standardised "prevalence of blindness excluding definite non-onchocercal causes" and the CMFL. It has previously been reported that blindness levels can be as much as 2.5 times higher, (Anderson et al 1974) or 5 times higher, (Prost 1980), in the savanna than in the forest. Our study goes further and shows zero onchocercal blindness in Yahense forest communities with CMFL of 40 to 70 mf/s where the onchocercal blindness would have been in the range of 4-7%, had the communities been in the savanna.

Advanced lesions of the anterior segment of the eye, viz, sclerosing keratitis and iritis are absent even at very high CMFL levels in the Yahense forest foci, whilst prevalence of these lesions show a deep linear increase with the CMFL in the savanna. Lesions of the anterior segment of the eye have been reported to be absent in the forest in previous studies, (Budden 1963, Monjusiau et al 1965, Prost 1980). In one study, the prevalence of iritis was found to be similar in the forest and the savanna (Anderson et al, 1974). However, these authors conceded that severe iritis occurred mainly in the savanna and this statement would seem to support the approach adopted in this study, which subdivided eye lesions into the early and the advanced form, and used only advanced iritis which is the more onchocerciasis specific, in the comparative analysis.

Most previous studies have reported a lower prevalence of eye lesions of the posterior segment of the eye in the forest than in the savanna, (Budden 1963, Monjusiau et al 1965, Prost 1980). This study confirms this and shows further that it remains true even after correction for the intensity of infection in the community. Just as is found in all studies, severe sclerosing keratitis which is found uniquely in the savanna bioclimatic zone may obstruct the viewing of the fundus which may be harbouring an onchocercal eye lesion of the posterior segment of the eye. This factor may lead to an underestimate of the prevalence of optic atrophy and choroido-retinitis in the savanna. In this regard therefore, the difference between the prevalence of lesions of the posterior segment of the eye in the Yahense forest and in the savanna given by our study may even be an underestimation.

All these results show a completely different pattern of onchocerciasis at the ocular level in the Yahense forest, given a certain intensity of infection in the skin. The question that poses therefore is why this different pattern of ocular disease is encountered in the forest.

Past comparative studies (Budden 1963, Anderson et al 1974) have reported lower ocular microfilarial loads in the forest as compared to the savanna, and concluded that this was a reflection of the difference in the general level of infection between the two bioclimatic zones. Our analysis suggests that this deduction may be an oversimplification. The community microfilarial load in the anterior chamber of the eye, CMFL/AC and in the cornea, CMFL/C correlate well with the community microfilarial load, CMFL, in both the savanna as well as in the Yahense forest in our study. However, the average amount of microfilarial invasion into the anterior chamber of the eye or cornea is, for a given level of the microfilarial load in the skin, significantly less in the Yahense forest than in the savanna. This finding suggests that microfilariae in the Yahense forest are less capable than microfilariae from the savanna to invade the eye.

Furthermore, a given level of microfilariae in the eye is associated with a higher prevalence of severe eye lesions in the savanna than in the Yahense forest. Microfilariae in the eye produce no advanced sclerosing keratitis, the occasional early sclerosing keratitis and the rare advanced iridocyclitis in the Yahense forest. In the savanna, there is a steep linear relationship between lesions of the anterior segment of the eye and the CMFL/AC. In the posterior segment of the eye, the prevalence of optic atrophy and choroido-retinitis, for a given microfilarial load in the anterior chamber of the eye, is always less in the Yahense forest than in the savanna. These observations contrast with the report from a previous study which considered the lower ocular microfilarial loads in the forest compared to that in the savanna as adequate to explain the lower prevalence of eye lesions in the forest bioclimatic zone, (Budden 1963). It would appear that in the Yahense forest, a certain microfilarial load in the eye would be associated with a less eye pathology than a similar load in the eye in the savanna bioclimatic zone. In other words, not only are the microfilariae harboured in the skin in the Yahense forest little able to invade the eye, but also, these microfilariae may be less pathogenic to the eye as well. This observation accords with the results from an experiment in which microfilariae originating from the savanna bioclimatic zone showed a higher capacity of invasion into as well as a higher pathogenicity to the rabbit cornea, compared to the microfilariae originating from the forest (Garner & Duke 1972). These findings do certainly suggest the existence of a microfilarial strain in the Yahense forest which may be different from the microfilariae found in the savanna as has been postulated earlier, (Duke et al 1966).

It may therefore be concluded that a completely different epidemiological pattern of ocular onchocerciasis exists without doubt in the Yahense forest in the form of a less prevalence of ocular pathology even at very high intensities of infection. This pattern of onchocerciasis is the result of infection with microfilariae which are less capable of invading the eye from the surrounding skin, and are also probably less pathogenic to the eye. These observations are consistent with the hypothesis of the existence of a different parasite strain in the rainforest which produces a less eye invasive and eye pathogenic microfilariae compared to the usual savanna strain.

REFERENCES

Anderson,J., H.Fuglsang, P.J.S.Hamilton, T.F.de C.Marshall. Studies on onchocerciasis in the United Cameroon Republic. II. Comparison of onchocerciasis in rainforest and sudan-savanna. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 68 (1974) 209-222.

Armitage,P. *Statistical methods in medical research.* Blackwell, Oxford (1971).

Budden,F.H. Comparative study of ocular onchocerciasis in savanna and rainforest. *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 57 (1963) 64-70.

Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna. *Tropical Medicine and Parasitology,* 37 (1986) 263-270.

Duke,B.O.L., D.J,Lewis, P.J.Moore. *Onchocerca-simulium* complexes I - Transmission of forest and Sudan-savanna strains of *Onchocerca volvulus* from Cameroon, by *Simulium damnosum* from various West African bioclimatic zones. *Annals of Tropical Medicine and Parasitology,* 60 (1966) 318-336.

Garner,A., B.O.L.Duke, J.Anderson. A comparison of the lesions produced in the cornea of the rabbit eye by microfilariae of the forest and Sudan-savanna strains of *Onchocerca volvulus* from Cameroon, II The pathology. *Tropical Medicine and Parasitology,* 24 (1972) 385-396.

Monjusiau,A.G.M., J.Lagraulet, R.d'Haussy, G.W.Goeckel. Aspect ophtalmologiques de l'onchocercose au Guatemala et en Afrique occidentale. *Bulletin of the World Health Organization,* 32 (1965) 339-355

Prost,A., J.Prod'hon. Le diagnostique parasitologique de l'onchocercose, revue critique des méthodes en usage. *Médecine Tropicale,* 38 (1978) 519-532.

Prost,A. Le polymorphisme des onchocercoses humaines ouest-africaines. *Annales de Parasitologie Humaine Comparée,* 2 (1980) 239-245.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization,* 64 (1986) 667-681.

Remme,J., K.Y.Dadzie, A.Rolland, B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. I. West African savanna. *Tropical Medicine and Parasitology,* 40 (1989) 340-347

ADDENDUM: OTHER APPLICATIONS OF THE METHODOLOGY

An important application of the analytical methodology, which was introduced in the previous chapters, concerned the analysis of the epidemiological pattern of ocular onchocerciasis in foci of *S.soubrense* (which has recently been reclassified as *S.sanctipauli* s.n.) in the forest zone of Southern Ivory Coast, and its comparison with the pattern in the savanna. For the purpose of this study, ophthalmological surveys have been undertaken in 11 villages from these forest foci. The analysis has been completed and the results have been the basis for important decisions on vector control operations.

The villages were not selected randomly. Quite the contrary, an attempt was made to include the most severely affected villages by selecting those villages which were located on the river banks and closest to the most productive breeding sites. Nevertheless, the level of endemicity was relatively low. The standardised prevalence of mf ranged from 47% to 77%, but the CMFL in females was below 10 mf/s in eight of the villages and the CMFL in males was around 20 mf/s in all but one village. These forest foci were therefore typically areas for which the low prevalence of blindness was no proof for the existence of a forest strain of the parasite. Even if the locally transmitted parasite had been the savanna strain, one would not expect significant blindness rates with these low endemicity levels and it was particularly for this area that the new analytical methodology proved indispensable.

The low CMFL values made the analysis difficult, but there were nevertheless several statistically significant differences in the community patterns of ocular mf loads and ocular lesions between the *S.soubrense* foci and the savanna. For given levels of the CMFL, ocular mf loads were much lower in the *S.soubrense* foci than in the savanna. The same was true for the prevalence of early and advanced sclerosing keratitis, the prevalence of advanced optic atrophy and the prevalence of blindness after exclusion of non-onchocercal causes. However, the ocular mf loads were all so low in the *S.soubrense* foci that no significant difference could be detected in the relationship between the prevalence of ocular lesions and mean ocular mf loads, as had been demonstrated for the forest foci of *S.yahense*. Because of these findings, larviciding is no longer contemplated in the forest areas where *S.soubrense* is the sole vector.

The OCP is currently facing a similar problem in the western extension area where there exists great uncertainty concerning the boundary of the blinding form of onchocerciasis in Sierra Leone and the role of different vectors, notably *S.soubrense* type B. A first round of epidemiological surveys has shown high CMFL levels in nearly all parts of the country but great variation in the levels of blindness according to simple visual acuity tests. For this reason a series of ophthalmological surveys are presently being undertaken in order to clarify the situation through a similar comparative analysis of the epidemiological patterns of ocular onchocerciasis. Once this has been completed, it is intended to use the same approach in foci of the vector *S.squamosum* in the southern extension of the Programme area.

A very different application is the utilization of the relationships between the prevalence of ocular lesions and blindness and the CMFL in the savanna to describe the endemicity level and public health importance of onchocerciasis in different savanna areas using skin snip data only. This is the basis for an ongoing programme of epidemiological mapping of the western and south-eastern extension areas of the OCP. It involves skin snip surveys in hundreds of randomly selected villages using a stratified random sampling technique and stratification based on ecological and entomological criteria. The objectives are two-fold. The first is to obtain reliable estimates of the total number of people infected and of the number at risk of ocular disease and blindness in the extension areas as baseline information before the start of control. The second objective is to obtain an epidemiological map of the endemicity levels of onchocerciasis throughout the extension areas and the identification of foci where there is a high risk of blindness.

This mapping has provided essential information for the planning of mass treatment with ivermectin (see also chapter 5). Since ivermectin is a microfilaricide and does not kill the adult worm, annual mass treatment will have to be provided over a long period. It is therefore important to identify the areas and the villages where onchocerciasis is a sufficiently severe public health problem to warrant such an intensive effort. For each focus with a high endemicity level of onchocerciasis, according to the epidemiological mapping, a second round of much more detailed epidemiological mapping is undertaken in order to identify the villages to be included in the mass-treatment campaign.

Chapter 4

Epidemiological Evaluation of the Impact of Vector Control and Prediction of Epidemiological Trends during the Control Period

INTRODUCTION

Chapter 4 deals with the epidemiological impact of vector control in the OCP. In 1983, it was realized that the limited decrease in the standardized prevalence of mf in the skin, which appeared to be disappointing to some observers who feared the need for vector control well beyond the planned 20 years, was in fact to be expected. What was needed was a completely different approach to the analysis of the epidemiological evaluation data which would take the dynamics of the parasite and of the human population into account.

As an important first step, a force-of-infection model for onchocerciasis was developed in order to arrive at a better understanding of the expected age specific trends in the prevalence and intensity of *O.volvulus* infection (see chapter 4.1). This allowed the identification of more appropriate statistics for the analysis of the epidemiological data. The subsequent re-analysis of the existing skin snip data resulted in a very different appreciation of the epidemiological impact of vector control. This new interpretation of the skin snip results was also much more consistent with the findings of the ophthalmological evaluation after 7-8 years of control which are given in chapter 4.2

Nodulectomy surveys, which were undertaken in 1982 and 1983 in selected villages from within and outside the Programme area, are discussed in chapter 4.3. They allowed an assessment of the changes in the population dynamics of the adult worms and the decline of their reproductive potential during the vector control period.

Chapter 4.4 gives the results of an integral analysis of all existing entomological, parasitological and ophthalmological evaluation data, collected during the first 11 years of vector control, and provides the conclusions on the impact of vector control on transmission, infection and disease in different parts of the OCP area.

Even though the force-of-infection model had provided very valuable predictions of expected epidemiological trends during the first 8-10 years of vector control, it was based on certain assumptions which made it inappropriate for predictions beyond this period. A more sophisticated host-parasite model was therefore developed in 1985 and, using this host-parasite model, it was predicted that the parasite reservoir would be virtually eliminated after 15 years of effective vector control. Chapter 4.5 provides the latest results of skin snip surveys which were undertaken after 14 years of control and shows to what extent the observed trends in the prevalence and intensity of onchocerciasis infection have followed the predictions of 1985.

Chapter 4.1

A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin Area

Bulletin of the World Health Organization, 64 (1986) 667-681

A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area

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A simple force-of-infection model for onchocerciasis has been developed for a study of the age-specific epidemiological trends during a period of vector control in the Onchocerciasis Control Programme in the Volta River basin area (OCP). The most important factors included in the model are the longevity of an infection, the aspect of superinfection, age-specific exposure, and the intensity of transmission during the pre-control period. The aim of the study was to determine the most appropriate statistics for the epidemiological evaluation in the OCP. There was generally good agreement between the epidemiological trends, predicted by the model, and the observed trends in the prevalence and mean load of microfilariae in skin snips taken from a cohort population from 23 villages in an area with 8 years of successful vector control in the OCP. It is concluded that the epidemiological trends during the control period are not uniform but depend on the initial age and the initial endemicity level of the population. The epidemiological indices for cohorts of children, born before the start of control, will not show a decrease during the first 8 years of interruption of transmission. The prevalence is too insensitive to be useful for the evaluation in hyperendemic villages during most of the control period. The most sensitive and meaningful statistic for a comparative analysis and for the assessment of epidemiological changes is the geometric mean microfilarial load in a cohort of adults. This index, which is called the Community Microfilarial Load (CMFL), is now routinely used in the OCP. The new analytical methodology has enabled a much better appreciation of the significant epidemiological impact of 8 years of vector control in the OCP. Several related aspects of the pre- and post-control dynamics of onchocerciasis infection are also discussed and priorities are formulated for further work on applied modelling of onchocerciasis.

INTRODUCTION

The Onchocerciasis Control Programme in the Volta River basin area (OCP) has been operational in the savanna areas of seven West African countries since 1975. Its objective is to put an end to onchocerciasis as a disease of public health and socioeconomic importance and to ensure that there will be no recrudescence of the disease thereafter.[a] In the absence of an appropriate drug for large-scale treatment, the strategy of the OCP has been to interrupt trans-

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[a] *Proposal for a long-term strategy for the Onchocerciasis Control Programme*. Unpublished WHO document, OCP/JPC5.7 (1984).

mission by larvicidal control of the vector, *Simulium damnosum* s.l., and to maintain this control for a sufficiently long period to allow the human reservoir of infection to decrease to an insignificant level following the natural ageing and death of the adult *Onchocerca volvulus*.

Both entomological and epidemiological evaluations of the impact of vector control have been undertaken in the OCP since 1975. The main aim of the entomological evaluation has been to provide feedback to the control operations by supplying weekly data on the vector density. One entomological index, the Annual Transmission Potential (*1*), provides indirect information on the risk of disease transmission. Although this index has played an important role in evaluating the reduction in transmission brought about by vector control, it cannot provide an estimate of the actual risk of infection for the populations living in the OCP area. The final assessment of the impact of vector control on transmission of the parasite and development of disease has therefore to come from the epidemiological evaluation, which involves the examination every 3–4 years of the population of about 150 indicator villages in the OCP. The most extensive data available on infection with *O. volvulus* in those populations have come from the results of microscopic examinations of skin snips. Two skin snips were taken from each individual at each examination and the numbers of microfilariae per skin snip (mfs) were counted and recorded.[b]

At the start of OCP there existed considerable uncertainty about the epidemiological trends which could be expected during the control period and this has complicated the selection of appropriate statistics and the interpretation of the observed results. Hitherto the index most extensively used for epidemiological evaluation in OCP has been the cross-sectional and age and sex standardized prevalence of microfilariae in a population. Analysis of the skin snip data after 5 years of control (*2*), and a similar unpublished analysis after 8 years of control, have shown that the decrease in the cross-sectional prevalence has been very slight. It was not very clear what the implications of this modest decrease were for the future epidemiological trends in the OCP, but it was realized that the prevalence was not a sensitive index for the epidemiological changes that had taken place because ophthalmological examinations in a sample of the indicator villages had revealed dramatic reductions in ocular microfilarial infestations during the same period (*3*, *4*).

Only for one part of the population was it obvious what results could be expected, i.e., the group of children born since the start of control who should remain free of infection if complete interruption of transmission had been achieved. Although the results for these children in the OCP have yielded very important information,[c] they have one limitation. Even in endemic areas without vector control, infections among young children are relatively rare, and this index is therefore not a very sensitive measure of ongoing transmission during the first 5–8 years of control, which is more likely to affect the older population. This fact, and the need for sensitive statistics to measure the regression of the initial reservoir of infection, made it important to arrive at a better understanding of the epidemiological trends in the population born before the start of control. It is this population only which will be considered in the present paper.

During the pre-control period, most of the indicator villages in the OCP were hyperendemic where the prevalence among adults was virtually 100% and where superinfection was the rule. In those persons who were heavily infected at the onset, most adult worms may have died after a number of years of successful vector control, but their human hosts remain as positive cases until their last productive adult female worms die and the microfilariae from these worms are no longer detectable by standard skin snip examination. Thus, although the prevalence in adults remains virtually constant, a major reduction in the intensity of infection may have taken place and the epidemiological situation, including the risk of ocular lesions and other pathology, will have improved dramatically.

The above reasoning implies that a sensitive index for the skin snip data should reflect the reduction in the number of productive female worms. Adult worms live relatively well protected in nodules and it is believed that their death is mainly due to the natural process of ageing. Hence the life expectancy of adult worms and the actual age of each worm at the start of vector control are important factors influencing the subsequent epidemiological trends. The number of adult worms per patient and the age of each worm cannot be measured in practice. However, because of their importance for the epidemiological trend we have developed a model to predict the expected trends after taking these factors into account and to determine the most appropriate statistical indices for the epidemiological evaluation. We opted for a catalytic model for onchocerciasis because of our interest in the risk of separate infections rather than in incidence alone. In catalytic models the risk of infection is called the "force of infection".

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[b] PROST, A. ET AL. *Methods of mass epidemiological evaluation of onchocerciasis: their utilization in a vector control programme.* Unpublished WHO document, ONCHO/WP/75.14 (1975).

[c] REMME, J. ET AL. Trends in the epidemiology of onchocerciasis after nine years of vector control in OCP. In: *Report of the tenth meeting of the Scientific Working Group on Filariasis.* Unpublished WHO document, TDR/FIL-SWG(10)/84.3.

FORCE-OF-ONCHOCERCIASIS-INFECTION MODEL

General considerations and definitions

The catalytic model assumes that a "force of infection", β, acts upon all members of a population (*5*). β may depend upon age, sex and locality, but it is usually assumed to be constant over time for each subpopulation, an assumption which makes these models most appropriate for endemic diseases which are in an equilibrium state. Onchocerciasis is definitely an endemic disease in areas without vector control, though the vector density, and hence the intensity of transmission, may show considerable annual variations as a result of varying hydrological conditions. The classical simple catalytic model is restricted to diseases that can affect individuals only once during their lifetime and for which the infection results in a change from a susceptible and test-negative state to the immune and test-positive state when reinfection can no longer occur. Because of this limitation we had to modify the catalytic model in order to include superinfection—a characteristic of onchocerciasis—and the longevity (see below) of each individual infection. Our emphasis on separate infections makes it necessary to define and consider the different phases of each infection.

During the blood meal of an infective blackfly on man, third-stage *O. volvulus* larvae may be transmitted. After maturing and mating, the adult female worms start producing microfilariae, which eventually reach the skin where, once they attain a certain threshold concentration, they can be detected by microscopic examination of a skin snip. Production of microfilariae continues, possibly interrupted by brief periods of non-fecundity, throughout the productive lifespan of the female worm, and it ceases only when the worm dies or possibly a short time before its death. After the end of the productive lifespan, microfilariae can still be detected, but only for a limited period because their longevity of around 1-2 years (*6*) is relatively short in comparison with the longevity of the macrofilariae. The above phases are illustrated in Fig. 1.

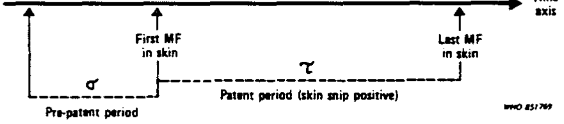

Fig. 1. Lifespan of *O. volvulus* in the human host (MF = microfilaria).

It is only during the patent period that skin snips can provide information on the presence of infection. Pre-patent infections cannot be detected with the currently available tests. However, the entomological data provide indirect information on the risk of infective bites, particularly during a period of successful vector control when this risk is close to zero following the virtual elimination of the blackfly population. In our model we shall therefore consider only the pre-patent period (with duration σ) and the patent period (with duration τ).

Although no quantitative information exists, it is believed that the majority of the transmitted third-stage larvae do not reach the adult stage which produces microfilariae. However, since those larvae which perish prematurely are of no significance to the available epidemiological data, we shall only consider those larvae which develop into productive female worms. Consequently an onchocerciasis infection is here defined as: "the infection of an individual by infective larvae and the subsequent development of one adult fertilized female worm which produces microfilariae to the extent that they can be detected in the skin".

The longevity of an infection is the period between the infective bite and the disappearance from the skin of the last microfilariae produced by this infection, and it has the duration of $\sigma + \tau$ years. In this paper we shall ignore the variability in the duration of the pre-patent and patent periods and assume that σ and τ are constant. This simplification is probably not of serious import for the pre-patent period, which is relatively short. However the variability in the length of the patent period may be of considerable significance when predicting the "tail" of post-control epidemiological trends. This question will be further discussed below.

Model for the pre-control situation

Let F(x) be the probability that an individual of age x has at least one patent infection and $P_k(x)$ the probability that he has k patent infections. The basic hypothesis of the catalytic model specifies that

$$F(0) = 0 \qquad (1)$$

$$\frac{dF(x)}{dx} = \beta(x)\ (1 - F(x)) \qquad x > 0 \qquad (2)$$

where $\beta(x)$ is the age-dependent force of infection. The solution to (2) is

$$F(x) = 1 - \exp\{-\int_0^x \beta(t)dt\} \qquad x > 0 \qquad (3)$$

It is assumed under the catalytic model that an infection changes a susceptible individual into a positive case for the rest of his life. The above equations have therefore to be modified in order to incorporate the specific characteristic of onchocerciasis that each infection has a limited duration with a pre-patent period σ and a patent period τ.

The previous assumption of a constant longevity implies that no infections can die out below the age of $\sigma+\tau$ years. For this age group therefore the above equations are still valid though they require a minor modification to incorporate the delaying effect of the pre-patent period, which changes equation (1) and (3) into

$$F(x) = 0 \qquad x \leqslant \sigma \qquad (4)$$

$$F(x) = 1 - \exp\{-\int_0^{x-\sigma} \beta(t)\mathrm{d}t\} \qquad \sigma < x \leqslant \sigma+\tau \qquad (5)$$

From the age of $\sigma+\tau$ onwards the prevalence of onchocerciasis no longer depends on all previous infections, but only on those which are patent at that moment. Previous infections which resulted from an infective bite more than $\sigma+\tau$ years ago are no longer patent. Infections which occurred during the last σ years are still pre-patent and therefore do not affect the prevalence. Consequently, for the population over the age of $\sigma+\tau$ years equation (3) should be modified for onchocerciasis as follows:

$$F(x) = 1 - \exp\{-\int_{x-\sigma-\tau}^{x-\sigma} \beta(t)\mathrm{d}t\} \qquad x > \sigma+\tau \qquad (6)$$

An important parameter in the last two equations is the age-specific force of infection $\beta(x)$. Several catalytic models have been developed for different relationships between the force of infection and age (*7*, *8*). The most widely applied is the simple catalytic model, with a force of infection which is assumed to be independent of age, i.e., $\beta(x) = \beta$.

Children. For onchocerciasis the above assumption is definitely not correct for the younger age groups. It is well known that young children, who stay most of the time within the village, are relatively little exposed to the bites of *S. damnosum* s.l., which is only found biting at low densities in the clearings around the houses. However, with increasing age, the degree of exposure increases as the children begin to play further away from home and along the river banks, and when they begin to accompany their parents to work in the fields. In most rural areas in the OCP it is reasonable to say that both male and female children accompany their parents in their daily activities from the age of about 10 years, and from then on they are fully exposed to the bites of *S. damnosum* s.l. The hypothesis of an age-independent exposure is therefore only tenable for the population aged 10 years and over, and it is only from that age onwards that a simple catalytic model, with a constant force of infection, will be used.

It is very much more difficult to give an exact specification of the relationship between the force of infection and age for children less than 10 years old. The epidemiological trends for children are not expected to show a decrease until many years after the establishment of vector control, and the data from these age groups are therefore of limited value for epidemiological evaluation. However, in order to demonstrate this important conclusion we have attempted to quantify roughly the relative exposure to infection among children. We assumed that the force of infection in the youngest age group of 0–3 years is only 5% of the value β for adults, while for the age group 4–6 years we assumed a value of 15% and for the age group 7–9 years a value of 40%.

Adults: age $>10+\sigma+\tau$ years. The hypothesis that the force of infection is independent of age from 10 years old onwards allows us to develop further the equation for F(x) for the older age groups. According to equation (6), the probability of being a positive case at age x is a function of the age-specific force of infection operating over the age interval $x-\sigma-\tau$ to $x-\sigma$ years. If $x>10+\sigma+\tau$, the above hypothesis implies that the force of infection is constant over this interval and consequently:

$$F(x) = 1 - \exp\{-\int_{x-\sigma-\tau}^{x-\sigma} \beta\mathrm{d}t\}$$

$$= 1 - \exp(-\beta\tau) \qquad x > 10+\sigma+\tau \qquad (7)$$

i.e., for the population over the age of $10+\sigma+\tau$ years, the probability of an individual having at least one patent infection is independent of age and depends only on the force of infection β and the patent period τ.

For these age groups it is also possible to incorporate the aspect of superinfection and to derive a formula for the theoretical distribution of the number of patent infections per person. Using a reasoning similar to that in the previous paragraph it follows that the number of patent infections a person has at age x is equal to the number of new infections that have occurred during the age interval $x-\sigma-\tau$ to $x-\sigma$. Since infections during this interval are assumed to occur independently of each other, and with a constant rate β, it follows that the number of patent infections is the result of a Poisson process operating over a period of duration τ; and hence

$$P_k(x) = \frac{(\beta\tau)^k \exp(-\beta\tau)}{k!} \qquad x > 10+\sigma+\tau \qquad (8)$$

which is the well known Poisson distribution with a mean equal to $\beta\tau$. For the population over the age of $10+\sigma+\tau$ years the mean and the distribution of the number of patent infections per person are therefore also independent of age, and depend only on the force of infection and the patent period. It should be noted that the pre-patent period does not affect the equations for $F(x)$ and $P_k(x)$ but only the age from which they become valid.

Post-control model in adults after interruption of transmission

The aim of the present force-of-infection model is to predict the expected trends in prevalence and intensity of infection after vector control, and to develop appropriate statistical methods for the analysis of the epidemiological evaluation data. The first step in the analysis is to describe the trends after completely successful vector control so that, later on, these results may be used as a basis for comparing trends in other areas where vector control has been less than completely successful. In this section we assume that transmission has been interrupted from the moment that vector control started, and that the force of infection is therefore zero during the control period. Let y denote the number of years of successful vector control and x the age of an individual at the start of vector control. Then $F(x,y)$ is the probability that an individual with an initial age x has at least one patent infection after y years of control; and $P_k(x,y)$ is the probability that he still has k patent infections at that moment.

Interruption of transmission through vector control will not immediately be reflected in the epidemiological data. Pre-patent infections which resulted from infective bites during the last years before control will continue to become patent at the same rate as before. Therefore during the first σ years of control the epidemiological indices will not yet be affected and $F(x,y)$ will remain equal to $F(x)$ in equation (7) just as $P_k(x,y)$ stays equal to $P_k(x)$ in equation (8). It is only after σ years of control that the interruption of transmission begins to affect the epidemiological results for the older age groups. Infections which are still patent after y years of control are only those resulting from infective bites received during the period between time $y-\sigma-\tau$ and the start of vector control. Since the force of infection was constant over this period for individuals who were at least $10+\sigma+\tau$ years of age at the start of control, it follows that

$$F(x,y) = 1-\exp[-\int_{y-\sigma-\tau}^{0}\beta\,dt]$$

$$= 1-\exp[-\beta\,(\sigma+\tau-y)]$$

$$x>10+\sigma+\tau;\ \sigma<y<\sigma+\tau \qquad (9)$$

and

$$P_k(x,y) = \frac{[\beta(\sigma+\tau-y)]^k\ \exp[-\beta(\sigma+\tau-y)]}{k!}$$

$$x>10+\sigma+\tau;\ \sigma<y<\sigma+\tau \qquad (10)$$

Thus, for the population over the age of $10+\sigma+\tau$ years neither the post-control prevalence of patent infections nor the distribution of the number of patent infections depends on the actual age of the subjects, but only on the pre-control force of infection, on the length of the pre-patent and patent periods, and on the duration of control. The mean number of patent infections per person after at least σ years of control is equal to $\beta.(\sigma+\tau-y)$, i.e., it is a function of the duration of control and will decrease in a linear manner to zero after $\sigma+\tau$ years of control. After y years of control ($y>\sigma$), the mean number of patent infections will have decreased by a proportion equal to $(y-\sigma)/\tau$, and this relative decrease is independent of the value of the force of infection during the pre-control period, and hence independent of the initial endemicity level.

EPIDEMIOLOGICAL TRENDS PREDICTED BY THE MODEL

Before any predictions can be made from the model, we have to provide estimates of the parameters σ, τ and β. The pre-patent period σ and the patent period τ depend on the life-cycle of *O. volvulus* and are general parameters which are applicable to all villages. Limited previous studies suggest that an average pre-patent period of about one year might be a reasonable figure (*9, 10*). The observed trends in the OCP (Fig. 9, 11) suggest an estimate of about 10 years for the average patent period τ.

The force of infection β is a strictly local parameter which varies greatly between villages. β reflects the intensity of transmission before control and determines the initial endemicity level for each village. Even within villages it is probably not justifiable to apply a single force of infection to all adults and it may be necessary to treat the male and female populations separately, with a considerably higher force of infection for the males.

Epidemiological trends by age: $\beta=0.4$

Using the above estimates for σ and τ and an arbitrary force of infection of 0.4 infections per person per year, Fig. 2 and 3 show, respectively, the predicted trends for prevalence (as %) and for the

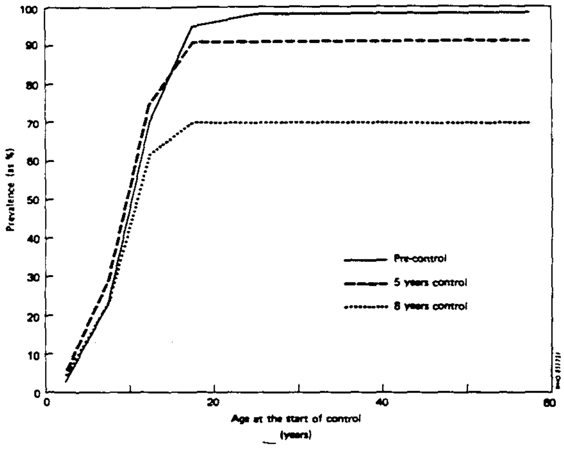

Fig. 2. Predicted age-specific prevalence by duration of control.

mean number of patent infections per person, both before and 5 and 8 years after control. A force of infection of this level results in an overall prevalence which would be classified as hyperendemic using the criteria of Prost et al. (*11*), but with an intensity of infection that is relatively low for OCP villages. The age in all graphs represents the age at the start of control and the results are presented by age cohorts, using the same age grouping as for the observed results in the next section.

Before control both the prevalence and the mean number of patent infections (i.e., the intensity of infection) increase with age until they reach a plateau from the age of around 20 years onwards. The reason for this levelling off is that an equilibrium has been reached between the rate at which new infections become patent and that at which old infections lose their patency and die off. The post-control results for the prevalence and the mean number of infections for the adults of 20 years and over also show plateaux, and the decrease in the intensity of infection is much more pronounced than the decrease in prevalence, especially during the first years of control. For the younger age groups the post-control trends are distinctly different. Although the prevalence and mean number of patent infections before control are low in persons under the age of 10 years, they do not yet show a decrease during the first years of interruption of transmission, as is shown more clearly in Fig. 4.

Relative trends by age in the intensity of infection

Fig. 4 shows the relative changes predicted in the mean number of patent infections for different age cohorts 5 and 8 years after control. The mean number of infections has increased after 5 years of control in all cohorts of children with an initial age of less than 15 years; and, after 8 years of control, the means are still higher or only slightly lower than those before control. The reason for this different trend in the younger age groups is the disequilibrium between new and old infections. Most infections among children are recent or "young" infections which will need most of the $\sigma+\tau$ years to reach the end of their patency. A relatively large number of their infections

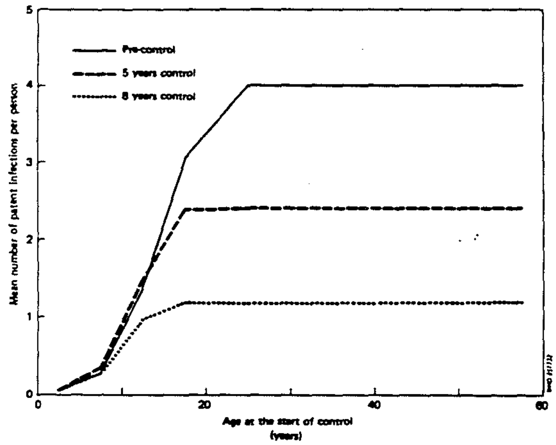

Fig. 3. Predicted age-specific mean number of patent infections by duration of control.

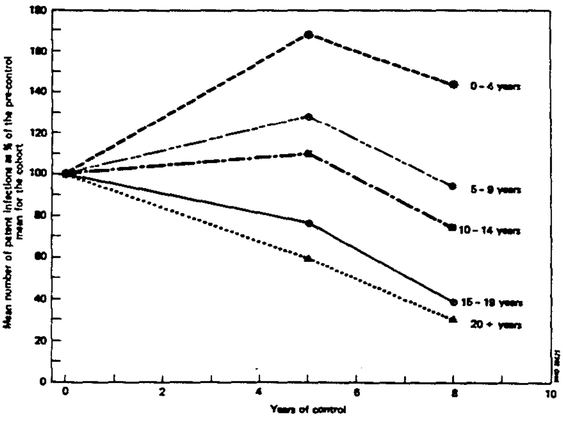

Fig. 4. Predicted relative trend in the mean number of patent infections by age cohort.

are still pre-patent at the start of control and this is the reason for the initial increase in the mean number of patent infections per child after control is established. Only in the cohort aged 15–19 years does the proportion of old infections increase to the extent that their post-control trend begins to resemble that of adults. These predictions for the relative trends in the age-specific intensity of infection are valid for any value of the force of infection β, and hence for all endemicity levels. By contrast, the predicted absolute trends in both prevalence and intensity of infection are very dependent on the actual value of the force of infection.

Epidemiological trends in adults by endemicity level

The predicted post-control trend in the prevalence among cohorts of adults, with an initial age of at least 21 years (i.e., $10+\sigma+\tau$) years, is shown in Fig. 5 for force-of-infection levels ranging from 0.05 to 2 infections per person per year. During the first years after control is established the prevalence in adults is predicted to decrease only in populations with a low endemicity level, in which some individuals, who have only a few old but no recent infections, change early from the positive to the negative state. The higher the force of infection and the level of endemicity, the less likely it is that adults will be found who have not been infected during the last years before the start of control, and the longer it will take for the prevalence to show any decrease. However, in the most hyperendemic populations, once the prevalence does finally begin to decrease, it will continue to fall quite dramatically.

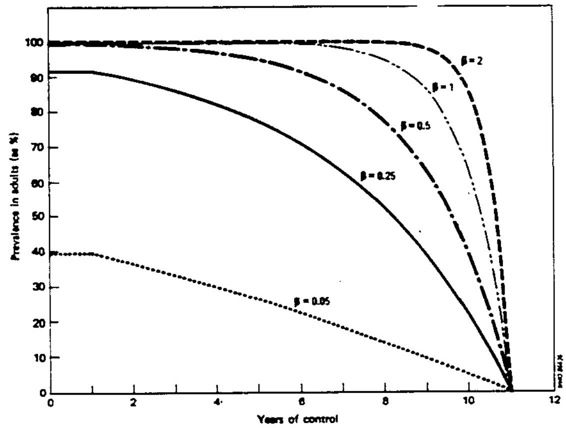

Fig. 5. Predicted trend in prevalence in cohorts of adults by endemicity level.

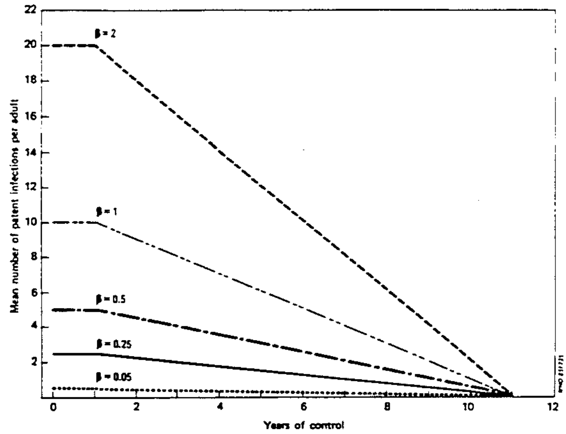

Fig. 6. Predicted trend in the mean number of patent infections in cohorts of adults by endemicity level.

The initial stability in the prevalence among cohorts of adults in hyperendemic villages, after control is established, does not mean that no change in the intensity of infection has taken place. Quite the contrary is true, as can be seen in Fig. 6, which shows the trend in the mean number of patent infections in adults for the same force-of-infection values as were used in Fig. 5. The higher the endemicity level and the initial number of patent infections per person, the more pronounced is the absolute decrease in the mean number of infections after interruption of transmission. For each level of the force of infection β, and assuming constant values for σ and τ, the decrease is linear and all lines show a converging trend to an endpoint after 11 years of control.

In reality, of course, neither the prevalence nor the mean number of infections per person will drop to a value of zero after exactly 11 years of control as predicted in Fig. 5 and Fig. 6. These predictions are based on the assumption that the value of τ is constant, while in fact the variability in the patent period is unknown; and this will be a significant factor determining the length of the "tail" in the post-control epidemiological trends.

OBSERVED EPIDEMIOLOGICAL TRENDS IN THE OCP AND THEIR COMPARISON WITH THE PREDICTIONS OF THE MODEL

The sample population studied

In order to test the validity of the force-of-onchocerciasis-infection model, and its ability to predict the epidemiological trends after establishment of

Simulium control, we re-analysed the skin snip data from 23 villages in OCP. Each of these villages had one "pre-control" survey, done before or during the first year of control, and two follow-up surveys. These villages were selected from areas where the entomological evaluation showed that vector control had been successful throughout the control period, with the virtual elimination of the blackfly population in several of these areas. Furthermore, no children born after the start of control had become infected in any of these 23 villages. Other selection criteria were that a standard methodology had been used for all surveys and that the second and third surveys were done after approximately 5 and 8 years of control, respectively. The reason for taking the periods of 5 and 8 years of control was simply that this yielded the largest number of villages with at least 8 years of control. The sample was not representative of the indicator villages in OCP for it contained a relatively high proportion of meso- and hypoendemic villages, but this is fortunate for our present purpose because it allows an analysis over a wide range of endemicity levels. In order not to bias our conclusions the actual epidemiological trend for each individual village was not used as a selection criterion.

The data from the 23 villages were analysed by age cohorts and included only those individuals who were examined at each survey. Because of the hypothesis that there is a differential exposure of the two sexes, the data for males and females were analysed separately. The total sample consisted of 2346 people, of which 1186 were males and 1160 females.

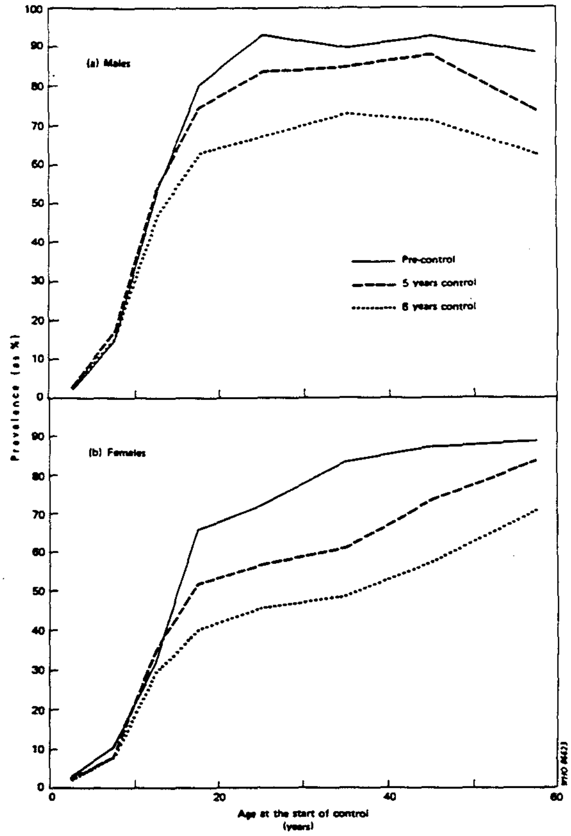

Fig. 7. Observed age-specific prevalence in males and in females by duration of control.

Epidemiological trends by age for the total sample population

Prevalence. Fig. 7a and 7b show, for the 23 villages together, the age-specific prevalences for males and females, respectively. Although the pooling of prevalences for different villages may distort the post-control trends, these graphs allow a first comparison between the observed data and the model's predictions (see Fig. 2), in particular with regard to the predicted levelling-off of the prevalence after the age of about 20 years. For males the observed data show this clearly, both before and after control. The predicted slow initial decrease in the prevalence among adults after control is also evident. For the females, however, the results are not exactly as predicted. Although the prevalence increases rapidly up to the age of 15–20 years, there is no complete levelling-off and the prevalence still increases, albeit relatively slowly, from that age onwards. The pre-control prevalences for females are lower than those for males and it is interesting to note the more rapid decrease in the prevalence for adult females after control was established. In children the results are generally as predicted: the pre-control prevalences are relatively low, and do not decrease during the first 8 years of vector control.

Intensity of infection. The most important conclusions from the model concerned the post-control trends in the mean number of patent infections per person. Unfortunately it is impossible in practice to determine the number of productive adult female worms per person, but it is possible to estimate the intensity of infection by assessing the number of microfilariae found in skin snips. As these microfilariae have been produced by the adult female worms, one might postulate that a quantitative relationship exists between the mean number of patent infections and the mean microfilarial load. Consequently it is of interest to know whether the predictions for the age-specific trends in the mean number of patent infections correspond with the

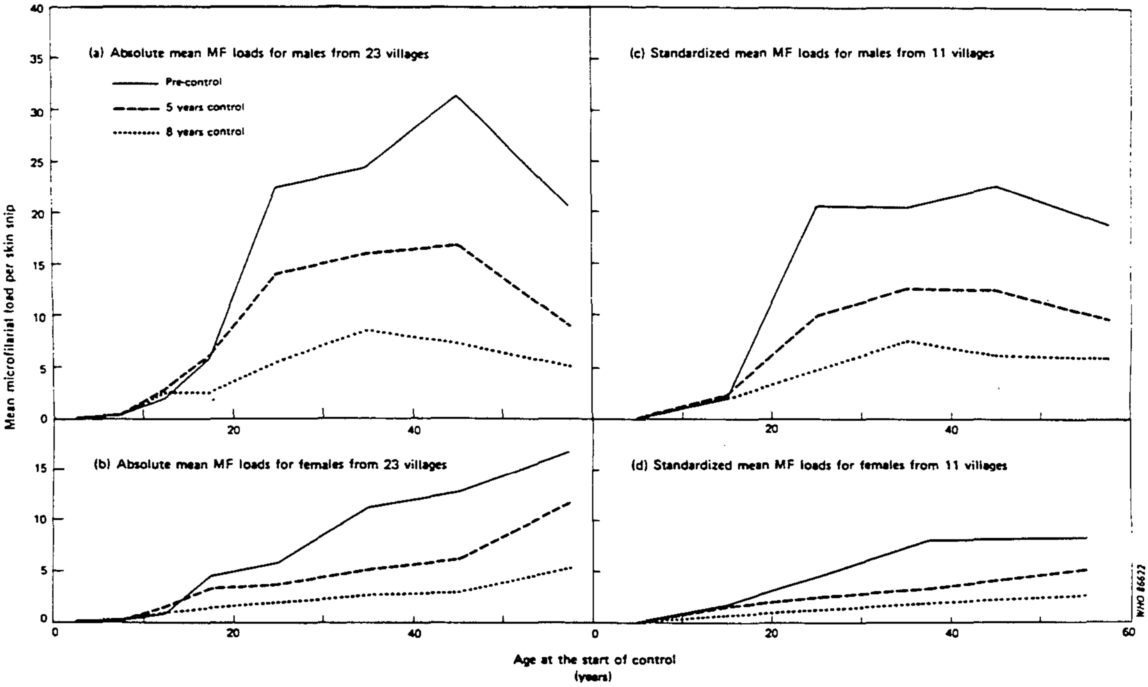

Fig. 8. Observed age-specific mean microfilarial (MF) load in males and in females by duration of control.

observed trends in the mean microfilarial load.

The mean microfilarial loads for the different age cohorts of males and females, respectively, in the 23 villages are shown in Fig. 8a and 8b. As is the common practice for microfilarial counts, we used a geometric mean and, following the philosophy of the force-of-infection model, we calculated the mean microfilarial load for the whole cohort population which had been at risk, including both the skin-snip positive and the skin-snip negative cases, and using the $\log(x+1)$ method.

The mean microfilarial loads for males plotted by age cohorts (Fig. 8a) agree quite well with the predicted mean number of infections per person (Fig. 3). The mean microfilarial load shows a sharp increase between the ages of 10 and 20 years in the pre-control surveys. From the age of 20 years onwards the loads level off and fluctuate around 25 microfilariae per snip. The post-control results also show plateaux from the age of 20 onwards, although at much lower levels, and for adults the decrease in microfilarial loads (Fig. 8a) is clearly more pronounced than the decrease in prevalence (Fig. 7a). The mean load for the oldest age group drops slightly in all surveys.

For the females the mean microfilarial loads plotted by age cohorts (Fig. 8b) are less close to the predictions in Fig. 3. The widest divergence is seen in the low value for the 20–30-year age group, and the pre-control loads continue to increase slightly from that age onwards to the oldest age group. The lack of correlation between the predicted and observed results may be due to women from uninfected or less endemic villages who have married and moved into the study villages during the last years before control, and who have therefore not been exposed during the full $\sigma+\tau$ years as assumed under the model. The microfilarial loads in children of both sexes are so low that trends cannot be assessed and these results will be discussed later.

Intensity of infection after standardization. A disadvantage of pooling the data from 23 villages (Fig. 8a and 8b) is that the results may be affected by variations in the age distribution of the populations of the different villages. Overrepresentation of certain age groups in villages with a very high or a very low endemicity level may cause artificial irregularities in the epidemiological patterns by age. To correct for this we repeated the analysis after standardization for endemicity, but it was only possible to do this for the 11 largest villages, which had at least some individuals in each of the age cohorts, and even then slightly larger age groups had to be used. The average endemicity level for these 11 villages was lower than for the local sample because the smallest villages, which were excluded, usually had the highest endemicity of onchocerciasis.

After standardization the observed microfilarial loads for males (Fig. 8c) showed a much closer agreement with the predicted age-specific pattern for the number of patent infections per person (Fig. 3). Also the standardized microfilarial loads for females had become constant from the age of 30 years onwards (Fig. 8d), although they still remained lower in the 20-29-year age group, which is the age group most affected by the marriage and moving into the study villages of women from other, usually less endemic villages during the last years before the start of control.

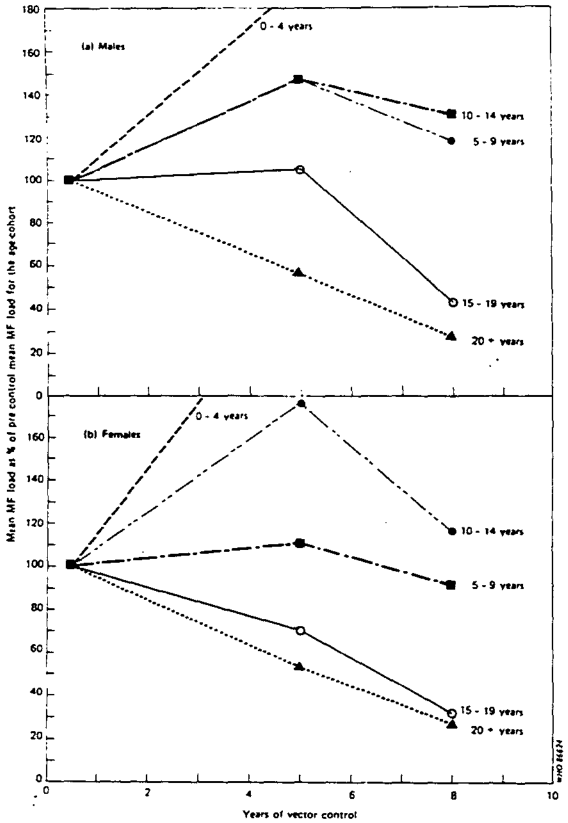

Fig. 9. Observed relative trend in the mean microfilarial (MF) load in males and in females by age cohort.

Relative trends by age in the intensity of infection

One of the most important predictions of the model was that after control, the relative trend in the mean number of patent infections will depend on the age at the start of control. The means for children under 15 years would increase during the first 5 years of control, whereas the mean for adults would show a linear decrease; and the proportional decrease in adults would be independent of both age and endemicity level. If this last prediction were true for the observed microfilarial loads, then it would provide us with the required tool for a comparative analysis of the epidemiological data.

Fig. 9a and 9b show, for males and females respectively from the 23 villages, the relative trends in the mean microfilarial loads of each age cohort. For each cohort the post-control microfilarial loads are expressed as percentages of the pre-control load. Just as in the model predicted (see Fig. 4), there is a marked increase in the microfilarial loads for both males and females in the age group 0–4 years, in which nearly all the pre-control infections were still pre-patent at the start of control, and in which the pre-control prevalence and load were close to zero. The relative increase of more than 200% in the microfilarial loads in this age group, in which the pre-control prevalence for males and females combined was as low as 2.4%, was based on a change in the mean load from only 0.018 to 0.037 microfilariae per skin snip. However, the results become more meaningful for the age groups 5–9 years (pre-control prevalence, 13%) and 10–14 years (pre-control prevalence, 43%), both of which showed similar upward trends 5 years after control and were still higher than the pre-control loads after 8 years. In both sexes the observed trend for the age group 15–19 years is also approximately as predicted, with an initial stagnation during the first 5 years followed by a more rapid decrease between the 5th and 8th years of control.

Since the microfilarial loads level off after the age of 20 years in both pre- and post-control surveys, the trends for adults are presented as one cohort for each sex. However, the hypothesis of an age-independent post-control trend for adults was further tested with an analysis of variance on the logarithm of the ratio between the post- and pre-control microfilarial count plus one per person. No significant differences were found between the adult 10-year age groups (5 years of control, $P=0.33$; 8 years of control, $P=0.19$) or between the sexes (5 years of control, $P=0.33$; 8 years of control, $P=0.51$), facts which provided further justification for pooling the results for the whole population with an initial age of more than 20 years. The observed post-control trends for both males and females agree very well with the predictions of the model. Indeed the observed trends are even more directly linear than the predicted trend and do not clearly show the delaying effect of the pre-patent period.

Epidemiological trends in adults by endemicity level

The most important difference between the adult populations in different villages is the initial endemicity level of *O. volvulus* infection which, according to the model, will affect the absolute trend in prevalence and intensity of infection among adults after control, but the relative trend in the intensity of infection among adults should be independent of the initial endemicity level. In order to test these predictions we first separated the adults from each of the 23 villages into male and female populations because of the observed difference in endemicity between the two sexes. Then the 46 subpopulations were classified into 5 groups according to their endemicity level, using as the criterion for endemicity the mean pre-control microfilarial load for the subpopulation.

Trend in prevalence in adults. The observed trends in prevalence in adults by endemicity level are shown in Fig. 10. The pre-control prevalences for the three groups with the highest endemicity levels are very similar and are all close to 100%, thus demonstrating the limitations of the prevalence as a measure of endemicity. Only for the group with less than 5 microfilariae per snip, a group poorly represented among OCP indicator villages, is the pre-control prevalence distinctly lower. The post-control prevalence figures observed during the first 8 years of control are comparable with the predicted trends (see Fig. 5) and show clearly that the rate of fall in the prevalence depends to a great extent on the initial endemicity level. For the two highest endemicity levels (>50 and 30–49 mfs) there is virtually no change in the prevalence during the first 5 years of control, and only after 8 years does it begin to drop marginally. For the two next lower endemicity levels (15–29 and 5–14 mfs) the prevalence is already beginning to decrease during the first 5 years of control and the decrease becomes more rapid between the 5th and 8th years. Only in the lowest endemicity group (<5 mfs) does the prevalence show a nearly linear decrease.

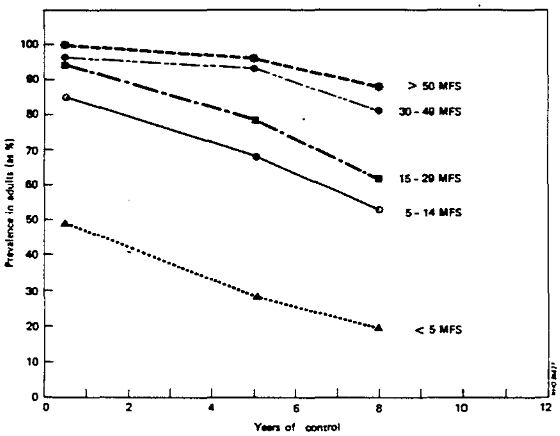

Fig. 10. Observed trend in prevalence in cohorts of adults by endemicity level (MFS = number of microfilariae per skin snip).

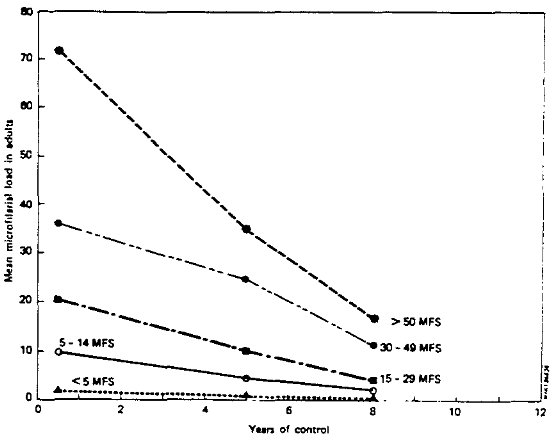

Fig. 11. Observed trend in the mean microfilarial load in cohorts of adults by endemicity level (MFS = number of microfilariae per skin snip).

Trend in microfilarial loads in adults. Fig. 11 shows the mean microfilarial loads in adults at each endemicity level before and after control. At all levels of endemicity the mean loads show a decrease during the first 5 years of control and this continues up to year 8. For four of the endemicity levels the decrease is nearly linear and only in the group with a mean of 30–49 microfilariae is the decrease somewhat slow during the first 5 years of control. The figures for the individual subpopulations in this group showed that the slower decrease was mainly due to a different trend in one village, for which both the male and female subpopulations were classified in this endemicity group. In this village the mean microfilarial load actually increased between the pre-control survey and the 5-year follow-up, although the trend between the 5th and the 8th years of control was comparable to the other subpopulations in this group. One possible explanation of this discrepancy may be that the pre-control data for this village were of poor quality and that the pre-control mean load had been underestimated. The largest absolute decrease was seen in the group with the highest endemicity level (>50 mfs) for which the prevalence had remained nearly constant during 8 years of control. All the regression lines show a tendency to converge on a zero point after about 10–11 years of control and the general trend is very similar to that predicted by the model (see Fig. 6).

Relative trend in microfilarial loads in adults. Table 1 gives the number of adults and the mean pre-control microfilarial loads for each endemicity level, together with the percentage decrease in microfilarial loads after 5 and 8 years of control. The percentage decreases in microfilarial loads are nearly identical for four of the endemicity levels. Only in the group with a mean of 30–49 microfilariae is the decrease noticeably slower, especially during the first 5 years of control, as a result of the different trend in the village mentioned above. With the exception of this village, all the data confirm the prediction that, after satisfactory control, the decrease in the mean microfilarial load in adults is linear over time and that the relative decrease is the same for all endemicity levels.

DISCUSSION

The force-of-onchocerciasis-infection model has some obvious oversimplifications, such as the assumption of a constant patent period, but its strength lies in the fact that it addresses the questions of superinfection, the longevity of infection, and age-dependent exposure. The results predicted by the model are remarkably similar to the results observed in the OCP; and it appears that the basic reasoning of the model is correct. This has some important implications for the epidemiological evaluation of the impact of vector control on onchocerciasis and for the interpretation of the epidemiological trends.

Table 1. Percentage decrease in mean microfilarial load in cohorts of adults by endemicity level

Pre-control endemicity level	No. of adults	Pre-control mean microfilarial load	Percentage decrease in mean microfilarial load after control for:	
			5 years	8 years
⩾50 mfs	88	71.7	51.9	77.1
30–49 mfs	271	37.0	32.2	71.3
15–29 mfs	323	21.6	49.0	77.0
5–14 mfs	277	9.9	53.5	75.4
<5 mfs	203	1.9	54.0	74.1
All adults	1162	15.3	45.2	72.6

The most important conclusion is that one cannot expect a uniform epidemiological trend after successful vector control. For a resident population, all the epidemiological indices will of course drop to zero once transmission has been interrupted for a period in excess of the maximum longevity of infection. But the rate and manner in which the different epidemiological indices decrease during the period of control depend largely on the initial age of the population concerned and on the degree of endemicity of onchocerciasis.

In children in endemic areas most infections are of recent origin and the adult female worms still have most of their productive lifespan ahead of them when transmission is interrupted by *Simulium* control. The prevalence and mean microfilarial load in children will not therefore show any decrease during the first 5–8 years after interruption of transmission and, owing to the disproportionate number of pre-patent infections, both indices will in fact usually show an increase during the first years of control. The data obtained from children born before the start of control are therefore of limited value for evaluation during the early years of control.

For adults, on the other hand, from the age of 20 years onwards, there is, under pre-control conditions, an equilibrium between the rate at which new infections become patent and old infections die off. After transmission has been interrupted by vector control, this equilibrium is maintained for a relatively short time equal to the average pre-patent period. Once that period has passed it is only the rate at which old infections die out that determines the epidemiological changes. The mean number of active infections will decrease in a linear manner towards zero after a period of control that will approximate to the average longevity of infection. The way in which these changes are reflected in the indices of epidemiological evaluation depends on which index is used. The prevalence which, by definition, is not concerned with the intensity of infection, will not show any immediate decrease except in those populations with the lowest endemicity levels. The higher the level of endemicity, the longer it will take for the prevalence to show a decrease, but the more abrupt will be its final fall. These characteristics mean that the prevalence is too insensitive an index to be of practical use over most of the control period in most of the villages followed up in OCP, for it will fail to differentiate between satisfactory and unsatisfactory control.

A much more sensitive index of the epidemiological changes resulting from *Simulium* control is the geometric mean microfilarial load among a cohort of adults who are at least 20 years of age at the time when control was first established. This index, which is now used routinely in OCP, is known as the Community Microfilarial Load or CMFL. During the first 8 years of successful vector control in OCP the observed changes in the CMFL were very similar to the trends predicted by the model for the mean number of patent infections per person. The decrease in the CMFL was linear and independent of age. Its absolute decrease depended on the initial endemicity level in such a way that the higher the endemicity the faster was the decrease in the CMFL; and it is this characteristic of the CMFL which gives it a clear advantage over the prevalence. Furthermore, the CMFL, by measuring the intensity of microfilarial infection, reflects the risk of the development of serious eye lesions and blindness, which are the principal factors determining the public health and socioeconomic importance of onchocerciasis (*12*). The considerable decrease in the CMFL among the highest endemicity groups after control is established is therefore of major epidemiological significance in OCP, in spite of the fact that the prevalence in these groups has remained high.

The relative decrease in the CMFL is independent of the initial endemicity level, and it is this property that makes it a useful and sensitive statistic for the comparative analysis of post-control trends. Furthermore, it enables data from different villages to be pooled, provided their relative trends are similar. Finally, in areas where vector control has been successful, the trend in the CMFL can also be used to estimate the average longevity of infection. The results of these applications of the CMFL in the analysis of OCP results will be presented elsewhere.

The force-of-onchocerciasis-infection model has also provided further information on the dynamics of onchocerciasis in areas with ongoing transmission. Study of the pre-control data from OCP villages has shown that under normal conditions of transmission, the microfilarial load increases sharply between the ages of 10 and 20 years but levels off thereafter. Several authors have correctly emphasized that serious pathology in onchocerciasis is due to the cumulative effects of intense infection (*13*). However, the term cumulative tends to be misinterpreted as the continuous accumulation of female worms with increasing age. The OCP pre-control data, together with the force-of-infection model, suggest that in fact most of the accumulation occurs between the ages of 10 and 20 years. From then on, the mean number of infections and the mean microfilarial load remain more or less constant at a high level for the rest of the subject's lifetime, with the microfilariae exerting their pathogenic effect throughout this period. However, the intensity of infection among adults, as measured by the CMFL, can vary greatly between villages, even though their standardized prevalences may be very similar. It appears, therefore, that the CMFL is a better index of endemicity, and one which is also more directly related to the intensity of transmission during the pre-control period.

Wada (*14*) previously used a force-of-infection model in the analysis of cross-sectional data on onchocerciasis infection in 12 villages in Guatemala. The predicted age-specific prevalence curves fitted poorly to the observed results, because the simple catalytic model used ignores the factors of superinfection and longevity of infection. These two factors were included in a detailed transmission model for onchocerciasis by Dietz (*15*). However, in this latter model it is assumed that death of the adult worm occurs at a constant rate, independent of worm age. This assumption is the major explanation for the discrepancy between the post-control trends, originally predicted by this model, and the trends that have now been observed after 8 years of control in the OCP—trends which appear to confirm the conclusion of parasitologists that death of the adult *O. volvulus* is mainly due to a process of ageing of the worm. Though the present force-of-infection model takes the effect of ageing into account, it does so in a very simplified way, by assuming that the patent period is constant. The good agreement between the model's predictions and the observed data indicates that this simplification was acceptable for the first 8 years of control. However, the variability in the patent period will become an important factor when the duration of control approaches the average longevity of an infection and quantitative predictions for the final epidemiological trends in OCP would not be justified with the present model. For this reason we are at present developing a more sophisticated host-parasite life-history which will take account of the variability in the patent period, as well as other aspects, such as differential exposure in various sections of the human population, annual variations in the force of infection during the pre-control period, age-dependent microfilarial productivity of the adult worms, and mating and fertilization of *O. volvulus*.

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RÉSUMÉ

MODÈLE DE FORCE D'INFECTION POUR L'ONCHOCERCOSE ET APPLICATIONS DE CE MODÈLE À L'ÉVALUATION ÉPIDÉMIOLOGIQUE DU PROGRAMME DE LUTTE CONTRE L'ONCHOCERCOSE DANS LE BASSIN DE LA VOLTA

Un modèle simple de force d'infection a été mis au point pour l'onchocercose pour étudier les tendances épidémiologiques en fonction de l'âge au cours d'une période de lutte antivectorielle dans le cadre du programme de lutte contre l'onchocercose dans la région du Bassin de la Volta (OCP). Les principaux facteurs pris en compte sont la longévité de l'infection, les facteurs de surinfection, l'exposition par âge et l'intensité de la transmission au cours de la période pré-intervention. L'étude avait pour but de déterminer quelles sont les statistiques les plus appropriées pour l'évaluation épidémiologique du programme OCP car l'on ne savait pas très bien quel avait été l'impact épidémiologique du programme au cours des huit premières années ni à quelles tendances épidémiologiques il fallait s'attendre pour les années à venir. Les tendances observées ont généralement assez bien concordé avec la modélisation en ce qui concerne la prévalence et la charge microfilarienne moyenne des biopsies cutanées prélevées sur une cohorte de population de 1186 hommes et 1160 femmes vivant dans 23 villages d'une région où des activités de lutte antivectorielle sont menées efficacement depuis huit ans dans le cadre du programme OCP.

On peut en conclure que les tendances épidémiologiques pendant la période d'intervention ne sont pas uniformes mais que le taux de diminution des différents indices épidémiologiques et la manière dont s'opère cette diminution pendant la période considérée dépendent dans une large mesure de l'âge initial de la population concernée et du degré d'endémicité de l'onchocercose. Les indices épidémiologiques relatifs aux cohortes d'enfants nés avant le début des opérations de lutte ne marquent pas de diminution au cours des huit premières années où la transmission a été interrompue étant donné que la plupart des infections survenues chez ces enfants sont d'origine récente au moment de la mise en place du programme et que les vers femelles adultes ont encore devant eux leur cycle vital productif.

Pour les adultes de 20 ans et plus, on observe en revanche, pendant la période pré-intervention, un équilibre entre le taux d'apparition de nouvelles infections et le taux de disparition des anciennes. Après interruption de la transmission grâce aux activités de lutte antivectorielle pendant une période dépassant l'intervalle de prépatence, c'est uniquement le taux de disparition des infections anciennes qui déterminera les changements épidémiologiques. Mais sauf en cas de très faible endémicité, cette diminution du nombre d'infections évolutives ne se traduira pas par une baisse immédiate de la prévalence qui, par définition, ne dépend pas de l'intensité de l'infection. La prévalence n'est donc pas un indice assez sensible pour permettre l'évaluation dans les villages d'hyperendémie et cela pendant la presque totalité de la période d'intervention, et ce n'est que lorsque la durée des activités de lutte approchera la durée moyenne d'infection que la prévalence commencera à diminuer fortement dans ces villages.

L'instrument statistique le plus sensible et le plus significatif pour une analyse comparative et pour l'appréciation des changements épidémiologiques est la charge microfilarienne moyenne dans une cohorte d'adultes âgés d'au moins 20 ans au moment où le programme de lutte a été mis en place. Cet indice, que l'on appelle charge microfilarienne communautaire (CMFC), est désormais systématiquement utilisé dans le cadre du programme OCP. Au cours des huit premières années de lutte, la CMFC a accusé la diminution linéaire prévue, indépendamment de l'âge et du sexe. Comme prévu également, la diminution relative de la CMFC était indépendante du niveau d'endémicité — constatation qui fait de la CMFC la statistique idéale pour une analyse comparative des tendances dans des régions où les activités de lutte sont plus ou moins avancées. Enfin, la CMFC est considérée comme un meilleur indice de l'endémicité que la prévalence. Cette nouvelle méthode analytique a permis une bien meilleure appréciation de l'impact épidémiologique des huit années de lutte antivectorielle dans le cadre d'OCP. L'article aborde également plusieurs aspects connexes de la dynamique pré- et post-intervention de l'infection onchocerquienne et énonce un certain nombre de priorités pour les travaux sur la modélisation appliquée à l'onchocercose.

REFERENCES

1. Walsh, J. F. et al. Standardization of criteria for assessing the effect of *Simulium* control in onchocerciasis control programmes. *Transactions of the Royal Society for Tropical Medicine and Hygiene*, **72**: 675–676 (1978).
2. Kirkwood, B. et al. Variations in the prevalence and intensity of microfilarial infections by age, sex, place and time in the area of the Onchocerciasis Control Programme. *Transactions of the Royal Society for Tropical Medicine and Hygiene*, **77**: 857–861 (1983).
3. Dadzie, K. Y. et al. The evolution of ocular onchocerciasis in the Volta river basin over a period of five years of vector control. *Tropenmedizin und Parasitologie*, **34**: 41–46 (1984).
4. Dadzie, K. Y. et al. The effect of 7–8 years of vector control on the evolution of ocular onchocerciasis in the West African savanna. *Tropical medicine and parasitology* (in press).
5. Muench, H. *Catalytic models in epidemiology*. Cambridge, MS, Harvard University Press, 1959.
6. Duke, B. O. L. The effects of drugs on *Onchocerca volvulus*. 1. Methods of assessment, population dynamics of the parasite and the effects of diethylcarbamazine. *Bulletin of the World Health Organization*, **39**: 137–146 (1968).
7. Griffiths, D. A. The effect of measles vaccination on the incidence of measles in the community. *Journal of the Royal Statistical Society, Series A*, **136**: 441–449 (1973).
8. Remme, J. et al. The force of measles infection in East Africa. *International journal of epidemiology*, **13**: 332–339 (1984).
9. Duke, B. O. L. Observations on *Onchocerca volvulus* in experimentally infected chimpanzees. *Tropenmedizin und Parasitologie*, **31**: 41–54 (1980).
10. Prost, A. Latence parasitaire dans l'onchocercose. *Bulletin of the World Health Organization*, **58**: 923–925 (1980).
11. Prost, A. et al. Les niveaux d'endémicité dans l'onchocercose. *Bulletin of the World Health Organization*, **57**: 655–662 (1979).
12. WHO Technical Report Series, No. 597, 1976 (*Epidemiology of onchocerciasis*: report of a WHO Expert Committee).
13. Anderson, J. et al. Studies on onchocerciasis in the United Cameroon Republic. III. A four-year follow-up of 6 rain-forest and 6 Sudan-savanna villages. *Transactions of the Royal Society for Tropical Medicine and Hygiene*, **70**: 362–373 (1976).
14. Wada, Y. Theoretical approach to the epidemiology of onchocerciasis in Guatemala. *Japanese journal of medical science and biology*, **35**: 183–196 (1982).
15. Dietz, K. The population dynamics of onchocerciasis. In: Anderson, R. M., ed. *The population dynamics of infectious diseases: theory and applications*. London/New York, Chapman and Hall, 1982.

Chapter 4.2

The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna

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The effect of 7–8 years of vector control on the evolution of ocular onchocerciasis in West African Savanna

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Summary

The evolution of ocular onchocerciasis was studied in a cohort of 1170 persons over 5 years of age who were examined before the start of and after 7–8 years of effective vector control in 12 originally hyperendemic villages in the central part of the OCP area. The proportion of the cohort which at the outset of vector control was free from ocular onchocerciasis or had an early or recent infection in the form of punctate keratitis only, remained largely free of or lost their signs of ocular infection respectively and only a very insignificant proportion acquired microfilariae in the eyes or developed a severe onchocercal eye lesion at the initial stage. The proportion of the cohort with a heavy ocular microfilarial load had a reduced risk of developing severe eye lesions and no risk of going blind. The proportion of the cohort with already existing severe eye lesions at the advanced stage remained largely unchanged and some lesions at the initial stage disappeared. Blindness occurred only in those who had severe eye lesions at the outset and was comparatively less than in areas of on-going transmission.

Introduction

At present the only effective way of controlling onchocerciasis is by vector control. By this means onchocerciasis was eradicated from the Kodere Valley focus in Kenya where the vector was *Simulium neavei* (Roberts et al. 1976), and partial control was achieved in an *S. damnosum* s.l. focus in Mali (Thylefors and Rolland 1977).

Studies in areas of on-going transmission (Anderson et al. 1976, Budden 1955, 1976, Rolland 1974, Rolland et al. 1978) have shown that ocular onchocerciasis is a progressive disease, its progress being related to repeated inoculation of infective larvae over many years leading in turn to an increase in the intensity of microfilarial infection. The associated build-up of microfilarial concentrations in the eyes may, after a period of some years, cause severe eye lesions that are liable to deteriorate and often end in causing blindness. *Simulium* control interrupts transmission of *Onchocerca volvulus* so that persons born after the onset of control will remain parasite free, but it does not eliminate the parasite reservoir from persons who are already infected. The course of existing onchocercal ocular manifestations in such persons who are already infected is not clearly known in the setting of vector control.

The Onchocerciasis Control Programme in the Volta River Basin area (OCP), which aims to secure the long-term control of *S. damnosum* s.l. and onchocerciasis over a large part of the savanna zone of West Africa, has provided the opportunity for a prospective study of this nature. The effects on ocular onchocerciasis of 3 years (Rolland and Thylefors 1979, Thylefors and Tönjum 1980) and 5 years (Dadzie et al. 1984) of vector control have previously been reported. The present paper, using the same previous approach (Rolland and Thylefors 1979, Dadzie et al. 1984) to facilitate the comparison of effects, describes the course of ocular onchocerciasis in patients who have lived for 7–8 years in an area of effective vector control.

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Materials and methods

Selection of Study Villages. The study cohort was drawn from 12 villages, with populations ranging from 95 to 600 persons, median 356, situated in the central part of the OCP area where onchocerciasis was heavily endemic. The prevalence rate of onchocerciasis was over 60% in all but one village and the blindness rate over 2% in all villages except 3 and around 10% in 4 (Fig. 1).

All 12 villages had had satisfactory vector control since 1975 or 1976. The Annual Biting Rates (ABR) of *S. damnosum* s.l. in the settlement areas of the communities concerned had been maintained around or below 1000 flies/man/year[1], and the Annual Transmission Potentials (ATP) around or below 100 *O. volvulus* infective larvae/man/year[1] during the 7–8 year period of control.

Population Census and Selection of the Study Cohort. During the first survey 2432 persons were examined. 124 of them were blind and were excluded from further analysis because they were considered to have reached the end stage of ocular onchocerciasis and their lesions could not evolve further. Of the original examinees, 1170 reattended during the second survey and were included in the analysis.

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[1] These levels of ABR and ATP were established by a working group of the Onchocerciasis Control Programme Scientific Advisory Panel, Report No. SAP/77, as representing the maximum values of these indices of transmission which would be compatible with a tolerable (i.e. non-blinding) level of onchocerciasis in West African savanna areas.

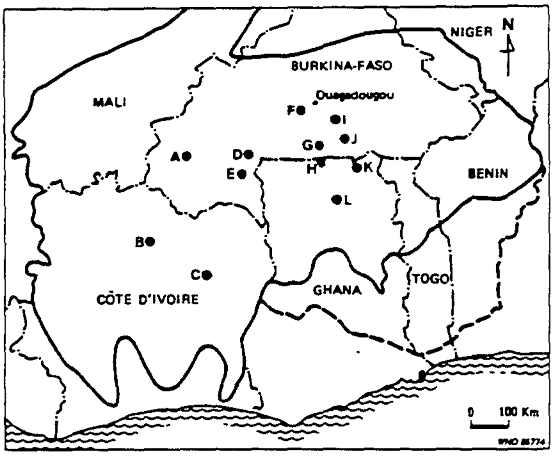

Fig. 1 Map of the area covered by the Onchocerciasis Control Programme (OCP) showing the location of 12 villages.

General Ocular Examination. Visual acuity was assessed using either the illiterate E- or the Sjogren Hand-test at 5 metres distance in daylight without correction for refractive error. Blindness was defined as inability to count fingers at 3 metres with the better eye. After positioning the patient with the head down between the knees for at least 2 minutes, microfilariae in the anterior chamber of the right eye, and then the left, were counted at x16 magnification with the slit-lamp (Haag-Streit 900). Dead microfilariae in the cornea and also punctate (fluffy) opacities were then counted, followed by a count of living microfilariae in the cornea using retro-illumination and x25 slit-lamp magnification. Thereafter onchocercal and other eye lesions of the anterior segment were looked for and recorded.

When there was no contra-indication, the pupils were dilated with 0.5% mydriaticum eye drops, and then a slit-lamp examination of the lens and anterior vitreous was performed. Direct and indirect ophthalmoscopy followed to look for onchocercal and other lesions of the fundus of the eye. Measurement of the intraocular pressure and visual fields was not done routinely at the initial examination, but the latter test was always carried out at the second examination 7–8 years after the start of vector control. The results of the examinations were recorded in coded form for each eye separately for computer analysis.

Coding of microfilarial counts. Counts of dead and living microfilariae in the cornea, of onchocercal punctate opacities and of microfilariae in the anterior chamber of the eye were recorded by code for each eye separately, coding a zero count as "0"; a count of 1–4 as "1"; of 5–19 as "2"; of 20–49 as "3"; of 50–99 as "4"; of 100–500 as "5"; and of over 500 as "6". Severe onchocercal eye lesions, viz. sclerosing keratitis, iridocyclitis with or without synechiae, choroido-retinitis and primary or post-neuritic optic atrophy were also coded according to their grading.

Classification of Onchocercal Ocular Manifestations. For the purpose of analysis in the present study, just as in the previous study (Dadzie et al. 1984), ocular onchocerciasis is classified into grades of increasing severity, first for each eye separately and then for each person according to the eye with the more severe grade of ocular findings.

Group 0 included those persons with no signs of ocular onchocerciasis.

Group I included persons with punctate keratitis only, i.e., those at the stage of early and recent infection when the host's immune defence mechanism is presumed to be unimpaired. This group may therefore have a lower risk of developing severe eye lesions in the absence of superinfection.

Group II were those with a light microfilarial load, i.e., those having less than 20 microfilariae in the cornea or the anterior chamber, and no other lesion of ocular onchocerciasis except punctate keratitis which may or may not have been present.

Group III were those with a heavy microfilarial load, i.e., those having 20 or more microfilariae in the cornea or the anterior chamber, but no other lesion of ocular onchocerciasis except punctate keratitis which may or may not have been present. It is well-known that microfilarial invasion of the cornea may ultimately cause sclerosing keratitis, but other severe onchocercal eye lesions follow intraocular microfilarial invasion. Thus the index number of microfilariae in the cornea or anterior chamber, or both, has been used to divide the subjects into those with light and heavy ocular microfilarial loads and hence having a low or high risk of development of one or the other of severe onchocercal eye lesions, using an arbitrary cut-off point of 20.

Group IV included persons having severe eye lesions at the early or initial stage. They may also have had visible microfilariae in the cornea or anterior chamber.

The initial stages of the various severe onchocercal eye lesions were defined as follows:

a) *sclerosing keratitis:* peripheral opacity at the nasal, temporal or inferior part of the cornea or the combination of 2 of these distributions;

b) *iridocyclitis:* an acute or chronic condition without synechiae;

c) *optic atrophy:* early pallor of the disc;

d) *choroido-retinitis:* mottling of retinal pigment epithelium.

Table 1 Re-attendance rate by age and sex after 7–8 years of vector control

	Males		Females		Total	
age (in years)	Examined 1st survey	Re-attendance (in %)	Examined 1st survey	Re-attendance (in %)	Examined 1st survey	Re-attendance (in %)
5– 9	212	61.8	187	46.5	399	54.6
10–14	253	42.3	207	26.6	460	35.2
15–19	110	40.0	89	38.2	199	39.2
20–29	155	52.3	237	52.3	392	52.3
30–39	165	72.1	218	69.7	383	70.8
40–49	122	63.9	110	50.9	232	57.8
50+	117	45.3	126	38.9	243	42.0
	1134	54.1	1174	47.4	2308	50.7

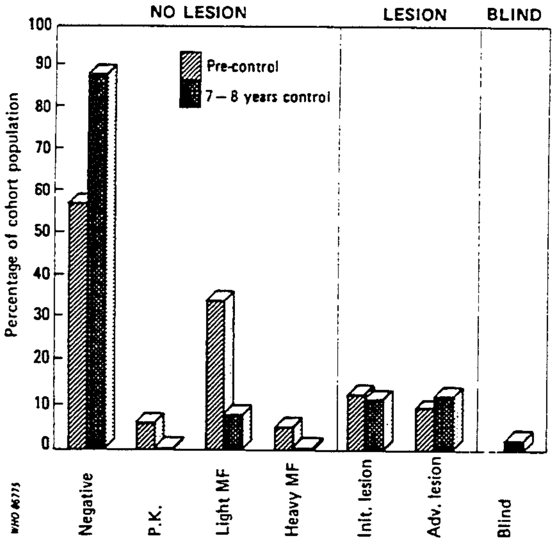

Fig. 2 Distribution of ocular onchocerciasis before and after control

Group V included those persons showing severe onchocercal eye lesions at an advanced stage, which had developed beyond the "initial stage" defined above but had not yet caused blindness. Again persons in this group may also have had visible microfilariae in the cornea or anterior chamber.

Group VI included all persons who became blind from ocular onchocerciasis after the start of vector control.

The classification of persons in the cohort into the above-defined groups was done by computer diagnosis, thus ensuring a maximally objective classification. This contrasts with the classification in the previous study (Dadzie et al. 1984) which was done by the observer.

Observer variance. Three different ophthalmologists were involved in collecting the data. All three had had considerable experience with the standardized methods used in the surveys. However, no systematic test to assess observer variation was done. One of the ophthalmologists was involved in the collection of some of the data at the examination before the start of, and after 7–8 years of vector control. The other two ophthalmologists were involved in the collection of data from only one or other of the two examinations.

Results

Table 1 shows the distribution by age and sex of the population examined before the start of vector control and the proportion of the population re-examined after 7–8 years. The proportion re-attending was about 51%, slightly lower than that recorded after a 4-year interval in a similar survey by Anderson et al. (1976). Re-attendance was lowest in the age group 10–20 years in which the males tend to migrate in search of work and the females marry and move away to the villages of their husbands.

The distribution of different manifestations of ocular onchocerciasis by age and sex in the cohort population at the first examination was compared with that in the part of the population which was present in the first survey but absent on the second occasion. 52% of the "absentees" had no signs of ocular onchocerciasis compared with 46.8% of the cohort. However this difference is partly due to the fact that, among the absentees, there was a disproportionately higher number of younger persons, who do not usually have signs of ocular onchocerciasis. After correction for age, the absentees were still slightly less infected but the difference was borderline statistically significant; $0.025 < p < 0.05$, (chi square test).

Fig. 2 compares the distribution of ocular onchocerciasis in the study cohort classified in an ascending order of severity before and 7–8 years after the start of vector control.

After 7–8 years of vector control, over 70% of the cohort showed no evidence of ocular onchocerciasis as compared with 46% before control started. Onchocercal punctate keratitis had dropped from 5% to 0.3% and the prevalences of light and heavy loads of microfilariae in the eye (without any serious onchocercal eye lesion) had dropped from 27.3% and 4.2% respectively to 6.7% and 0.4%. The proportion of the population with severe eye lesions, whether at the initial or advanced stage, remained more or less unchanged. The 124 blind persons at the first examination who were excluded from the cohort for reasons stated earlier, do not feature in the histogramme.

Fig. 3 A shows the ocular findings at 7–8 years in those 532 persons who were negative for ocular onchocerciasis at the initial examination (Group 0). Nearly all of them

Table 2 Development of new eye lesions after 7–8 years of vector control

		Anterior segment lesions						Posterior segment lesions						Total initial lesions		Total advanced lesions	
		SK		IR		Total		CR		OA		Total					
	Number examined	i	a	i	a	no.	%	i	a	i	a	no.	%	no.	%	no.	%
No. MF	532	1	0	0	0	1	0.2	2	0	12	0	14	2.6	15	2.8	0	0
Punct.	58	0	0	0	0	0	0	2	0	4	0	6	10.3	6	10.3	0	0
Light	319	6	1	1	2	10	3.1	17	3	22	11	53	16.6	46	14.4	17	5.3
Heavy	49	1	0	0	2	3	6.1	5	4	0	6	15	30.6	6	12.2	12	24.5
Total	958	8	1	1	4	14	1.5	26	7	38	17	88	9.2	73	7.6	29	3.3

SK = sclerosing keratitis, IR = iritis, CR = choroido-retinitis, OA = optic atrophy, i = ocular lesion at the initial stage, a = ocular lesion at the advanced stage

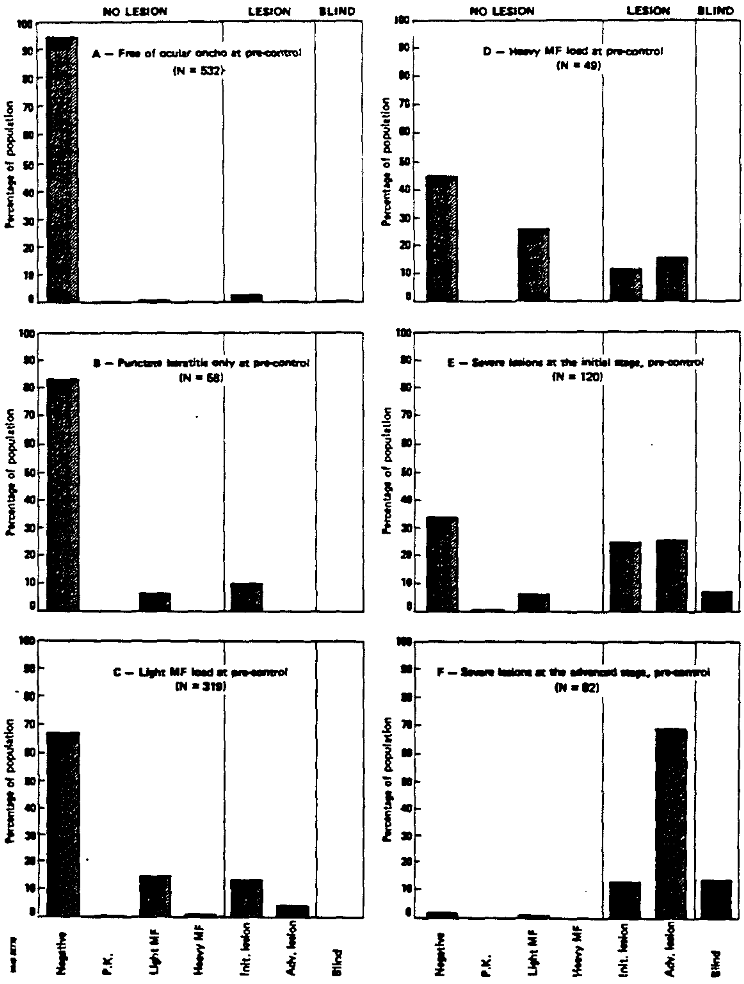

Fig. 3 Evolution of ocular onchocerciasis in populations classified according to the severity of their ocular manifestations at the pre-control examination

had remained free of ocular involvement. Only 2% had microfilariae in the anterior segment of the eye; 3% had developed severe ocular lesions at the initial stage; and three persons had gone blind as a result of uncomplicated senile cataract.

Fig. 3 B shows the ocular signs at 7–8 years in those 58 persons who showed lesions of onchocercal punctate keratitis only at the first examination (Group I). 83% had become negative for ocular signs, some 7% had microfilariae in the anterior segment of the eye and nearly 10% had developed severe eye lesions at the initial stage. The number of those who had acquired microfilariae in the anterior segment of the eye was 4 times higher, and of those who had developed a severe eye lesion 3 times higher than those in Group 0.

Fig. 3 C similarly shows how the ocular signs developed in those 319 persons who had a light ocular load of microfilariae at the start (Group II). In this group 67% had become negative and some 18% had developed severe eye lesions, of which some 4% had attained the advanced stage. The number who had developed a serious lesion was 6 times higher than those in Group 0 who were originally negative (cf. Fig. 3 A).

Fig. 3 D shows the ocular signs at 7–8 years in 49 persons who had a heavy load of ocular microfilariae at the initial examination (Group III). In this group almost 30% had developed a severe lesion and more than half of these were at the advanced stage. On the other hand, over 40% of persons in this group, who would have been at a very high risk of developing ocular lesions in the absence of vector control, had lost their ocular parasites and showed no signs of ocular onchocerciasis. It is noteworthy that no case of onchocercal blindness occurred in the group.

Table 2 gives the types of severe ocular onchocercal lesions that had formed over 7–8 years in the study cohort. It can be seen that in cases where there were no previous signs of ocular onchocerciasis or where there was only an early infection in the form of punctate keratitis, the serious

Table 3 Evolution of ocular lesion in cases classified as being at the initial stage (group IV) at the first survey

Type of initial stage lesion seen at the first survey	number of cases	Status of the lesion after 7–8 years of control Disappeared		initial stage		Advanced stage	
		No.	%	No.	%	No.	%
Scler. keratitis	43	27	62.8	15	34.9	1	2.3
Iritis	45	30	66.7	8	17.8	7	15.6
Choroido-retinitis	29	7	24.1	7	24.1	15	51.7
Optic atrophy	38	17	44.7	8	21.1	13	34.2

eye lesions which had developed to the initial stage over the 7–8 year period involved mainly the posterior segment, and it was the optic nerve that was apparently predominantly affected. In those cases which showed ocular microfilariae at the first examination, a greater number of serious lesions had developed over the succeeding 7–8 years. Some of them were in the anterior segment but lesions of the posterior segment still predominated and apparent optic nerve pallor was still slightly more common than choroidoretinitis.

Fig. 3 E shows the evolution of ocular onchocerciasis in 120 cases recorded at the first examination as having a severe ocular onchocercal lesion at the initial stage (Group IV). In over one-third of the cases the lesion could not be detected 7–8 years later and these cases had apparently recovered from their ocular disease. In another third, the lesions remained unchanged. In the final third the lesions had progressed to the advanced stage and 8% of the group had gone blind. More detailed analysis of these results showed that those subjects who had apparently lost their lesion 7–8 years after the start of vector control had lighter initial loads of ocular microfilariae (50% had zero and 45% 1–19 microfilarial counts) than did those subjects whose lesions had deteriorated over the same period (45% had 20+ and 42% 1–19 counts).

Table 3 shows the evolution of cases with severe ocular lesions at the initial stage (Group IV) at the first survey during the 7–8 years of vector control. Nearly two-thirds of the onchocercal ocular lesions in the anterior segment of the eye have disappeared and the majority of the remaining third have stayed put. In the posterior segment of the eye, a lesser proportion of lesions (choroido-retinitis 24%, optic atrophy 45%) was recorded as having disappeared, and a considerably higher proportion (choroido-retinitis 52% and optic atrophy 34%) was recorded as having progressed to the advanced stage.

Fig. 3 F shows the evolution of ocular onchocerciasis in 92 cases recorded at the first examination as having a severe ocular onchocercal lesion at the advanced stage (Group V). In over 80% of cases in this group the lesion remained unchanged and some 14% of the group had gone blind. In only about 3% of cases was the lesion recorded as having disappeared, and the significance of this finding will be discussed later.

Table 4 shows the lesions accounting for the new cases of blindness discovered at the examination made 7–8 years after the start of vector control. Twenty-five people out of the cohort population of 1170 had gone blind, but the cause of blindness in seven of them was unrelated to onchocerciasis[2]. In the remaining 18, onchocerciasis was considered to be the cause of blindness, which gives an incidence rate for blindness due to onchocerciasis of 0.2% per annum. From Table 4 it can be seen that the main blinding lesions in this study were complicated cataract (10 cases), and total corneal opacity associated with absolute glaucoma (6 cases). These lesions represent the final stage of long-standing severe ocular onchocerciasis and, although posterior segment lesions were probably also present in these cases, the invisibility of the fundus made it impossible to confirm this belief. However, these cases did confirm the fact that the presence of a heavy load of microfilariae in the eye at the initial examination was a very important factor predisposing to blindness.

Discussion

The re-attendance rate (51%) in this study was low, but still acceptable considering the long interval of 7–8 years between examinations. Absenteeism was mainly due to migration and death. In one village only were there a few persons who refused to present themselves at the follow-up examinations.

The distribution of ocular onchocerciasis at the initial examination was shown to be essentially similar in the study cohort and in the section of the initial population that was absent at the second examination. Thus the study cohort can be considered to be representative of the population in the 12 villages examined.

Anderson et al. (1976, 1978), Budden (1955), Rolland (1974), and Rolland et al. (1978) have shown by means of longitudinal population studies that, under conditions of on-going transmission, there is a grave deterioration in the state of ocular onchocerciasis. The present study shows that 7–8 years of successful vector control can change the evolution of ocular onchocerciasis. Instead of more people developing serious ocular lesions, there was a marked reduction in the proportion of persons showing ocular microfilariae. Thus the proportion of people free from detectable ocular microfilariae and from any serious lesion of ocular onchocerciasis increased from 46% to 71% after 7–8 years of vector control. The proportion of people carrying microfilariae in the eyes was reduced to a quarter of its previous value, and cases with heavy loads of ocular parasites virtually disappeared. However, the proportion of the population showing any degree of one of the four serious lesions of ocular onchocerciasis remained unchanged.

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[2] Seven persons blind due to uncomplicated senile cataract, one of whom also had band-shaped keratopathy.

Table 4 Cases of new onchocercal blind in the cohort population after 7–8 years of vector control

	First examination			Second examination		
	Severe lesions at the initial stage			Blinding lesions		
Ocular parasite load	Anterior segment	Posterior segment	Combined lesions	Anterior segment	Posterior segment	Combined lesions
Light	IR			Compl. cataract		
			IR + SK CR			abs. glaucoma + corneal opacity
Heavy	SK + IR			Compl. cataract		
	IR					abs. glaucoma + corneal opacty
	IR + SK			Compl. cataract		
	IR					abs. glaucoma + corneal opacity
		OA				abs. glaucoma + corneal opacity
	Severe lesions at the advanced stage			Blinding lesions		
Light			IR CR + OA	Compl. cataract		
			SK CR + OA	Compl. cataract		
Heavy	IR + SK			Compl. cataract		
	SK + IR			Compl. cataract		
		CR + OA		Compl. cataract		
		CR				abs. glaucoma + corneal opacity
			SK + IR OA + CR	Compl. cataract		
			IR OAgl			abs. glaucoma + corneal opacity
			SK CR + OA	Compl. cataract		
			IR + SK CR + OA			IR CR + OA
			IR + SK CR + OA			IR + SK CR + OA

IR = iridocyclitis, SK = sclerosing keratitis, CR = choroido-retinitis, OA = optic atrophy, OAgl = glaucomatous optic atrophy, Compl. cataract = complicated cataract, abs. glaucoma = absolute glaucoma, light = microfilarial count <20, heavy = microfilarial count >20

The increase in the proportion of persons without ocular onchocerciasis came about mainly as a result of the following:

a) Group 0 initially free from ocular parasites, remained up to 95% uninfected.

b) 82% of Group I, with onchocercal punctate keratitis, lost this ocular sign.

c) 66% of Group II, with a light load of ocular microfilariae, lost their ocular parasites.

These findings should be compared with those of Rolland (1974) and Rolland et al. (1978) who showed that under conditions of on-going transmission in the same area of West African savanna, at least 50% of the population without ocular onchocerciasis acquired ocular microfilariae and/or developed serious eye lesions over a period of 6–9 years.

It is noteworthy that in the present study some serious eye lesions developed within Groups 0, I and II with either nil or light loads of ocular microfilariae at the outset, but the proportion so affected was minimal and those lesions which developed were limited to the initial stage. Recognition of the initial stage of severe eye lesions is difficult in some cases and the recorded incidence of lesions at this stage may not always have been accurate. At the second examination made in the present study most of the new lesions recorded were in the posterior segment of the eye. While it is possible that the incidence of such posterior segment lesions at the initial stage may have been overestimated, it must also be remembered that onchocercal lesions of the posterior segment of the eye can occur at a low intensity of infection (Budden 1955) and this type of lesion may well be the most likely to develop in the circumstances following an interruption of transmission due to vector control. The question that arises is why these lesions of the posterior segment appear and continue to progress, even though slowly, whereas lesions of the anterior segment of the eye have almost ceased to form. A possible explanation could be that posterior segment lesions, once initiated, may continue to progress without further stimulation by the causative agent (be it the microfilariae or the presence of immune complexes), while such stimulation may be necessary for the progression of lesions of the anterior segment. Another factor may be a general change in the host reaction in the absence of continued superinfection.

Vector control also modifies the risk factors predisposing to blindness. Thus, after 7-8 years of vector control, no blindness had occurred in Group III which had a heavy load of ocular microfilariae but no overt lesions, and less than 30% of this group had developed a serious eye lesion 7–8 years later. Furthermore, over 40% of persons in this group had lost all trace of ocular microfilariae. This contrasts with the results found among people with heavy ocular microfilarial loads in areas of ongoing transmission where, after 6–9 years, 50% develop serious eye lesions and over 5% go blind (Budden 1955, Rolland 1974, Rolland et al. 1978).

The present study indicates that, in over 40% of persons recorded in the first survey as having a serious eye lesion at the initial stage (Group IV), the lesion had disappeared by the time of the second examination 7–8 years later (Fig. 3 E). Most of the lesions which disappeared were in the anterior segment of the eye. It is conceivable that the disappearance of microfilariae from the cornea could arrest the development of an early sclerosing keratitis, with subsequent regression of the pre-existing lesion. Similarly, an iridocyclitis without synechiae may resolve when the causative microfilariae are removed.

It is probable, therefore, that successful vector control, by interrupting transmission and preventing superinfection, not only reduces the risk of new severe eye lesions developing, but also arrests the further evolution of some lesions and may even result in a regression of the early stages of lesions in the anterior segment of the eye.

With regard to records of the disappearance of some severe lesions at the initial stage in the posterior segment, the possibility of erroneous diagnosis (either positive or negative) due to inter- or intraobserver variation cannot be excluded. The difficulty of reliably assessing optic disc pallor by ophthalmoscopy is known in clinical ophthalmic research, and such an assessment is invariably associated with observer variations.

Among the 92 persons re-examined who had been recorded in the first survey as having severe eye lesions at the advanced stage (Group V), 3 cases were found to be without any sign of ocular onchocerciasis at the survey made 7–8 years after the start of vector control, and one case showed only a light load of microfilariae. Further investigation showed 3 of these subjects to have iritis with synechiae at the first examination but the synechiae had subsequently broken down and disappeared. The fourth case, which had also shown iritis with synechiae, was found to be due to trauma and unassociated with onchocerciasis.

The majority of severe eye lesions were found to remain unchanged over the 7–8 years following the start of vector control, and this represents an important deviation from the natural history of uncontrolled onchocerciasis in West African savanna, where, with on-going transmission, there may be a 25%–50% incidence of blindness over a similar period among people who already had a severe eye lesion (Rolland 1974, Rolland et al. 1978). In the present study, blindness developed in only 8.6% of people with an already existing severe eye lesion. These cases were mainly those who already had such advanced eye lesions at the start of vector control that their ultimate deterioration to blindness would have been inevitable and, indeed, would probably have proceeded independent of the causative agent. A few others showed a severe lesion at the initial stage but also had a very heavy microfilarial load. It is conceivable that in this latter group blindness could have been prevented by careful chemotherapy.

It can therefore be concluded that after 7–8 years of effective *Simulium* vector control, most of those persons who have light ocular microfilarial loads when control starts will lose their ocular infection. Others who have a heavy ocular microfilarial infection at the outset will have a reduced risk of developing severe eye lesions and will no longer be at risk of going blind. Some of those with a severe eye lesion at the outset may still go blind, but the risk of this happening will be reduced; most of such cases will remain unchanged, but some anterior segment lesions may even improve.

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References

Anderson, J., H. Fuglsang, T.F. de C. Marshall: Studies on onchocerciasis in the United Cameroon Republic. III. A four-year follow-up of 6 rain-forest and 6 Sudan-savanna villages. Trans. roy. Soc. trop. Med. Hyg. 70 (1976) 362–373

Anderson, J., H. Fuglsang, T.F. de C. Marshall, A. Radolowicz, J.P. Vaughan: Studies on onchocerciasis in the United Cameroon Republic. IV. A four year follow-up of six rain-forest and six savanna villages. The incidence of ocular lesions. Trans. roy. Soc. trop. Med. Hyg. 72 (1978) 513–515

Budden, F.H.: Incidence of human infection with onchocerciasis in different communities in relation to the incidence and type of the ocular lesions. Brit. J. Ophthal. 39 (1955) 321–332

Budden, F.H.: The natural history of ocular onchocerciasis over a period of 14–15 years and the effect on this of a single course of suramin therapy. Trans. roy. Soc. trop. Med. Hyg. 70 (1976) 484–491

Dadzie, K.Y., A. Rolland, B. Thylefors: The Evolution of Ocular Onchocerciasis in the Volta River Basin Area over a Period of Five Years of Vector Control. Tropenmed. Parasit. 35 (1984) 41–46

Roberts, J.M.D., E. Neumann, C.W. Göckel, R.B. Highton: Onchocerciasis in Kenya 9, 11 and 18 years after elimination of the vector. Bull. Wld Hlth Org. 37 (1967) 195–212

Rolland, A.: Résultats de deux examens oculaires pratiqués à 6 ans d'intervalle dans deux villages onchocerquiens de Haute-Volta. Bull. Organ. mond. Santé 51 (1974) 257–261

Rolland, A., B. Thylefors, C. Pairault: Evolution sur 9 ans de l'onchocerose oculaire dans une communauté villageoise d'Afrique occidentale. Bull. Organ. mond. Santé 56 (1978) 805–810

Rolland, A., B. Thylefors: Aspects évolutifs de l'onchocerose oculaire en Afrique Occidentale, après trois ans de Lutte Antisimulidienne. Tropenmed. Parasit. 30 (1979) 482–488

Thylefors, B., A. Rolland: Situation dans un foyer d'onchocercose du Mali après treize ans de contrôle antisimulidien; aspects oculaires. Ann. Soc. belge Méd. trop. 57 (1977) 577–582

Thylefors, B., A.M. Tonjum: A three-year follow-up of ocular onchocerciasis in an area of vector control. Bull. Wld Hlth Org. 58 (1980) 107–112

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Chapter 4.3

The population dynamics of Onchocerca volvulus after 7-8 years of vector control in West Africa.

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Population dynamics of *Onchocerca volvulus* after 7 to 8 years of vector control in West Africa

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Summary

In an attempt to describe the changing population dynamics of *Onchocerca volvulus* during a period of vector control, nodulectomies were undertaken in 256 patients from ten villages in the Onchocerciasis Control Programme (OCP) and in 74 patients from two villages in an area with ongoing transmission. A total of 1198 nodules were excised and 4350 adult worms were isolated and examined for viability and productivity. In the OCP villages, the worm population is ageing and dying without replacement by new generations of parasites and various findings signal a breakdown of the worm population after about 12 years interruption of transmission. The sexual activity of the worms was significantly reduced. A Productivity Index was developed to measure the microfilariae production at the nodule level. The reduction in this index for the OCP villages correlates closely with the decline over the control period in the community microfilarial loads in the skin. The results show that it is not only the longevity of the parasite which will determine the duration of vector control, but that the reduced productivity of the ageing parasite population is of equal importance.

Key words: *Onchocerca volvulus;* Onchocerciasis Control Programme; nodulectomy; longevity; productivity.

Introduction

The Onchocerciasis Control Programme in West Africa (OCP), launched in 1974, aims at the long-term control of onchocerciasis as a disease of public health and socio-economic importance. The strategy of the programme is to interrupt the transmission of the parasite, through control of the vector *Simulium damnosum* s.l., for a sufficiently long period to allow the initial reservoir of infection in man to die out naturally. Once this reservoir has fallen to insignificant levels, the risk of recrudescence of onchocerciasis will be minimal and vector control operations may be scaled down and replaced by less costly activities. The required duration of vector control depends mainly on the longevity and fertility of the adult parasite harboured by the infected human populations.

A first indication of the maximum longevity of infection was given by Roberts et al. (1967) who observed in Kenya the survival of a residual population of living parasites 11 years after the eradication of the vector and the complete disappearance of microfilariae from the skin in the human population after 18 years. Based on these findings, the OCP was initially planned to last for a period of about 20 years. Very little new has been learned since then on the longevity and the fertility of the adult worm and, as the programme was approaching the end of its first decade of control, it became important to arrive at a better understanding of the population dynamics of *Onchocerca volvulus*. A study of the adult worm population has therefore been undertaken by the OCP in several villages since 1982, using the collagenase technique which enables the routine examination of excised nodules on a large scale. The first aim of the study was to identify reliable criteria and parameters to follow the decrease of the live worm population. The second aim was to compare the reproductivity of the worm population from a non-controlled area with the reproductivity of populations with ageing worms in the programme area using a quantitative assessment of the intra-uterine stages. The results, obtained from various epidemiological situations, are presented in this paper, and show some of the main parasitological trends in the Onchocerciasis Control Programme.

Material and Methods

At the start of the OCP, the collagenase technique (Schulz-Key et al., 1977) had not yet been developed and it was not possible to obtain intact adult worms for examination. Baseline data on the composition and the reproductivity of the worm burden in the villages sampled are therefore lacking for a direct comparison with our recent investigations. To make up for the handicap, two hyperendemic villages for onchocerciasis, located outside the OCP in an area with ongoing transmission in Mali, were chosen as controls. These villages are Manambougou, on the left bank of the Niger river, and Missira, at the bend of the Baoule river (see Fig. 1). Nodulectomies were carried out on 74 inhabitants in 1982 and 1983. Ten other villages were selected inside the OCP area in Burkina Faso and northern Ghana where vector control started during the years 1975–1977. Of these four villages, Lamiougou and Bangasse on the upper, Tagou and Kompiembiga on the lower Koulpeolgo river basin, have always had extremely satisfactory vector control with the virtual elimination of the vector population since 1976. Niarba, on the White Volta river basin, has also experienced similar successful vector control since the start of operations in 1976. The villages of Boko and Folonzo, both in the western part of Burkina Faso, had been under vector control since 1975 and light transmission may have occurred as a result of reinvasion of infective flies during the first three years but control was fully achieved afterwards. In Bonga (Burkina Faso), Nakong and Yagaba (Northern Ghana),

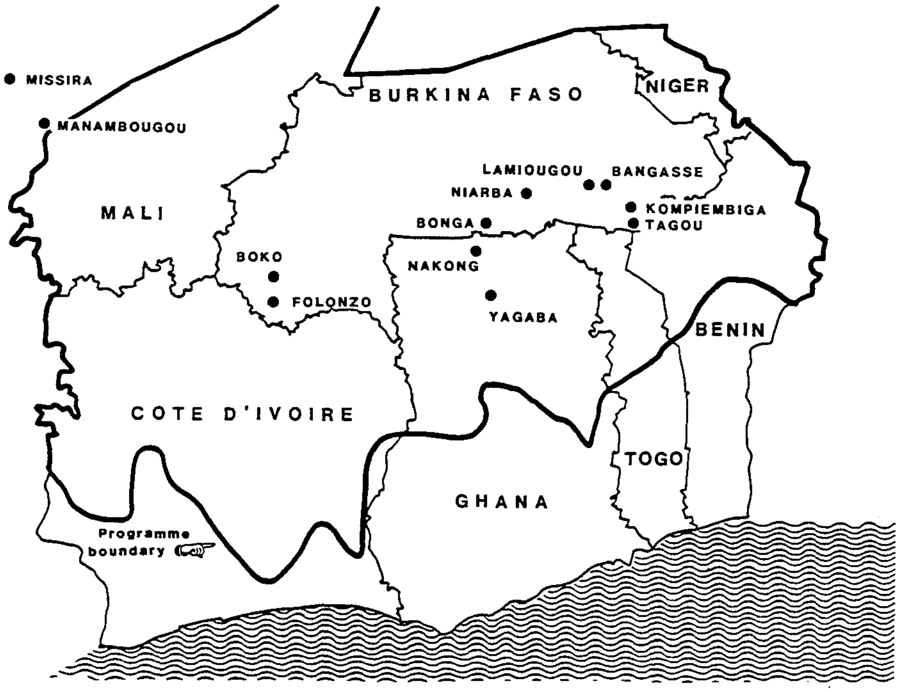


Fig. 1. The OCP area and the locations of the study villages.

vector control had started in 1976, but has not always been completely satisfactory. A local vector breeding outbreak was detected by the entomological evaluation in this area in 1981, and may have resulted in a localized resurgence of transmission.

For each village, a complete physical examination of the inhabitants was undertaken to search for signs of onchocerciasis. Patients older than 15 years among nodule carriers who volunteered underwent nodulectomy which, as a general rule, consisted in the removal of nodules from either the left or the right side of the body leaving one side free to allow lying to sleep at night in minimum comfort. As many nodules as possible were removed however, for ethical reasons, the final decision with regard to the number of sites to be operated respected the patient's wish. The number of patients operated varied from one village to the other and depended on the number of nodule carriers who volunteered. A total of 1198 nodules were surgically removed from 330 patients. The excised nodules were weighed with an accuracy of 0.1 g and their macroscopical characteristics were recorded before and during the digestion of the nodular tissue. The viability and the morphology of each worm were examined and the age grading recorded as described by Schulz-Key et al. (1980). The nodule, rather than the person operated, was taken as the sampling unit and the results of the analysis of the viability and the morphology will be presented as means or proportions per nodule. A special attention was given to the actual phase of reproduction. The female worms were classified into five groups: females with empty uteri, with one-cell-stages, with embryonated stages and living microfilariae, with only dead remnant microfilariae, or with remnant microfilariae and additional oocytes of a new reproductive cycle. Morphologically undamaged female worms were cut into small pieces, the intrauterine stages were squeezed out in a special mortar with an adjusted pestle. The number of developmental stages was then assessed as described by Schulz-Key et al. (1980). All but one of these

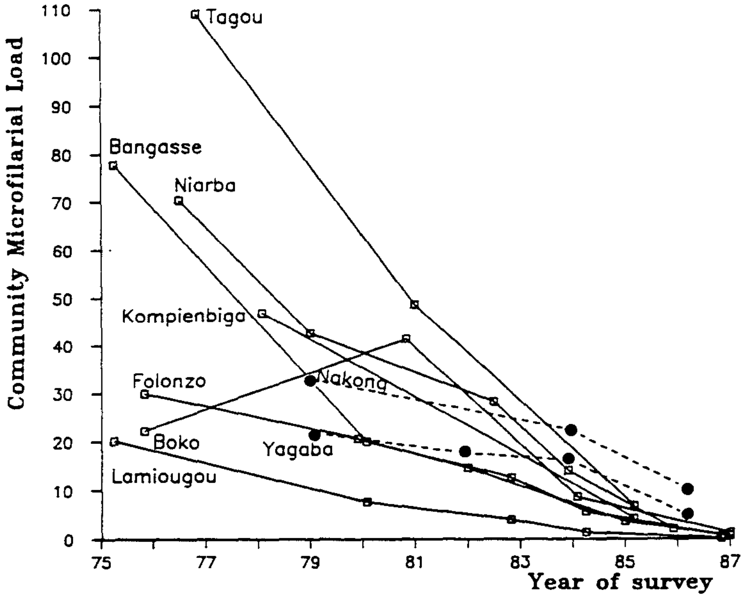


Fig. 2. Trends in the community microfilarial load in the study villages in the OCP area.

ten OCP villages had been, since the beginning of the Programme, regularly followed-up in epidemiological surveys during which one skin biopsy was performed with a Holth corneo-scleral punch at each iliac crest and examined according to the OCP standard methodology. Thus, the results of the worm analysis could be compared with the evolution of the skin microfilarial loads in the villages surveyed.

Results

Changes in skin microfilarial loads inside the vector-controlled area

Fig. 2 gives, for the follow-up villages, the evolution of the community microfilarial load (CMFL), which is the geometric mean number of microfilariae emerging per skin snip for a cohort of adults who have been examined at each survey (Remme et al., 1986). In seven of the villages the reduction in the CMFL was more than 90% at the last examination. Two villages in northern Ghana, Nakong and Yagaba, for which no baseline data are available for 1976, showed only a slight reduction in the microfilarial loads between 1979 and 1984 followed later by a more accelerated decrease. In Boko at the Comoe river basin in Burkina Faso a remarkable increase of the microfilarial densities was observed in 1980 followed by a considerable reduction in 1984 and 1986. This village was initially analysed separately, but, since the results of the worm analysis were not significantly different from those for the neighbouring village

Table 1. Number of excised nodules per village and general caracteristics of the adult worms examined

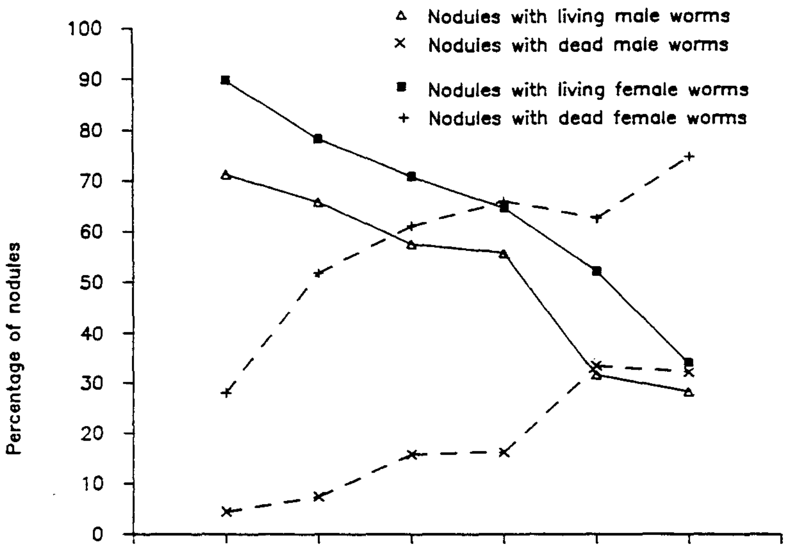
Village	No. of excized nodules	Geom. mean nodule weight (grams)	Number of non-calcified nodules	Male worms		Female worms		Sex ratio of living worms (M:F)
				total	% dead	total	% dead	
Manambougou...	158	0.67	155	258	1.9	442	12.0	1:1.54
Missira	116	0.77	116	197	4.6	307	10.1	1:1.47
Boko	82	0.88	81	121	5.0	214	24.3	1:1.41
Folonzo	70	0.56	70	102	6.9	181	28.2	1:1.37
Yagaba	110	0.54	110	144	15.3	241	33.6	1:1.31
Nakong	94	0.48	94	126	14.3	229	45.0	1:1.17
Bonga	45	0.55	44	59	10.2	103	35.0	1:1.26
Tagou	104	0.59	103	152	10.5	261	36.4	1:1.20
Kompiembiga ...	183	0.49	177	221	17.2	398	45.7	1:1.18
Niarba	118	0.54	114	137	35.0	219	43.4	1:1.39
Lamiougou	70	0.48	65	50	42.0	100	67.0	1:1.14
Bangasse	48	0.50	41	26	61.5	62	66.1	1:2.10
Total	1198		1170	1593		2757		

of Folonzo, they were combined and presented together. Following the pattern so far observed in the OCP, the decrease in the prevalence of microfilariae carriers is, in all villages, remarkably slower than that of the microfilarial loads in the skin.

Observations on nodules and adult parasites outside the vector-controlled area

Nodules: The geometric mean weight of the 274 excised nodules was 0.7 g (Table 1). There was no difference in relation to sex of the inhabitants, but there was a significant increase of the nodule weight in patients between 30 and 50 years old followed by a significant decrease in patients over 50 years. Only 1.1% of the nodules were calcified.

Adult worms: Fig. 3 A shows that 71% of the nodules contained living male worms (range 1 to 17), and 90% of the nodules harboured living female worms (range 1 to 20). Degenerated male worms were only occasionally found in the form of calcified fragments or disintegrated non-calcified worms (Table 1). 11.2% of the female worms were degenerated and were found in 28% of the nodules. Three quarters of these females were calcified or partially calcified. Less than 10% of the worms were old, brownish with a heavily coated cuticle. Two-thirds of the females were relatively young, more or less transparent and had an almost clean cuticle. About 3% of the female worms were very small, less than 1 cm in length and did not contain oocytes. They represented the immature adults. Immature male and female worms were always associated with



Study Villages:	Manambougou Missira	Boko Folonzo	Yagaba Nakong Bonga	Kompiembiga Togou	Niarba	Lamiougou Bangasse
Year of examination:	1982/83	1983	1983/84	1983	1984	1984
Vector control since:	N.A.	1975	1976	1976	1976	1976
Estimated period without transmission:	N.A.	7–8 years (incomplete)	7–8 years (incomplete)	8–9 years	8–9 years	9–10 years (or more)

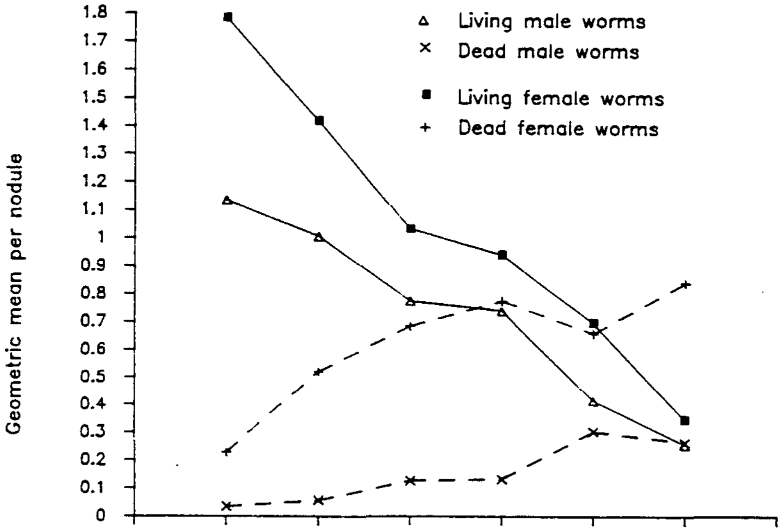
Fig. 3A. Percent ages of nodules with living or dead worms in the different village clusters.

old or even degenerated worms in the nodules. The reproductive activities of the female worms are recorded in Table 2 and are once more in accordance with our previous conclusions of the periodical, asynchronous release of microfilariae (Schulz-Key and Karam, 1986).

Observations on nodules and adult parasites inside the vector-controlled area

Nodules: The geometric mean weight of the excised nodules was significantly lower (15–31%), with the exception of Boko at the Comoe river basin, where the nodules were, on the average, even bigger than in the control villages (Table 1). The number of fibrous and caseous nodules had increased at the same time. The portion of calcified ones was around 3%. In Bangasse, even one out of every sixth nodule was calcified.

Adult worms: Fig. 3A shows a trend of reduced number of living adult worms with a longer period of interrupted transmission; only 30% of the nodules contained living adult worms in the area with no transmission for 9–10 years compared to 90% in the two control villages.



Study Villages:	Manambougou Missira	Boko Folonzo	Yagaba Nakong Bonga	Kompiembiga Tagou	Niarba	Lamiougou Bangasse
Year of examination:	1982/83	1983	1983/84	1983	1984	1984
Vector control since:	N.A.	1975	1976	1976	1976	1976
Estimated period without transmission:	N.A.	7–8 years (incomplete)	7–8 years (incomplete)	8–9 years	8–9 years	9–10 years (or more)

Fig. 3B. Mean number of living and dead worms per nodule in the different village clusters.

The living worms showed distinct signs of age, which we have already described in a previous paper (Schulz-Key et al., 1980). These were the consistence of the surface coat of female filariae, its colour, inclusions in the body cavity and in the organs, iron pigments and beginning of calcification. Nearly all the worms had become more or less opaque with the exception of several worms found in northern Ghana and at the Comoe river system.

The surface of the male worms was occasionally found charged with incrustations indicating a reduced migration from one nodule to another and therefore a reduced sexual activity. Up to five living male worms were found associated in nodules with only fragments of dead female worms. The sex ratio of living worms approached a more balanced ratio at the same time in all villages with the exception of the villages of Niarba and Bangasse, where the portion of dead worms was extremely high suggesting an imminent breakdown of the parasite population. Fragments of degenerate male worms were more difficult to detect than those of females, because they were often very small and sometimes mixed with the numerous fragments of calcified female worms.

Table 2. Content of the uteri of the live *Onchocerca volvulus* females per village cluster

Village clusters	No. of live females examined	% of total number of living female worms					
		immature females	mature, empty uteri	mature, one-cell stages only	mature, living mf and embr. stages	mature, remnant mf and oocytes	mature, remnant mf only
Manambougou/Missira (control villages)	634	2.7	20.8	17.4	53.0	4.1	2.0
Boko/Folonzo	292	0.0	25.8	19.7	45.4	8.1	0.1
Yagaba/Nakong/Bonga	353	0.0	30.8	19.9	32.8	12.9	3.6
Kompiembiga/Tagou	382	0.0	30.4	15.3	40.3	10.4	3.6
Niarba	124	0.0	36.4	28.9	16.5	9.9	3.6
Lamiougou/Bangasse	54	0.0	46.5	13.8	27.6	12.1	0.0

The mean number of living worms per nodule had distinctly decreased (Fig. 3 B) as compared to the non controlled areas (Schulz-Key et al., 1985). The percentage of reduction was as high as 77% for the male and 80% for the female worms in the Koulpeolgo basin. The reproductive activities of the female worms had changed remarkably. The portion of females just developing embryonated stages or microfilariae had decreased, whereas the portion of females with empty uteri had increased up to 47% (Table 2). The reproductive capacity of old worms decreased on average. The mean number of intra-uterine stages (embryonic stages and microfilariae) in gravid worms was reduced by up to 50% in some of the villages (Table 3). At the same time the portion of abnormal intra-uterine stages increased. The uteri were often filled with waste products. Sometimes they were even blocked with calcified particles or with big solid inclusions making a quantitative assessment in the suspensions more difficult.

The portion of male worms with only spermatids in the testes, i. e. of those which had just delivered sperms, was decreasing, whereas the portion of males with undelivered sperms increased. Male worms with completely empty testes became more frequent. They always represented old brownish worms, but their portion remained low.

Discussion

Nodules as sampling unit

Estimates of the worm load per person as an index in our analysis of the population dynamics of *Onchocerca volvulus* was not used as it seems inappropriate due to the following reasons: first, the total nodule load in patients cannot be excised by ambulatory nodulectomies, because the portion of unpalpable,

Table 3. Reduction in Productivity Index and in community microfilarial load within the OCP area

Village	Geom. mean no. of live female worms per nodule (x)	Proportion of gravid among live female worms (y)	Geom. mean no. of embryonic stages and mf in gravid female worms (z) (in 1000)	Productivity Index per nodule (x) (y) (z)	% of reduction in	
					Productivity Index	CMFL
Manambougou and Missira	1.75	0.53	159	147.4	0.0	–[a]
Boko	1.49	0.45	101	67.0	54.6	59.6[b]
Folonzo	1.31	0.47	100	60.9	58.7	69.2
Yagaba	1.02	0.37	152	57.7	60.8	77.0[c]
Nakong	0.98	0.27	73	19.5	86.8	68.8[c]
Bonga	1.14	0.32	113	42.0	71.5	–[a]
Tagou	1.16	0.45	96	49.6	66.4	76.1
Kompiembiga	0.78	0.37	111	31.9	78.4	66.3
Niarba	0.67	0.17	74	8.1	94.5	84.3
Lamiougou	0.32	0.18	91	5.1	96.5	93.6
Bangasse	0.29	0.42	83	10.1	93.2	93.1

[a] No longitudinal data
[b] compared to second survey
[c] between 1979 and 1986

deep lying nodules can be considerable and still remains unknown (Duke, 1970). Second, even subcutaneous nodules may be difficult to palpate as reported by Hamilton et al. (1974), who found that considerably more nodules were detected by the same observer during a second examination after one year as result of increased experience. The third and major limitation is that the average number of worms per person in a village depends largely on the intensity of transmission during the pre-control period (Remme et al., 1986). It is well known that the intensity of transmission varies greatly between villages and the confounding effect of this variability would severely complicate any direct comparisons between the OCP villages and the non-controlled villages.

Considering these reasons, we looked for other, more robust, parameters to describe the population dynamics of *Onchocerca volvulus*. The nodule, rather than the patient, was chosen as the sampling unit. This would not only be a better reflection of the actual practice in the field, but the results, if expressed per nodule, would be less susceptible to individual or local variations. This assumption is based on the finding that in both our present and previous studies (Schulz-Key and Albiez, 1977), the geometric mean number of living worms per nodule was rather similar and around 1.1–1.3 for male worms and 1.7–1.9 for female worms in villages without vector control. In addition, the nodule load itself proved to be relatively stable even several years after vector control. A similar observation was also reported by Parow (1983). However, one limitation to consider is the fact that old nodules are shrinking and losing some weight when the stimulus of living parasites is ceasing (Schulz-Key et al., 1980) thus making it more difficult for these nodules to be detected. Consequently, bias towards the detection of larger nodules during the control period is introduced. It is also thought that in the final phase of vector control, only completely calcified nodules will persist. This may explain the high proportion (15%) of calcified nodules in Bangasse.

Parasitological changes observed in the central area of the OCP

Changes in comparison with the non-controlled area: With the interruption of the transmission, no new parasites are being introduced into the final host. This resulted in a disequilibrium in the dynamics of the parasite population leading to the ageing and death of existing parasites without any replacement by young worms. In the non-controlled areas, almost 3% of the female worms were immature while none were found in the controlled area. In the controlled regions, there were clear signs of a senile population. The proportion of dead females was always higher wherever there was vector control. We do not know how long it takes for dead worms to be resorbed, nor do we know why some worms calcify completely whereas others do not show any signs of calcification. Calcified fragments obviously persist for a longer period and accumulate in the nodules to a certain extent. Therefore, during the first years of vector control, the reduction of the total number of worms might be caused mainly by the resorption of non-calcified ones.

Variations within the vector controlled area: Though there is a clear difference between the results obtained in the OCP and those from the non-controlled area, the difference is not homogeneous. In the eastern front of the OCP, the results from the 4 villages of the Koulpeolgo river basin show that the ageing of the parasite population was much more advanced than in the central and western area. Most of the worms were either very old or dead and calcified. The longitudinal data on microfilarial loads in the skin also indicate an onset of interruption of transmission in the East of Burkina Faso before vector control activities of the OCP. Two elements may account for this observation: first, the drought of the early seventies that has particularly affected this area, and second, its protection from reinvasion by the vector from adjacent western zones where vector control had started two years earlier. Thus these factors could have substantially reduced or interrupted the transmission already 2 to 4 years before the beginning of OCP vector control operations. In the two villages on the Comoe on the western flank of the initial Programme area the parasite population is clearly younger. These villages are located in the vicinity of the zone initially affected by reinvasion of infective simulids (Walsh et al., 1979) and a possible transitory transmission can not be excluded although the evolution of the community microfilarial load has been quite satisfactory for Folonzo throughout the control period and for Boko since the second follow-up survey.

In northern Ghana, on the Sissili and on the Kulpawn river basin, the presence of a few obviously young worms was an indication of some residual transmission after the start of the control operations. This is not surprising given the results of the entomological evaluation which showed that the vector density, though greatly reduced by vector control, had remained high enough for a localised transmission between 1980 and 1983, and particularly in 1981. The heterogeneity of the results from the zone under vector control reflects the diversity of the epidemiological patterns after the start of the vector control activities as well as the situation prior to these operations.

Longevity of the parasite

The longevity of the parasite can only be reliably determined when the epidemiological variations mentioned are considered. Information on the level of the transmission before 1975, as well as the data reflecting the entomological situation during the control period are therefore of great importance for the analysis. We have attempted to estimate the actual period of interruption of transmission using all the available information for the different OCP areas. In Figs. 3 A and B the examined villages are grouped by geographical clusters with similar estimates for the period without transmission. The reduction of 80% in the number of living worms per nodule after 9–10 years of interruption of transmission in Lamiougou and Bangasse may be the most important information on the longevity of *Onchocerca volvulus*. It indicates an imminent breakdown of the worm population in the near future which is supported by recent findings in one of the neighbouring villages which, though initially mesoendemic, did not show a single infected individual during the last follow-up skin snip examination in 1986. In previously mesoendemic villages near Dedougou (Black Volta, Burkina Faso, under vector control since 1975) we found prevalences of microfilariae carriers of less than 10% and only six nodule carriers out of 300 palpated inhabitants in 1985.

Although we lack sufficient epidemiological precontrol data, our results indicate that the average longevity is considerably shorter than the maximum longevity of infection of 18 years as observed by Roberts et al. (1967). The conclusion of Parow (1983) that vector control should continue for 20 years seems too pessimistic. It is based on observations of nodules excised in Burkina Faso in an area of OCP where the community microfilarial load decreased only after a delay of several years while wherever the vector control was satisfactory, this index started to decline in the early stages of the interruption of the transmission. The particular evolution of the parasitological trend in this area reflects a special situation, and underlines the importance of considering various epidemiological situations in the attempt to estimate the longevity of the parasite. The decrease of microfilarial loads in the skin (Fig. 2) and our observations on adult worms indicate a breakdown of the worm population 11–12 years after the beginning of vector control.

Sex ratio and reproductivity

The clear predominance of female worms in nodules gradually disappeared in the controlled areas as also observed by Büttner et al. (1983). A longer life expectancy of male worms might be suggested. But the male worms leave the nodules regularly to look for female worms in neighbouring nodules (Schulz-Key et al., 1980) and are in turn, often not recovered by nodulectomy. The observed shift in the sex ratio may be only the result of reduced migration of male worms. In very old worm populations (Niarba or Lamiougou and Bangasse) this reduced mobility may also explain the dramatic increase in the proportion of dead male worms in nodules.

The frequency of the reproductive cycles had slowed down and was closely related to the behaviour of the male worms (Kläger et al., 1985). The proportion of females with empty uteri increased (Table 3). More often worms with remnant intra-uterine microfilariae could be found. They had recently finished the release of microfilariae and remained then inactive for a longer period. Although microfilariae could not be observed in dead worms with certainty, female worms seem to be potentially reproductive until they die. Old females, still alive, but with a calcified tail, showed remnant microfilariae. The observed decrease in the productivity is not only due to ageing of the parasites but also to the reduced frequency of the cycles.

The productive potential of Onchocerca volvulus

The decrease in the initial number of live adult worms, as a result of the natural death of *Onchocerca volvulus*, and the reduced reproductivity of the surviving worms, are the two major factors which determine the fall in the total microfilarial production and in the microfilarial density in the human host population during the control period. The "productivity index" which measures the combined effect of both factors at the level of our sampling unit, the nodule, is used to demonstrate this phenomenon (Table 3). The reduction in the productivity index correlated with the observed reduction in the community microfilarial load during the control period. The good agreement with the results obtained independently (skin snips collected longitudinally) supports the validity of our approach to the worm analysis for the description of the population dynamics of *Onchocerca volvulus* during vector control activities.

The longevity of the adult parasite was considered to be the determining factor for the duration of vector control. However, the present study suggests that the ceasing reproductivity of the superannuated worm population plays a similarly important role for the control programme. Its major contribution to the depletion of the parasite reservoir will also help reduce the risk of transmission in case of a local outbreak of *Simulium damnosum* breeding. After an estimated period of 12 years without transmission in the upper Koulpeolgo river basin, this reservoir is nil or insignificant for some villages in 1986, indicating that in such areas, vector control could theoretically be suspended without risking resurgence. In practice, the high probability of recontamination of such areas by infected Simulium from neighbouring places, where the CMFL has not yet decreased below a safety threshold, requires OCP to maintain its vigilance.

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Büttner D. W., Albiez E. J., Parow D.: Parasitological studies on *Onchocerca volvulus* eight years after interruption of the transmission in Upper Volta. Bull. Soc. Path. exot. *76*, 669–675 (1983).

Duke B. O. L.: Onchocerciasis: deep worm bundles close to the hip joint. Trans. roy. Soc. trop. Med. *64*, 791–792 (1970).

Hamilton P. J. S., Marshall T. F. de C., Anderson J., Fuglsang H.: Observer variation in clinical onchocerciasis. Trans. roy. Soc. trop. Med. Hyg. *68*, 187–189 (1974).

Kläger S., Karam M., Schulz-Key H.: The reproductivity of male *Onchocerca volvulus* in areas with and without vector control. Trop. Med. Parasit. *36*, 21 (1985).

Parow D.: Die Veränderung der Makrofilarienpopulation bei Patienten mit Onchozerkose in Obervolta nach achtjähriger Unterbrechung der Übertragung. Thesis, Univ. Hamburg 1983.

Remme J., Ba O., Dadzie K. Y., Karam M.: A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area. Bull. Wld Hlth Org. *64*, 667–681 (1986).

Roberts J. D. M., Neumann E., Göckel C. W., Highton R. B.: Onchocerciasis in Kenya 9, 11 and 18 years after elimination of the vector. Bull. Wld Hlth Org. *37*, 195–212 (1967).

Schulz-Key H., Albiez E. J., Büttner W. D.: Isolation of living adult *Onchocerca volvulus* from nodules. Tropenmed. Parasit. *28*, 428–430 (1977).

Schulz-Key H., Albiez E. J.: Worm burden of *Onchocerca volvulus* in a hyperendemic village of the rain forest in West Africa. Tropenmed. Parasit. *28*, 431–438 (1977).

Schulz-Key H., Jean B., Albiez E. J.: Investigations on female *Onchocerca volvulus* for the evaluation of drug trials. Tropenmed. Parasit. *31*, 34–40 (1980).

Schulz-Key H., Karam M., Prost A.: Suramin in the treatment of onchocerciasis: the efficacy of low doses on the parasite in an area with vector control. Trop. Med. Parasit. *3*, 244–248 (1985).

Schulz-Key H., Karam M.: Parasitology Today. Periodic reproduction of *Onchocerca volvulus*. Parasitology Today *2*, 10, 284–286 (1986).

Walsh J. F., Davies J. B., Le Berre R.: Entomological aspects of the first five years of the Onchocerciasis Control Programme in the Volta river basin. Tropenmed. Parasit. *30*, 328–344 (1979).

Chapter 4.4

The effects of 11 years of Simulium control in the OCP on ABRs, ATPs, prevalence and intensity of O.volvulus infection and on the incidence and prevalence of eye lesions.

Working paper for the third WHO Expert Committee on Onchocerciasis
World Health Organization, Geneva, WHO/ONCHO/EC/WP/86.4 (1986)

INTRODUCTION

The objective of the OCP is to put an end to onchocerciasis as a disease of public health and socio-economic importance and to ensure that there is no recrudescence of the disease thereafter. Control of the disease as a public health and socio-economic problem may be achieved by reducing the transmission to such a low level that the residual rate of infection does not result in an epidemiological situation which gives rise to the development of severe eye lesions and blindness. A working group, which considered this question in 1977, concluded that an area under vector control could be considered safe for resettlement if the Annual Biting Rate (ABR) would be less than 1000 and the Annual Transmission Potential (ATP) less than 100 for two consecutive years. However, the present strategy of OCP is to interrupt transmission to insignificant levels by vector control and to maintain this control for a sufficiently long period to allow the initial reservoir of infection to fall to such low levels that vector control can be safely interrupted or greatly scaled down. This strategy requires a more stringent vector control with the virtual interruption of transmission over a period exceeding the productive lifespan of the adult female worm. It has not yet been possible to determine exact entomological criteria for this strategy because the significance of very low transmission potentials for the risk of infection is not clearly understood, but this question receives presently a high priority in the integrated analysis of the epidemiological and entomological evaluation data. It is important to keep both the objective of controlling the disease and the objective of eliminating the parasite reservoir in mind when discussing the results of the evaluation in the OCP.

RESULTS OF THE ENTOMOLOGICAL EVALUATION

For most catching points in the OCP, the entomological evaluation started only shortly before the start of the control operations in the different phases (see also Fig.1) and the lack of sufficient pre-control data complicates the general assessment of the changes in the entomological pattern which were brought about by vector control. However some historical data, collected by OCCGE and ORSTOM provide some important clues as to the impact of the large scale control implemented by OCP. Annual biting rates in the White Volta basin, along the Bougouriba, the Upper Comoe, the Leraba and the Upper Bandama reached easily levels of 50,000 to 250,000 in the sixties and early seventies. Local vector control along the latter three rivers from 1969 to 1975 managed only to bring these figures down to about 25,000 bites per man per year. Results on transmission potentials are more limited but suggest that the ATPs were usually over 2,500 and could reach levels as high as 10,000 along the White Volta and 18,000 along the Leraba. Most of these data were collected during the sixties, when the rains were heavy, but the little information available for the early seventies does not clearly suggest that the intensity of transmission was lower along those rivers during the droughts in those years.

Against the background of these figures the achievements of OCP are impressive: in a large part of the OCP ABRs are now measured in tens or hundreds and ATPs have often become nearly unmeasurable quantities. Based on the results of the entomological evaluation the OCP can be devided into four major zones: 1) The Central OCP Area, 2) The eastern reinvasion zone, 3) The western reinvasion zone and 4) Phase IVb which comprises the pre-forest zone in Ivory Coast where vector control only started in 1979 (see Fig.1).

The Central OCP Area.

In this area where the vector species were nearly exclusively *S. damnosum* s.s. and *S. sirbanum* and which covers about 85% of the original OCP area (excluding Phase IV), vector control by OCP has been very effective indeed. Already during the first year of control the ABRs for most points were brought down to values below 3,000 and the ATPs were kept below 300. A progressive reduction in these values was achieved during the next two years of control and after this period of attack the entomological situation has remained rather stable for most of the river basins involved. However, using the entomological results for the last 6 years of vector control, one can distinguish somewhat different entomological patterns and subdivide the Central OCP Area as follows:

1. In 50% of the Central OCP Area, *S. damnosum* has been virtually eliminated with ABRs usually equal to zero but rarely exceeding 100, and ATPs equal to zero throughout the area. This zone comprises the dry northern zones of the Programme area where the rivers flow only during the rainy season and where the pre-control epidemiological results often showed only hypo- or meso-endemicity levels. However this zone includes also notorious onchocerciasis areas like the mid White and Red Volta river basins and the lower Koulpeolgo basin in Burkina Faso, which had extremely high intensities of infection and blindness rates before the start of control.

2. More south of this zone, *S. damnosum* has not been eliminated but is usually only present at low densities with ABRs normally below 500 and rarely exceeding 1000. More important is that infective flies with L3 stage larvae in the head are never or only occasionally detected at most of the catching points; occasionally meaning that only one or two infective flies are found among the flies which are dissected over periods of two to three years. With such low numbers involved, it would be artificial to calculate exact ATPs and we classify such points therefore as having an ATP which is nearly unmeasurable with the present sampling methods and probably close to zero. With this in mind, and using the entomological results for the last 6 years, it can be concluded that vector control in the OCP has succeeded in bringing down the ATP to zero or close to zero in 90% of the Central OCP Area.

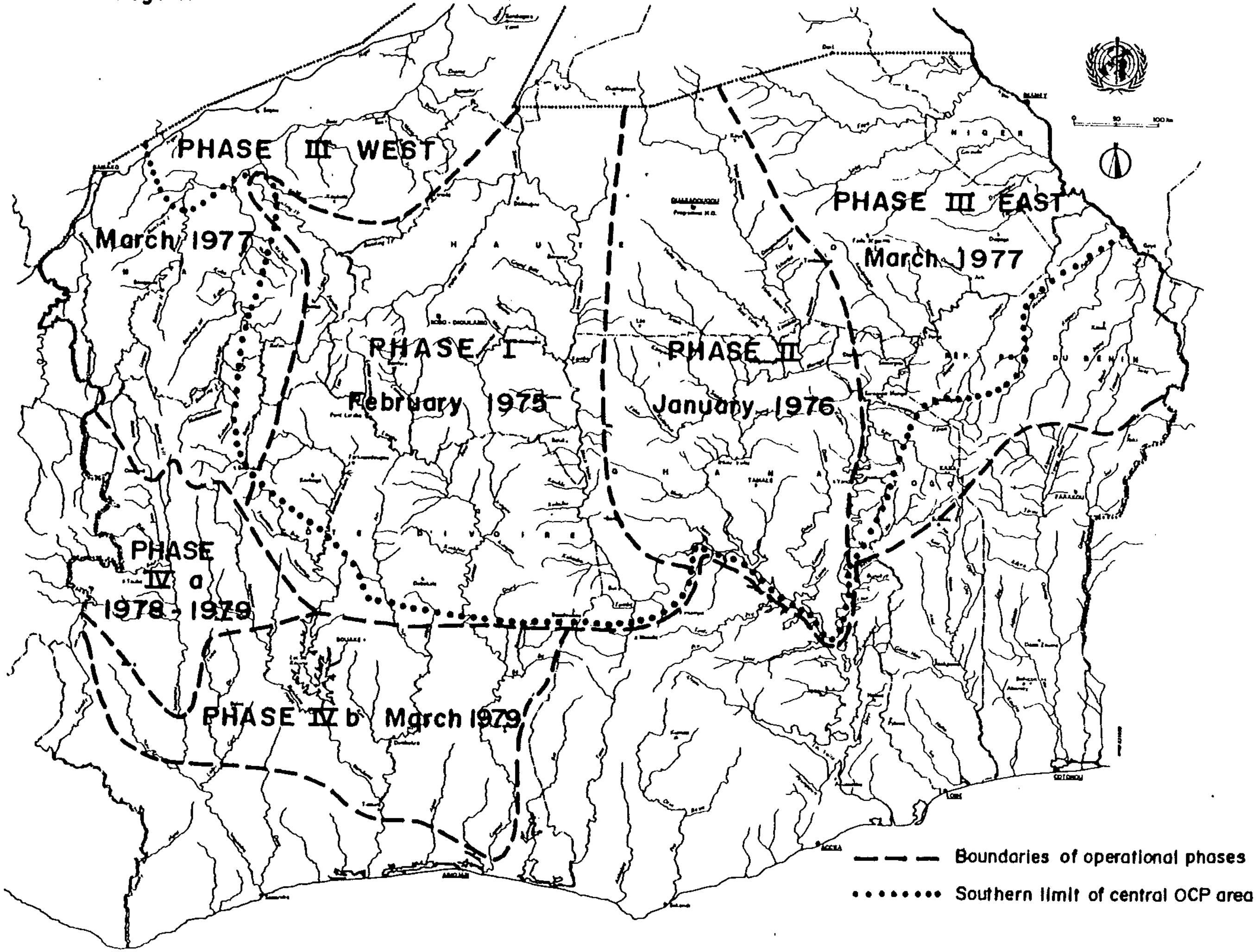
3. Less uniform are the results for the White Volta basin in Ghana, which includes the Red Volta, Sissili and Kulpawn rivers. Though the results here were generally as good as in the rest of the Central OCP Area for most of the control period, they were distinctly less satisfactory in 1981 as a result of treatment failures, and they were in several locations also not satisfactory in 1985 during a year of very heavy rains. In 1981 the ABRs reached levels of 2,000 to 7,000 in several catching points and the corresponding ATPs were between 100 and 700. Elevated ATPs were in 1985 only found along the Sissili, the Kulpawn and a stretch of the White Volta immediately below the Sissili, but reached here levels between 100 to 300. Also in the intermediate years were measurable ATPs recorded at four catching points in this latter area, though they rarely exceeded a value of 50-100.

4. A special case is the stretch of the Black Volta on the border area between Ivory Coast and Ghana between Tagadi and Bui, which contains the largest potential breeding site in West Africa. Control in this area has always been difficult, especially during the years 1978,1982 and 1985, when ABRs in the range of 15,000 to 25,000 were recorded. Though the ATPs were not high during the last 6 years around Tagadi, possibly as a result of the low population density in this area, they were around 500 in 1982 and 1985 in the Bui area and mainly due to infective flies from the savanna species of *S. damnosum* s.l.

South-eastern reinvasion zone.

Contrary to the Central OCP Area, the results of vector control have been very limited in the Mô, Kara and Kéran basin in Togo and the Alibori and Sota basin in Benin. These areas are subject to heavy reinvasion by older, and therefore relatively heavily infected flies from breeding sites in untreated areas south of the Programme boundary. The unsatisfactory results for the Mô and the Upper Kara are not surprising given the short distance to a rather artificial Programme boundary, but the results for the Upper Kéran are more remarkable. For several catching points in this area the situation has hardly improved over the years with ABRs reaching levels of 6,000 to 10,000 and ATPs reaching values up to 400 to 1,100. However the entomological situation improves dramatically at the slopes of the Atakora mountain ridge immediately north of this river where one abruptly comes into an area with perfect control

Fig. 1. LOCATION AND STARTING DATES OF OPERATIONAL PHASES



and ATPs equal to zero. The situation along the Alibori and the Sota in Benin is quite different: the ABRs and ATPs are relatively low along the Programme boundary which runs through an area with few potential breeding sites, and the heavy impact of reinvasion is felt more to the north, over longer distances, and in a more scattered fashion than in Togo. Nevertheless at some of the more sensitive catching points ABRs can reach levels of 15,000 to 30,000 and ATPs levels of 500 to 1,100. The reinvasion in the south-east has nearly always affected the same area and the problem can only be solved by extension of control far to the south, to the lower Ouémé and Mono river basins.

Western reinvasion zone.

Because of the main wind direction in West-Africa, reinvasion has always been a much bigger problem on the western flank of the Programme area. Phase I was the first area to be affected but the problem was significantly reduced when Programme operations started in phase III west and especially in phase IVa. However these latter areas were themselves subject to reinvasion from breeding sites in Guinea and reinvasion was especially heavy along the Baoulé and Bagoé in Mali and the Upper Sassandra and Marahoué in Ivory Coast (with ATPs reaching values of 500 to 1,300). Experimental larviciding on the Upper Sankarani river in Guinea in 1984 and 1985 had only a marginal impact on the reinvasion in Mali, and additional studies strongly suggest that the main source of the reinvasion is situated further west. On the other hand, experimental treatment in 1985 of the Upper Sassandra tributaries in Guinea had a spectacular effect on the reinvasion in phase IVa and phase I, where for the first time the ATPs dropped from levels between 400-1000 to ATPs between 0 and 50 while the effect of this extension was felt as far as the Leraba and the Bougouriba.

Phase IVb, southern extension in the Ivory Coast.

Vector control started only in 1979 in this area, which covers mainly the intermediate zone between the natural habitat of the savanna and the forest species of *S. damnosum*. Within a year of control, resistance to temephos developed in *S. soubrense* and it has been this species which has subsequently dominated the entomological situation in this area. Alternative larvicides have been used though not continuously and with varying degrees of success. However both ABRs and ATPs for *S. soubrense* have remained very high in most of this area but the epidemiological significance of these values remains unclear.

RESULTS OF THE EPIDEMIOLOGICAL EVALUATION

The final answer of the impact of vector control on the incidence of infection has to come from the epidemiological evaluation, which has also as objectives to study the regression of the reservoir of infection in the human host and to assess the decrease in the incidence of severe ocular pathology. For this purpose the population of about 150 indicator villages, which represent all the major river basins in the original Programme area and in phase IVa, is examined at intervals of about 3-4 years. Skin snip examinations and visual acuity tests were done at all surveys and these were supplemented by a detailed ophthalmological examination in a sample of about 30 villages. Follow-up surveys have not yet been done in the southern extension in the Ivory Coast (phase IVb) but these are planned for early 1986.

Epidemiological indices used in the OCP.

Epidemiological indices like the incidence and prevalence of infection are of limited value for the epidemiological evaluation of onchocerciasis during a period of vector control for a variety of reasons. Positive skin snip provide only definite evidence of incidence of infection during the control period for children born since the start of control, and this part of the population is therefore treated separately in the analysis. However, it should be noted that onchocerciasis infections in young children are rare, even in non-controlled areas, and during the first years of control, the results for this group are therefore not very sensitive for ongoing transmission. For the population which was exposed to infection during the pre-control period, it is practically impossible to separate the assessment of the incidence and regression of infection. This is particularly true for the group most at risk, i.e. the adults in hyper-endemic villages, who were already all infected at the start of control. It was therefore necessary to develop sensitive statistics for the regression of infection during the control period which would adequately describe the changing epidemiological situation and which could be used for a comparative analysis of the epidemiological trends in different areas.

A force-of-infection model for onchocerciasis was developed in order to predict the epidemiological trends during the control period and to determine the most appropriate statistics for the evaluation. Three important factors, taken into account in the model, were: age-dependent exposure to infection during the pre-control period, superinfection and the productive lifespan of *O. volvulus*. The predicted trends agreed quite well with those observed in a sample of villages in the Central OCP Area, and it was concluded that epidemiological trends during the control period are not uniform but depend on the age at the start of control and the initial endemicity level of the population. Though children, born during the pre-control period, are usually only lightly infected at the start of control, their prevalence and microfilarial load will not yet show a decrease during the first 5-8 years of control because of the relatively high proportion of young and pre-patent infections in this group. For adults from the age of 20 years onwards, there exists during the pre-control period an equilibrium between the rate at which new infections become patent and old infections die off. After interruption of transmission the microfilarial load in adults starts therefore to decrease immediately after an initial delay equal to the average pre-patent period. The prevalence of infection in adults is a very insensitive index during most of the control period, especially in hyper endemic villages where the heavily infected adults will only become skin snip negative when the very last adult female worms stop producing microfilariae. The three indices for the epidemiological evaluation of the incidence and regression of infection, which were determined as a result of this study and which are now routinely used in the OCP, are:

1. Infections in children born after the start of control. The number of observed infected children is compared with the number which would be expected without vector control, with the expected number calculated on the basis of the pre-control age-specific prevalences for each village.

2. The trend in the Community Microfilarial Load (CMFL), i.e. the geometric mean microfilarial load per skin snip for a cohort of adults.

3. The trend in the Community Microfilarial Load in the Anterior Chamber of the eye (CMFL/AC); also a geometric mean for a cohort of adults.

Results on the incidence and regression of infection

Central OCP Area

The epidemiological results available to date seem to confirm the conclusion from the entomological evaluation that transmission of onchocerciasis has been virtually interrupted in the Central OCP Area. Out of a total of 6700 examined children, which were born after the start of control, only one was found to be infected compared to an expected number of infected children of more than 400. For most of the Central area the CMFL shows the predicted, nearly linear, decrease and, after 8 years of control the CMFL had fallen by more than 70%. For villages which have been examined after 10 years of control, this linear decrease had continued, bringing the CMFL down by more than 90%. In those villages the microfilarial loads are now so low that also the prevalence in adults has started to fall abruptly as was predicted. Also the prevalence and microfilarial loads for children, born before the start of control, show now a significant decrease after having been stagnant during the first 5-8 years of control.

The trends in the CMFL are however not uniform throughout the Central OCP Area, and different patterns can be distinguished. For the majority of the villages the relative trend in the CMFL is nearly identical and shows a linear decrease towards a zero point after about 11 years of control. It is this finding which is the basis for the present estimate of 11 years for the average duration of onchocerciasis infection. However, in the north-east of the OCP, along the affluents of the river Niger and the affluents of the Oti/Pendjari in Niger and Burkina Faso, the CMFL has even decreased much faster, probably as a result of a significant reduction of transmission during the last years before control started officially. The droughts in the early seventies might have been partly responsible for this, but it is also believed that vector control operations in phase I and especially in phase II had significantly reduced the annual reinvasion of this area.

Somewhat different are the trends for the village Danguadougou along the Leraba and several villages along the Bougouriba, rivers which until this year were subject to reinvasion from the west. Along the Bougouriba the CMFL started its linear decrease only after an initial delay of 3-4 years suggesting that transmission has been important along this river till extension to phase IVa resulted in a significant reduction of the reinvasion. The decrease in CMFL in Danguadougou along the Leraba is even more delayed, but this is not surprising given its location next to the most infamous reinvasion point in the OCP, where ATPs of more than 500 were recorded till 1979 and while they remained around 100 till 1985. However, this problem seems to be very localized, because the trends in the CMFL for three other villages in this area, including one village at a distance of only 20 km, were very satisfactory.

Of special interest are the epidemiological results for the White Volta basin and the Bui area in Ghana, where vector control had encountered problems in the past. Unfortunately, quality control analysis has shown that the baseline skin snip data collected in 1975 and 1976 in Ghana are not reliable. This does not affect the results for children born since the start of control and none of these children have been found infected to date. However the analysis of the trend in the CMFL is severely affected because nearly all indicator villages in Ghana have valid skin snip data for only 2 surveys, done within an interval of three years, and this is insufficient for a proper trend analysis. Only 3 villages in Ghana have had three valid surveys, and the CMFL in two of these villages, which are situated along the Kulpawn river, shows a significantly slower decrease between the 3rd and 8th year of control. The importance of sufficient follow-up data in the Volta basin in Ghana has been clearly realised and all indicator villages in Ghana are presently being revisited by the epidemiological teams.

Ophthalmological surveys have been done at regular intervals in 21 villages in the Central OCP Area, representing all the major river basins and especially the most endemic zones. The latest results available are for the 7-8 year follow-up; the 10 year follow-up is presently underway and the first results of the analysis are expected in February 1986. Just as for the microfilarial load in the skin, the CMFL/AC showed a nearly linear decrease during the first 7-8 years of control in 19 of these villages, including three villages in the White Volta basin in Ghana. However the relative decrease in the CMFL/AC was distinctly faster than for the CMFL and after 7-8 years the CMFL/AC had already decreased by more than 80-90%. In the remaining two villages the decrease in the CMFL/AC was delayed, but this finding is in perfect agreement with the results for the CMFL, because one of these villages is located along the Bougouriba while the other was again the village Danguadougou, along the Leraba.

Western and south-eastern reinvasion zone

The results of the epidemiological evaluation show clearly that reinvasion is not just an entomological problem of operational concern, but that it is directly responsible for continuing transmission of the disease. Out of 1612 children, born since the start of control, no less than

37 children were found to be infected, 26 in the south-eastern zone and 11 in the western reinvasion zone. However the number of infected children is still considerably less than the expected number of 225, and this suggests that vector control has at least managed to significantly reduce the transmission in these areas by eliminating local breeding. This conclusion seems to be confirmed by the results for the CMFL which shows a decrease in all the villages in the western reinvasion zone, though the decrease is far less than that observed in the Central OCP Area. Furthermore the CMFL in several villages shows now a tendency to stabilize, suggesting that a new equilibrium at a lower transmission level has been reached. As could be expected from the entomological results, the trends in the CMFL in the western reinvasion zone are far from uniform and vary from trends which are slightly less satisfactory than predicted to the most unsatisfactory trend in one village along the Kankela-Ba where the CMFL has not decreased at all. Such very unsatisfactory results are more common in the south-eastern reinvasion zone, especially in the Mô, Upper Kara and Upper Kéran basin where the epidemiological evaluation has been particularly intense but where only few villages show a significant reduction in the CMFL. Somewhat better are the results along the Alibori and Sota in Benin, where the CMFL shows a distinct, though unsatisfactory, decrease; but also here were two villages found with no decrease at all in the CMFL after 8 years of control. One of these villages was also followed up ophthalmologically, and the results for the CMFL were again confirmed by the trend in the CMFL/AC, which had also not decreased during the same period. However, for 3 villages in the reinvasion zone along the Mô, Kara and Kéran, were the results for the CMFL/AC and for the CMFL were slightly different: though the CMFL had not decreased at all, the CMFL/AC showed a light decrease in all these villages. These differences, small as they are, are still interesting because, contrary to the other reinvasion zones which are reinvaded by the savanna species of *S. damnosum*, the pre-dominant reinvading species in this area is *S.squamosum* which might theoretically be responsible for the importation of a different parasite strain.

The evolution of ocular onchocerciasis

Central OCP Area

As mentioned above, the microfilarial load in the anterior chamber of the eye, which is known to be an important risk factor for the development of ocular lesions, in particular of the anterior segment of the eye, had decreased dramatically during the first 7-8 years of control. More spectacular has even been the decrease of the microfilarial load in the cornea and the decrease in punctate keratitis, and it have always been the ophthalmologists who were the first to realize the major epidemiological changes following vector control in the OCP.

The relatively rapid reduction of ocular infestations are the reason that the incidence of ocular lesions has been so low and that the evolution of ocular onchocerciasis during vector control has been so dramatically different from the evolution observed previously in uncontrolled areas. This is clearly demonstrated by the results of the ophthalmological examination of a cohort population from 12 villages which were followed up over a period of 7-8 years of control. That part of the population, which had no ocular infestations or lesions at the start of control, remained free from ocular onchocerciasis. People with light or heavy ocular infestations lost their infection gradually. Those, who were heavily infected had a distinctly reduced risk of developing eye lesions compared to non-controlled areas and none of these high risk cases went blind. In fact, very few new lesions were detected in the population which had no ocular lesions at the start of control, and these lesions were mainly early stage lesions of the posterior segment. For the vast majority of the cases who had already eye lesions, the situation remained unchanged. However, 40% of the people, who had initial stage lesions at the start of control, had even lost their lesion when they were re-examined after 7-8 years. Though this finding may be partly due to false positive or false negative classification of initial stage lesions which are difficult to diagnose, this group included a significant proportion of disappearing, early stage sclerosing keratitis and iridocyclitis without synechiae, for which it is conceivable that they might disappear in the absence of microfilariae. The incidence of blindness due to onchocerciasis was only 1.5% over the 7-8 year period, and involved exclusively people who had already, at the start of control, both onchocercal lesions and heavy microfilarial loads.

The 10-year follow-up, which is presently underway, will probably allow a quite definite conclusion on the impact of vector control on ocular onchocerciasis, including a more detailed assessment of the residual incidence of posterior segment lesions. The impressions of the ophthalmologists are already very encouraging: microfilariae in the eye have apparently nearly disappeared with no more than one or two positive cases per village in the six village examined to date.

Reinvasion areas

The evolution of ocular onchocerciasis in a cohort population from 5 villages in the reinvasion areas, and with 7-8 years of vector control, is intermediate between the evolution in non-controlled areas and in the Central OCP Area. Though ocular microfilarial loads have generally decreased, the decrease is much less than in the Central OCP Area, for both the loads in the anterior chamber and in the cornea. Consequently, the incidence and progression of all types of ocular lesions was lower than would be expected without vector control, but significantly higher than in the Central OCP. However, the incidence of blindness was similar to that recorded in the central area of the Programme, but the cohort population in the reinvasion zone was too small to give a reliable estimate of the incidence of blindness over a treatment period of 7-8 years.

CONCLUSIONS

Both the entomological and epidemiological evaluation have confirmed that vector control has been very effective in the Central OCP Area: infective simuliids have been rarely detected, all but one of the examined children born after the start of control have remained free of infection, the intensity of infection in children born before the start of control has not increased to dangerous levels but has now started to decrease, and the intensity of infection in adults has fallen dramatically. The intensity of infection in the community is now so low that microfilariae are hardly found anymore in the eye and even the prevalence of microfilariae in the skin has started its final descent. The incidence and progression of eye lesions seems to have been arrested and no case of blindness due to onchocerciasis has been recorded in those who were free of ocular lesions at the start of control. Based on all these findings it can be safely concluded that onchocerciasis is no longer a problem of public health and socio-economic importance and that the disease has been brought under control in the Central OCP Area.

On the other hand, in the reinvasion zones in the west and south-east, transmission has definitely not been interrupted, though elimination of local breeding in these areas has usually brought transmission down to much lower levels. But the remaining level of transmission is in many places still intolerably high and associated with high intensities of infection and a significant incidence of ocular lesions. Control of the disease can therefore not be claimed in these areas and will have to await the extension of vector control operations to the west and to the south.

With the achievement of the control of the disease in the Central OCP Area, the emphasis of the evaluation and research in this area has now shifted towards the assessment of the decline in the parasite reservoir and the related decrease in the risk of transmission. According to projections with a host-parasite simulation model, which was developed for the OCP, the reservoir of infection would have virtually died out after 15 years of interruption of transmission, and the observed trends to date agree very well with those predicted. However, the use of the model has also suggested that a very low incidence of infection in a previously hyper-endemic area, might easily remain undetected with the presently available epidemiological methods during many years of vector control, and the question of the significance of low transmission potentials has therefore received new attention. Results from the reinvasion areas suggest that ATPs, which vary between 500 to 1000, are associated with high rates of infection which maintain onchocerciasis as a public health problem. The epidemiological data for the few villages, where the nearest catching point has an average ATP of 300, show that transmission has not been interrupted, though the clinical significance of the remaining transmission has not yet been established. However, catching points with an average ATP below 300, are nearly all points where infective *S. damnosum* are only occasionally detected and where no reasonable quantification of the ATP can be given. Definite answers to this question of low transmission during the control period will be obtained during the next few years, when the fall in the prevalence becomes a significant feature, and when the children, born since the start of control, move into an age group which, under non-controlled conditions, would be fully exposed to the bites of *S. damnosum* s.l.

Our present impression is that virtual elimination of the reservoir will be achieved in most of the Central OCP Area, and definitely in the more northern part, but we do not exclude the possibility that some localised reservoirs will be detected, possibly along the Sissili, Kulpawn and in the Bui area. If such foci are sufficiently small, they may be eliminated using a special intervention strategy, probably based on strictly supervised drug treatment. But for most of the Central OCP Area we will be concerned with the question of when, and to what extent, we can interrupt vector control while ensuring that the cycle of transmission will not start all over again. Research into this direction, such as comparative xenodiagnosis, modelling and field experiments, has already began.

Chapter 4.5

The predicted and observed decline in onchocerciasis infection during 14 years of successful vector control with reference to the reproductive lifespan of Onchocerca volvulus.

INTRODUCTION

Since the start of operations in 1975, the strategy of the Onchocerciasis Control Programme in West Africa (OCP) has been to reduce transmission of the parasite *Onchocerca volvulus* to insignificant levels by means of vector control, and to maintain this control for a sufficiently long period to allow the initial reservoir of the parasite to fall so low that vector control can be safely interrupted (WHO 1989a).

The required duration of successful vector control depends primarily on the duration of onchocerciasis infection, which is a function of the reproductive lifespan of the adult *O.volvulus* and the longevity of microfilariae. In 1975, little was known about the duration of onchocerciasis infection. The only relevant information came from East Africa where cross-sectional skin snip surveys in three foci had shown that active onchocerciasis infection still persisted 9-11 years after the elimination of the vector, while no active infection could be demonstrated in another focus with 18 years of interruption of transmission. (Roberts et al 1967). It was mainly because of these findings that vector control in the OCP was originally planned to last for a period of 20 years (Walsh et al 1981).

Since 1975, epidemiological follow-up surveys have been undertaken in selected indicator villages which represent all the major river basins in the OCP. The objective of these surveys was to evaluate the impact of vector control on transmission and on disease, and to document the decline in infection levels in the human population. For long term planning and funding of the OCP it was important to arrive at accurate estimates of the reproductive lifespan of *O.volvulus* and to predict how many years of vector control were still needed before the parasite reservoir would fall to an insignificant level. It was therefore necessary to introduce epidemiological modelling in the analysis of the evaluation data. A first step was the development of a force-of-infection model for onchocerciasis (Remme et al 1986) which allowed a better understanding of age-specific epidemiological trends and resulted in new statistical methods for the comparative analysis of the epidemiological evaluation data. The use of this model led also to a preliminary estimate of 11 years for the average duration of onchocerciasis infection.

The force-of-infection model was based on certain simplifications, notably the assumption of a constant duration of infection, which made it inappropriate for the prediction of the final decline in the parasite reservoir. A more sophisticated simulation model was therefore developed which is based on the simulation of individual life histories of human hosts and adult female worms. The first predictions with this host-parasite model were made in 1985 and these indicated that onchocerciasis infection would be virtually eliminated after 15 years of interruption of transmission[1]. Since then, the same model has been used in the analysis and evaluation of the epidemiological trends and the results have been reported in various OCP reports. Examples of the predicted and observed epidemiological trends during 10-12 years of vector control have also appeared in the scientific literature (WHO 1987b, De Sole et al 1988, Remme and Zongo 1989) but the host-parasite model itself has not yet been published.

Between December 1988 and January 1989 the OCP has undertaken another round of epidemiological evaluations in indicator villages from the original Programme area which had been under vector control for 12-14 years. Because of the predictions of the host-parasite model, it was expected that the results of these surveys would provide important information on the impact of vector control on the parasite reservoir and on the reproductive lifespan of *O.volvulus*. The observed trends in the intensity and prevalence of infection during 12-14 years of successful vector control are reported in this paper and compared with the predictions which have been made in 1985.

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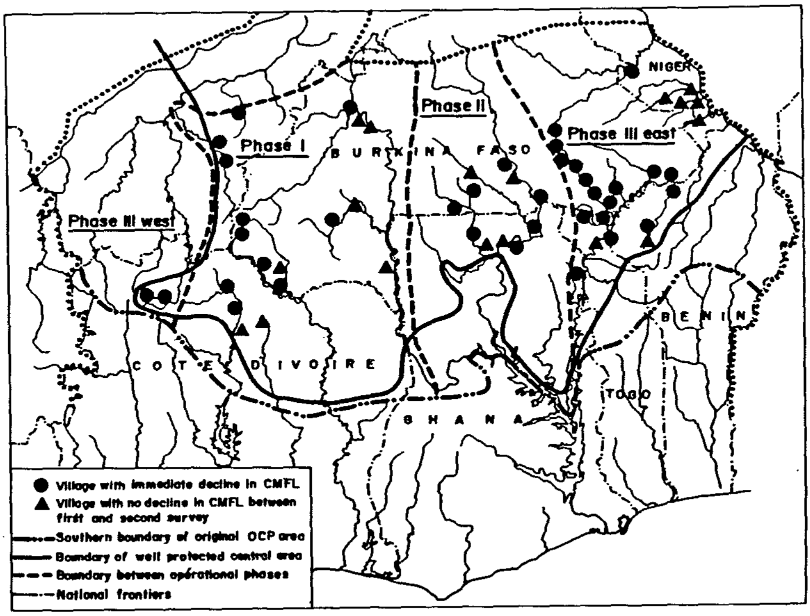
[1] *Onchocerciasis Control Programme in the Volta River Basin area: Progress report of the World Health Organization for 1985*. Unpublished WHO document. OCP/JPC/85.1 (1985)

Fig.1 Location of study villages in the well-protected central OCP area



MATERIALS AND METHODS

Skin snip surveys

In all epidemiological surveys in the OCP two skin snips are taken from the iliac crest of each person. These skin snips are incubated in distilled water for 30 minutes and subsequently examined by microscope for the presence of *O.volvulus* microfilariae (mf) and the number of mf per snip (mf/s) is counted (Prost and Prod'hon 1978). The results are recorded on standard OCP forms.

Study population

Selection of villages

The epidemiological follow-up surveys which were done between December 1988 and February 1989 in the original OCP area involved a total of 90 villages. In the present analysis only villages from well protected areas were included. Excluded were villages from the eastern and western border areas of the Programme which have been subject to reinvasion by infective simuliids from outside the OCP (WHO 1987b). Also excluded were villages from foci where there had been a relapse in transmission during the control period and from areas where vector control had been incomplete. Furthermore, only villages which had had at least 4 follow-up surveys during the control period were included. This left for the analysis a total of 55 villages which represented all the major river basins from the well-protected central OCP area (see Fig.1). Eighteen of these villages are located in Phase I where vector control started in 1975, and which had been under vector control for 14 years. Eleven villages are from Phase II where control started in 1976, and 26 villages from Phase III which came officially under control in 1977. In accordance with past practice, the duration of control in the Phase III villages of the Koulpeolgo river valley in Burkina Faso is taken as 13 years because larviciding along the White Volta in 1976 had already resulted in the complete protection of the neighbouring Koulpeolgo basin (Karam et al 1987).

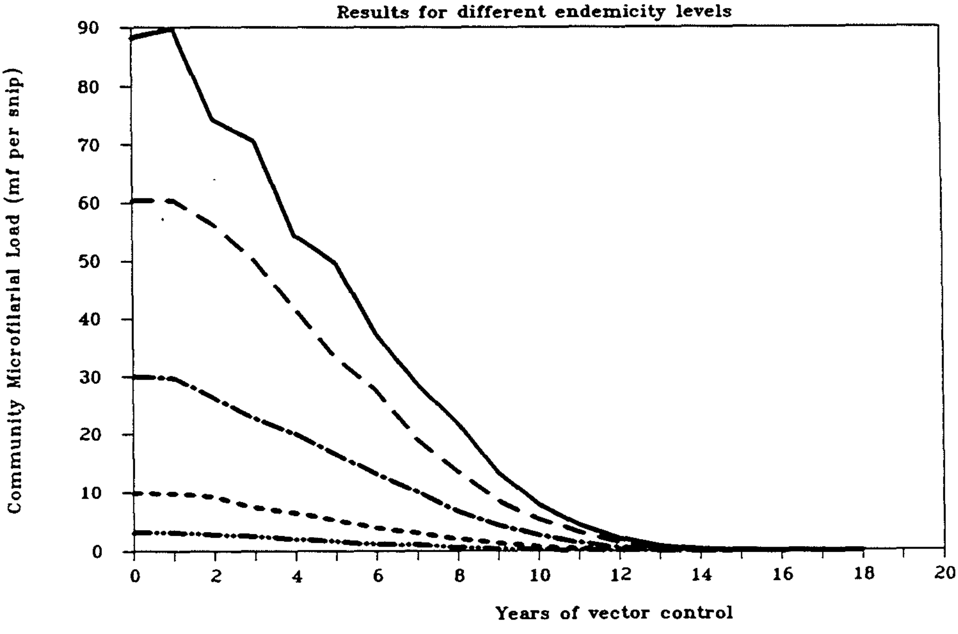
Cohort populations

The aim of the present paper is to describe the decline in onchocerciasis infection after interruption of transmission and with reference to the reproductive lifespan of *O.volvulus*. It has been argued previously (Remme et al 1986) that the most appropriate approach for such a study is to analyse the trend in the prevalence and intensity of onchocerciasis infection in cohorts of adults with an age of 20 years or more at the pre-control survey. This approach has also been used here. Furthermore, only adults who had undergone a skin snip examination at each survey have been included in the analysis. Since most indicator villages were small and some villages had as many as 7 surveys, this selection criterion resulted occasionally in very small cohorts. The total number of adults included in the analysis was 1,536. The average cohort size was 28 with a minimum of 9 and a maximum of 89.

Host-Parasite model

The Host-Parasite model was developed specifically for the analysis of the impact of vector control on the parasite reservoir in the human population. It uses the computer technique of microsimulation (Habbema et al 1984) which allows great flexibility in modelling the dynamics of onchocerciasis infection. After specifying model parameters concerning endemicity level, exposure heterogeneity, longevity and mf production of the adult female parasite, model output is obtained on the trends in mf loads in the human population. These loads are characterized by the distribution and summary statistics of microfilarial counts in skin snips. Furthermore, the output describes the distribution of adult female parasites, discerning alive and dead, and calcified and non-calcified worms. A formal description of the model is presented in Appendix I.

Fig.2: Predicted trend in CMFL during the control period

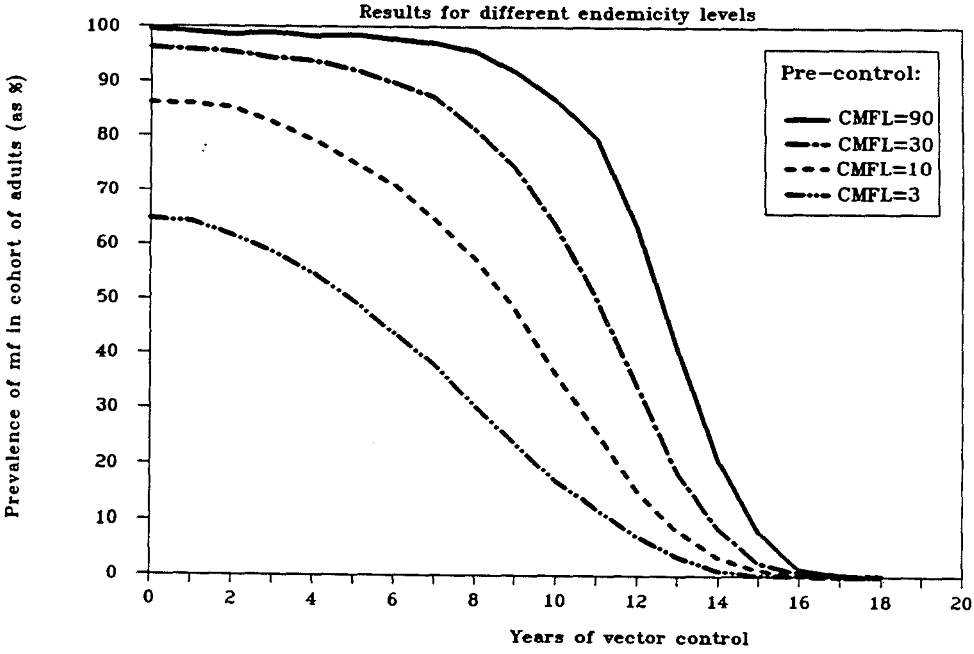


The quantification of the model has involved the incorporation of literature data and the fitting of the model to observed epidemiological results for the first 8 - 9 years of control between 1975 and 1984. This has resulted in the following model quantification which has been used since 1985 for the prediction of the epidemiological trends during the vector control period. The mean longevity of infection was 11 years for non-calcifying worms and 8 years for worms which calcified. In accordance with observations on the adult worms from nodulectomy surveys (Karam et al 1987), it was assumed that 20% of the adult worms would eventually calcify. The estimated variability of the longevity of infection was such that 95% of longevities were less than 15 years. After a pre-patent period of 1 year, the average contribution of a female worm to the skin snip count remains constant at 5.2 mf till the worm age of 8 years. From then onward, the mf contribution decreases annually with 0.4 mf per adult female worm in order to simulate the observed reduction in productivity in aged female worms (Karam et al 1987). The standard deviation for the human exposure index was 0.86 and the dispersal of mf in skin snip counts was characterized by a coefficient of variation of 0.84.

Data analysis

The skin snip data were processed and analysed on personal computers using routine computer programmes developed in the OCP. The pre-control endemicity level of a village is characterised by the Community Microfilarial Load (CMFL) which is the geometric mean number of microfilariae per snip in adults with an age of 20 years or above (Remme et al 1986). The CMFL was also used to describe the intensity of infection in cohort populations during the control period. The observed proportion of skin snip positives in a cohort during the last survey was compared with the predicted proportion for villages with the same pre-control endemicity level and duration of control. The goodness-of-fit between observed and predicted proportions was tested using a chi-square test with Yates' correction for continuity. In villages with a major increase in CMFL between first and second survey, the CMFL for the second survey was taken as the basis for determining the endemicity level and the prediction of the epidemiological trends during the remaining control period.

Fig.3: Predicted trend in prevalence of mf during the control period



RESULTS

Predicted trends in onchocerciasis infection in cohorts of adults

Fig.2 shows the predicted trend in the CMFL for different endemicity levels. These predictions are the result of simulations in which the precontrol force-of-infection was equal to 0.18, 0.51, 1.45, 2.75 and 3.95 infections per person per year respectively. After a delay equal to the pre-patent period, the CMFL falls in a nearly linear fashion during the first 8 years of control and tails off to values close zero after 12-14 years of control. The absolute decline in the CMFL depends on the initial endemicity level.

Fig.3 gives the predicted trend in the prevalence of infection, which also clearly depends on the initial level of endemicity. The higher the endemicity level, the longer it will take before the prevalence begins to fall but the faster will be its final descent. The host-parasite model predicts that onchocerciasis infection would have virtually died out after 15 years of control when only very few skin snip positive people can be found, mainly in the villages which had the highest levels of endemicity during the pre-control period.

Observed trends in Community Microfilarial Loads

Fig.4 shows the observed trend in CMFL in all 55 indicator villages and this figure allows a crude comparison with the predictions in Fig.2. The overall trend is quite similar, and after 12-14 years of control the observed CMFL is nearly equal to zero in all villages. It is difficult to use Fig.4 for an assessment of the relative trends in the CMFL. The villages were therefore subdivided according to their initial level of endemicity into three groups with CMFL values of 30-90 mf/s, 10-30 mf/s and 3.3-10 mf/s respectively. In addition, there was one hypo-endemic village with a pre-treatment CMFL of 0.2 mf/s and a prevalence in adults of 20% only.

Fig.4: Observed trend in the CMFL during the control period

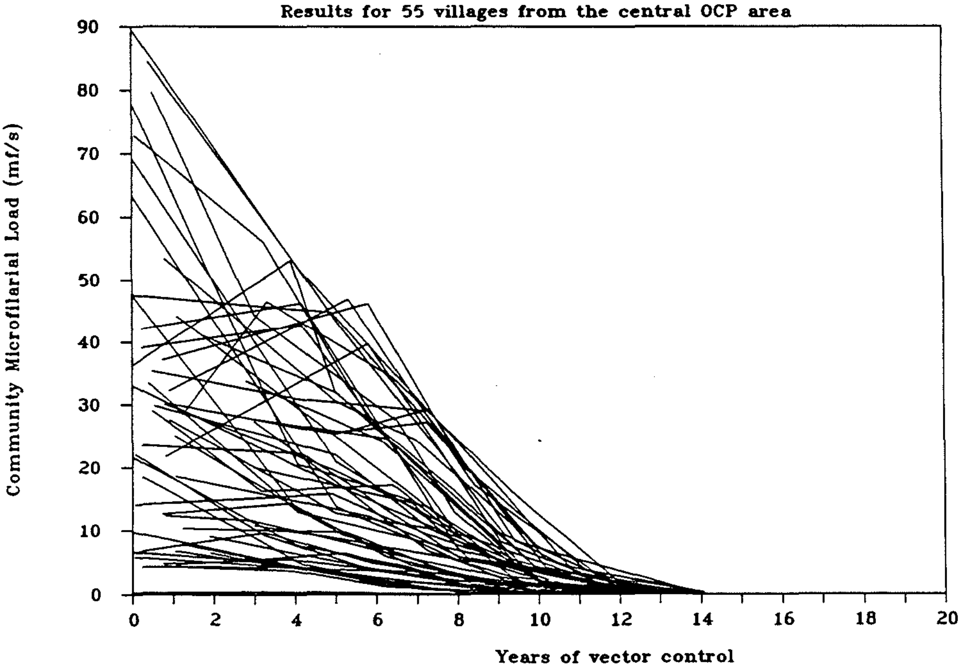
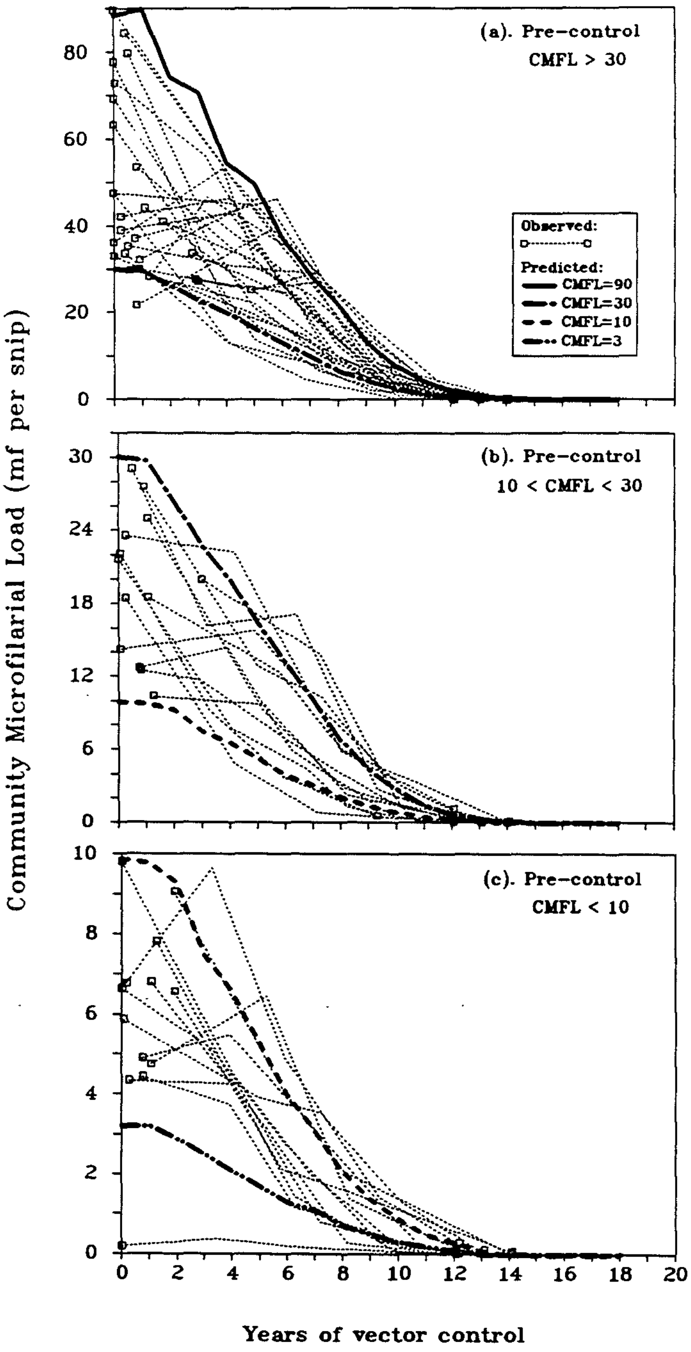


Fig.5 Observed trend in the CMFL for different endemicity levels



The trend in the CMFL is shown for each of the three endemicity groups in Fig.5. Overall, the trend is very much as predicted for each of the three groups and the relative trend is the same for all endemicity levels. However, there were differences between the predicted and observed trends for several villages. The most striking differences concerned the change in CMFL between the first and second survey. In each group there were several villages for which the CMFL hardly changed, or even increased, between the first and the second survey. This phenomenon was observed in 18 villages. In all but 3 of them, the CMFL followed the predicted trend again from the second survey onward. In the remaining 3 villages there was no change in the level of the CMFL till the third survey after 7-8 years of control, but this was followed by a subsequent rapid decline in CMFL. These 18 villages have been identified by a different symbol in figure 1 which shows that they were found in most river basins in the central OCP area. No clear geographical pattern emerges albeit that the proportion of this type of villages was high in the most north-eastern focus in Niger.

Observed trends in Prevalence of mf in cohorts of adults

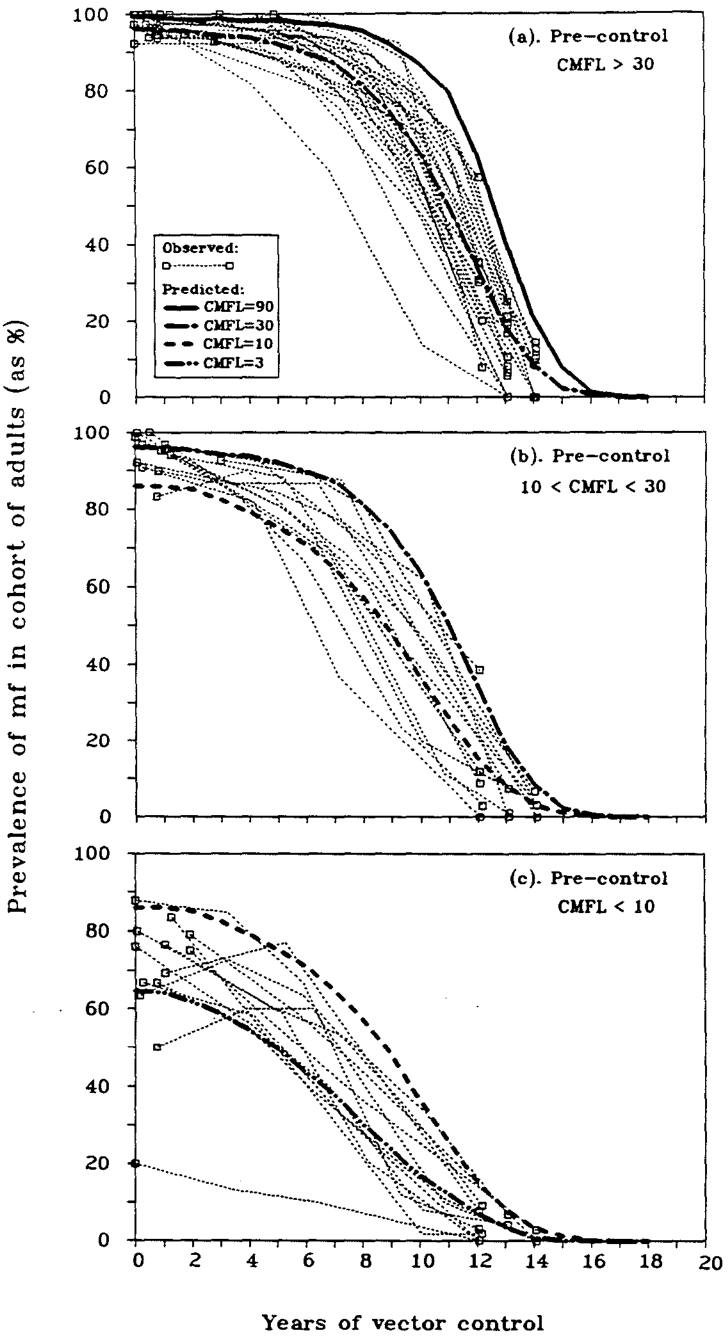
The observed trends in the prevalence of mf in cohorts of adults is shown in Fig.6 where the same grouping for endemicity level is used as above. The predicted accelerated fall in prevalence was observed in all villages and the rate of decline clearly depended on the initial endemicity level. Most remarkable was the sudden dramatic drop in prevalence in the group of villages with a pre-control CMFL of more than 30 mf/s. The observed decrease in prevalence was never significantly slower than had been predicted, but the decline was faster in several villages. The difference between the observed and predicted number of skin snip positive persons in the cohort was statistically significant for 3 of the most northern villages in Phase II ($P<0.001$ for one village and $P<0.05$ for two villages) and for 9 villages in Phase III east in Burkina Faso and North Togo ($P<0.01$ in six villages and $P<0.05$ in three villages). There were no significant differences for the 18 villages in phase I where the observed trends followed the predictions most closely. However, the predicted prevalences for the last survey in Phase I, which had been under vector control for as long as 14 years, might have been too low for the detection of a significant difference. The predicted and observed prevalence were therefore also compared for the last but one survey which was undertaken after 10-12 years of control in 15 of the 18 villages and after 8 years of control in the remaining 3 villages. Again no statistically significant differences were found.

DISCUSSION

The epidemiological follow-up surveys, which were undertaken after 12-14 years of successful vector control in the well-protected central area of the OCP, have provided unique information on the impact of control on the human reservoir of *O.volvulus*. The intensity of infection in the community, as measured by the CMFL, was close to zero in all 55 villages surveyed. It may be recalled that in non-controlled endemic areas the severity of onchocercal ocular disease in the community is directly related to the CMFL (Remme et al 1989). The extremely low values for the CMFL after 12-14 years of control leave therefore no doubt whatsoever that onchocerciasis has been eliminated as a problem of public health importance from the central area of the OCP, as has been claimed previously (WHO 1987b).

The most significant finding of the present study was the accelerated decline in the prevalence of infection which had fallen in accordance with the predictions made with the host-parasite model in 1985[a]. Particularly gratifying was the collapse in prevalence in those villages which had the highest level of endemicity during the pre-control period. The observed trends strongly suggest that vector control has practically interrupted transmission throughout the central OCP area and that the virtual elimination of the parasite reservoir has nearly been achieved. The trends are not inconsistent with the observations of Roberts et al (1967) in East Africa, but they indicate that the required duration of successful vector control is significantly

Fig.6 Observed trend in prevalence of mf for different endemicity levels



less than the 20 years originally planned for the OCP (Walsh et al 1981). In this connection it may be recalled that the above results refer exclusively to cohorts of adults, who were the most exposed and infected part of the population before the start of control. The prevalence in the total population was always lower, especially during the last surveys when there were no infections in children born since the start of control, and hardly any skin snip positive persons below the age of 25 years.

The host-parasite model is an important improvement over the force-of-infection model (Remme et al 1986) because of the inclusion of variability in the reproductive lifespan of the adult female worms which has resulted in much more realistic predictions for the later years of control. The good agreement between the predicted and observed trends supports the basic assumptions underlying the host-parasite model, including the hypothesis that the reproductive lifespan of the adult female worm is the main determinant of the epidemiological trends during a period of vector control. It also indicates that the quantification of the model was based on realistic estimates of the most important parasitological parameters. The estimate for the duration of infection between inoculation and last mf in the skin was 10.4 years on average with a variability factor which specified that 95% of all infections had a duration of less than 15 years. This corresponds to an average reproductive lifespan of *O.volvulus* of 9 to 9.5 years, if we accept that the average microfilarial longevity is in the order of 1 to 1.5 years as suggested by the results from chemotherapy experiments (Duke 1968). It should be noted that the above estimates represent only one possible quantification of the model. A detailed sensitivity analysis is presently being undertaken to determine the complete range of parameter values which are consistent with the observed epidemiological trends.

There were certain differences between observed and predicted trends which merit further discussion. In 18 of the 55 surveyed villages there was no decrease in CMFL between the first and second survey, while the model predicts a near linear decline after a delay of about one year corresponding to the pre-patent period. These differences may be due to random variations in the CMFL, in particular in the smaller cohorts, or to underestimation of skin microfilarial loads during the baseline surveys when many technicians were still inexperienced. But it is also plausible that some discrepancies reflect pre-control variations in transmission which have not been taken into account in the model predictions which were based on the assumption of an equilibrium situation with a constant force-of-infection during the pre-control period. In reality there may be great annual variations in the intensity of transmission as a result of varying hydrological conditions which determine the availability and productivity of *Simulium* breeding sites (Le Berre 1966). A relatively high intensity of transmission during the last one or two years before the start of control could explain an increase in CMFL between the first and second survey because most of the infections acquired during the last pre-control years might still have been pre-patent at the time of the first survey.

The observed epidemiological trends were significantly faster than predicted in several villages in Phase III east and in the northern half of Phase II. Entomological data for 1975 (Walsh et al 1981) suggest that larviciding in Phase I may have had an important effect on transmission in Phase II by eliminating populations of *S.damnosum* s.l. which would otherwise have been important sources of reinvasion. Similarly, control in Phase II may have reduced biting rates and transmission in Phase III east. The drought of the early seventies may have had an additional effect by severely limiting vector breeding in many of the most northern foci in the OCP (Karam et al 1987). All these factors together may be responsible for a faster decline in the parasite reservoir in large parts of Phase II and Phase III. However, there may be a completely opposite explanation for the differences in trends. It is possible that vector control in Phase I, and in the southern half of Phase II, had not sufficiently interrupted transmission during the first year of larviciding operations, and that successful control was only achieved during subsequent years. This would imply that the duration of infection has been overestimated in the model.

The combination of the observed and predicted trends indicates that the parasite reservoir will be virtually eliminated after 15 years of successful vector control, and in many areas even earlier. The question presently facing the OCP is when the expensive larviciding operations can be stopped without running a serious risk of recrudescence of infection and disease. To answer this question, research priority has been given to fly-feeding and transmission experiments in order to determine the significance of low mf loads for transmission, and to the further development and application of epidemiological modelling in order to predict the risk of recrudescence in different epidemiological situations. Such predictions cannot be made using the host-parasite model which does not address the transmission cycle of *O.volvulus*. But the favourable experience with this model, and with the technique of microsimulation, has been the basis for the recent development of a comprehensive transmission model (Plaisier et al) which allows the simultaneous simulation of a human and parasite population, the dynamics of the vector population and of interventions based on larviciding or chemotherapy.

REFERENCES

De Sole,G., O.Ba, K.Y.Dadzie, M.Karam, J.Remme. Epidemiological results of 12 years of onchocerciasis vector control in West Africa. *La Medicina Tropicale nella Cooperazione allo Sviluppo*, 4 (1988) 1-4.

Duke,B.O.L. The effects of drugs on *Onchocerca volvulus*. I. Methods of assessment, population dynamics of the parasite and the effects of diethylcarbamazine. *Bulletin of the World Health Organization*, 39 (1968) 137-146 .

Habbema,J.D.F., G.J.van Oortmarssen, J.Th.N.Lubbe, P.J.van der Maas. The MISCAN simulation programme for the evaluation of screening for disease. *Computer Methods and Programs in Biomedicine*, 20 (1984) 79-93.

Karam,M., H.Schultz-Key, J.Remme. The population dynamics of *Onchocerca volvulus* after 8 years of vector control in West-Africa. *Acta Tropica*, 44 (1987) 445-457.

Le Berre,R., Contribution à l'étude biologique et écologique de *Simulium damnosum* Theobald, 1903 (Diptera, Simuliidae). *Mémoires ORSTOM*, 17 (1966)

Plaisier,A.P., G.J.van Oortmarssen, J.D.F.Habbema, J.Remme, E.S.Alley. ONCHOSIM: A computer program for modelling the transmission and control of onchocerciasis (submitted for publication).

Prost,A., J.Prod'hon. Le diagnostique parasitologique de l'onchocercose, revue critique des méthodes en usage. *Médecine Tropicale*, 38 (1978) 519-532.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Remme,J., J.B.Zongo. Demographic aspects of the epidemiology and control of onchocerciasis in West-Africa. In: Service, M., ed. *Demography and vector-borne diseases*. Boca Raton, CRC Press (1989) Ch.24.

Remme,J., K.Y.Dadzie, A.Rolland, B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. I. West African savanna. *Tropical Medicine and Parasitology*, 40 (1989) 340-347.

Roberts,J.M.D., E.Neumann, C.W.Goeckel, R.B.Highton. Onchocerciasis in Kenya 9, 11 and 18 years after elimination of the vector. *Bulletin of the World Health Organization*, 37 (1967) 195-212.

Walsh,J.F., J.B.Davies, B.Cliff. World Health Organization, Onchocerciasis Control Programme in the Volta River Basin. In: Laird, M., ed. *Blackflies, the future for biological methods in integrated control,* London, Academic Press (1981) 85-103

World Health Organization. *WHO Expert Committee on Onchocerciasis: third report.* WHO Technical report Series, No. 752 (1987a)

World Health Organization. Twelve years of onchocerciasis control in Western Africa. *World Health Statistics Annual,* (1987b) 19-22.

APPENDIX I: Simulation of onchocerciasis infection in cohorts of adults using the Host-parasite model

Structure of the host-parasite model

The model describes the following aspects of onchocerciasis in a human population: new infections of individuals with possibility of multiple infections, the longevity of adult female parasites in the human hosts, and the age-specific contribution of each adult female parasite to the mf density in the skin. For the present analysis, only a fixed human cohort is considered, and apart from aging, all other human population dynamics (birth, death, migration) are neglected.

Infections

The human population is heterogeneous with regard to the risk of becoming infected. Part of this heterogeneity is modelled explicitly by defining age- and subpopulation-specific exposure. Thus, $Exa(a_i,s_i)$ denotes the relative exposure for the i-th person in age-class a_i and subpopulation s_i. Further individual variation is taken into account by using the exposure index Exi_i, which follows a (continuous) probability distribution of type Weibull with mean 1.0 and standard deviation s_{Exi}.

The force-of-infection, foi, denotes the rate at which a person with an average exposure acquires new infections. Only successful infections are considered, i.e. the inoculation of a female parasite which will succeed in becoming a mature worm producing microfilariae. For individual i the infection rate foi_i equals:

$$foi_i = foi \, . \, Exi_i \, . \, Exa(a_i,s_i)$$

The foi needs to be specified and can vary between time-intervals. Typically, the foi will be given a constant value in a pre-control situation, and foi=0 in case of complete interruption of transmission as a result of vector control.

Worm longevity and microfilarial offspring

For each parasite in a human host, the mf production (mo) is a function of worm age (w), counted from the moment of inoculation. The pre-patent period, the longevity of microfilariae, and the mating probability are not modelled explicitly, and are taken into account in specifying the function mo(w).

A distinction is made between non-calcifying and calcifying parasites, each having a specific distribution of the longevity Tl. Dead worms can be identified for some time Td, which also depends on calcification. Both Tl and Td are governed by a Weibull type distribution, for which the mean and standard deviation should be specified.

For a human host with a given microfilarial load there is variability in skin snip counts due to variable dispersal of microfilariae in the body and variability which is inherent in the skin snipping and counting procedure. This variability is also modelled according to a Weibull distribution.

Simulation

The model is implemented in a computer simulation program which is based on the technique of microsimulation (Habbema et al 1984). In microsimulation, individual life-histories of human hosts and adult parasites in each host are simulated. Events in the life-histories, e.g., human birth, human death, infection, death of adult parasites, are generated by random selection from the corresponding probability distributions. Output can be obtained at specified moments, when skin snip counts for each member of the human population are simulated, resulting in (age-specific) mf load distributions and CMFL values

When evaluating the impact of vector control following a stable endemic situation, the initial force-of-infection is simulated for a period of at least Tl+Td years before the start of control, to reach a stable parasite distribution in the human population.

Chapter 5

Community Trials of Ivermectin in Onchocerciasis

INTRODUCTION

In the past, chemotherapy has played a very limited role in the control of onchocerciasis because of the major limitations of the available chemotherapeutic agents. Only two drugs were recognized for the treatment of onchocerciasis, i.e. diethylcarbamazine (DEC) which is a microfilaricide but which does not appear to affect the adult worms, and suramin which is a macrofilaricide. Both drugs are associated with very serious adverse reactions following treatment. DEC treatment may result in severe systemic reactions, including shock, and it may aggravate ocular onchocercal disease, particularly in heavily infected patients who are most in need of treatment. Suramin may lead to similar reactions and in addition it has a significant intrinsic toxicity which may be fatal. Also the treatment regimens make these two drugs inappropriate for large scale treatment of onchocerciasis. DEC is administered in increasing doses during a period of more than a week, while suramin needs to be given intravenously over a period of 6 weeks under close medical supervision.

Against this background, it can be understood that there was great interest when Aziz and collaborators reported in 1982 in a small clinical trial that ivermectin, administered as a single oral dose, was an effective microfilaricide which was much better tolerated than DEC. These findings were confirmed during subsequent clinical trials, and the suggestion was also made that, in addition to its microfilaricidal effect, ivermectin may have a suppressive effect on the reproductive potential of the adult female worm. Ivermectin was registered in 1987 in France for the treatment of human onchocerciasis, and at that moment there appeared for the first time a prospect of onchocerciasis control based on chemotherapy.

This development was of direct importance for the OCP which had to decide if, and how, it was going to incorporate ivermectin treatment in its control operations. This decision was not easy to take because several major questions concerning the safety of ivermectin for use in mass treatment of onchocerciasis, its potential as a tool for transmission control and its effectiveness in preventing ocular disease remained to be answered. It became obvious in 1986 that these questions could only be answered in community trials and the OCP has, therefore, undertaken eight community trials of ivermectin in 1987 and 1988.

Chapter 5.1 provides the first results, and the most promising obtained to date, on the effect of mass treatment with ivermectin on the microfilarial reservoir and the transmission of *O. volvulus*. These results were obtained in a community trial in the Asubende focus in Ghana, the largest of all community trials and the trial with the highest levels of endemicity.

The results on adverse reactions following ivermectin treatment of more than 50,000 people in all the eight trials combined, and the conclusion on the safety of the drug for mass treatment, is given in chapter 5.2. This chapter includes an analysis of riskfactors, of the time between treatment and first reporting of adverse reactions, results on treatment coverage, and a comparison of the reduction in mf loads in foci with very different endemicity levels.

Chapter 5.3 gives the results of a 4 and 12 months ophthalmological follow-up examination after mass treatment with ivermectin in the three villages from the Asubende focus which had the highest endemicity levels of all villages in the eight community trials. This chapter provides some important new results on the effect of ivermectin treatment on ocular onchocerciasis and on the microfilarial repopulation of the eye in heavily infected persons.

Chapter 5.1

A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana.
I. Effect on the microfilarial reservoir and the transmission of *Onchocerca volvulus.*

Tropical Medicine and Parasitology, 40 (1989) 367-374

INTRODUCTION

Clinical trials have demonstrated that ivermectin is an effective and relatively well-tolerated microfilaricide for the treatment of onchocerciasis (Aziz et al 1982, Greene et al 1985, Lariviere et al 1985, Awadzi et al 1986, Diallo et al 1986), and the drug was registered for human use in October 1987 in France. However, before operational plans could be made for large scale ivermectin treatment in endemic areas, some questions concerning the potential of the drug as a tool in transmission control and its safety when used on a mass scale under field conditions, remained to be answered.

Fly feeding experiments on infected volunteers (Cupp et al 1986, Bissan et al 1986, Prod'hon et al 1987) have demonstrated that microfilarial uptake and infectivity of the vector are greatly reduced after treatment of the infected human host with ivermectin. It can thus be expected that mass treatment with ivermectin will result in an immediate reduction in *Onchocerca volvulus* transmission. However, it was not at all clear how much reduction could be achieved given that part of the population will not receive treatment, whether because they fall under the exclusion criteria or because of other reasons such as refusal, temporary absence, or because even in those treated, not all microfilariae will be eliminated. The potential of ivermectin as a tool in transmission control can, therefore, only be determined in community trials.

In 1987 the Onchocerciasis Control Programme in West Africa (OCP) started a series of 8 community trials of ivermectin, the largest of which was undertaken in the Asubende focus along the river Pru in Ghana. The present paper reports on the effect of mass ivermectin treatment on the reservoir of skin microfilariae (mf) in the human population and on the subsequent reduction in transmission of *O. volvulus* in this focus. Adverse reactions following ivermectin treatment are reported in a companion paper (De Sole et al 1989)

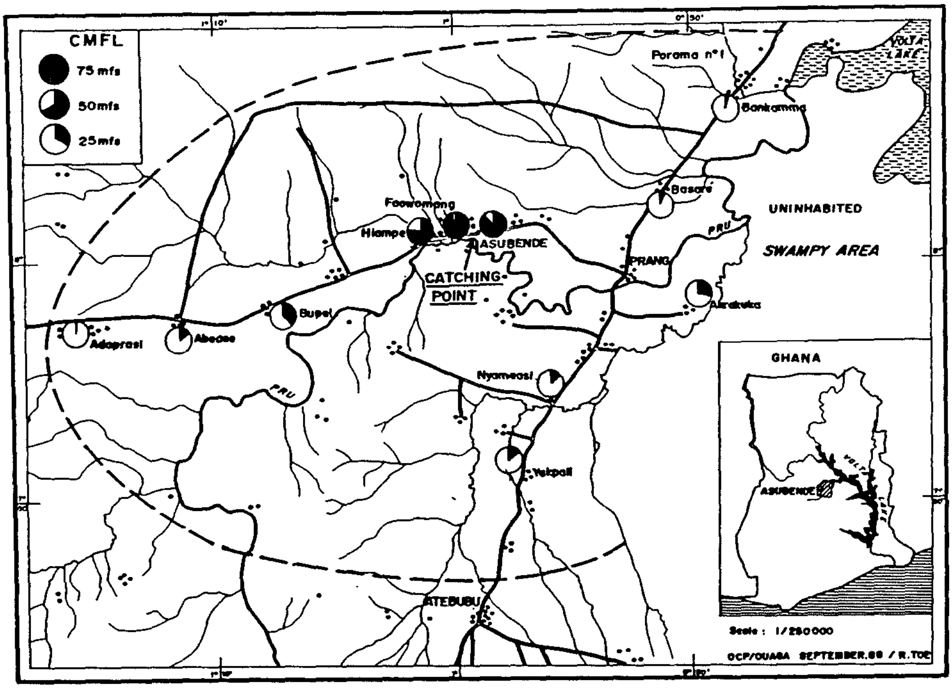
MATERIALS AND METHODS

Overview study design

Since 1986, the Asubende focus has been under vector control and man-biting rates have been reduced to low levels. To enable the study to take place, local larviciding was interrupted for 8 months to allow vector recolonization during a period of minimal long distance vector migration. This was considered to be ethically justified, given the short period that this focus has been under control and the important benefit ivermectin treatment was likely to bring to the heavily infected population in this hyperendemic focus. The study was designed as follows:

- Skin snip surveys were done in selected villages in order to determine the geographical distribution of *O. volvulus* infection in the study area and to collect baseline data for the description of the effect of treatment on the reservoir of microfilariae.
- Vector control was interrupted from July 1987 to mid-February 1988 to allow a local population of *Simulium damnosum* s.str. and/or *S. sirbanum* to establish itself and build up to an equilibrium level before ivermectin delivery.
- In October 1987 ivermectin was administered to the eligible population who were present and agreed to treatment.
- Follow-up skin snip surveys were done in December 1987 and in February 1988 in the holo-endemic villages which are located in the centre of the focus.
- Entomological evaluation was intensified from 1 August 1987 to 11 February 1988 with daily vector collections and dissection of all flies.

Fig.1 Study area and geographical distribution of Community Microfilarial Loads (CMFL)



The study area

The Asubende focus is located along the lower reaches of the Pru river in Ghana, just West of Lake Volta (Figure 1). Although not far from the forest, the Asubende focus was an integral part of the West African savanna belt until it was cut off when the Volta Lake was created in 1964. As a result, the area has become an isolated savanna focus enclosed between the Volta Lake to the east and north, and the West African forest belt to the south and west. The vectors are nearly exclusively the savanna vectors *S. damnosum* s.str. and *S. sirbanum*. There is virtually no transmission by *S. squamosum* or by other forest vectors and there is no large scale immigration of vectors from other foci. At the centre of the focus is a 25 km river stretch which contains the vector breeding sites. The most productive of these are found near the village of Asubende itself.

The central location of the breeding sites is clearly reflected in the geographical distribution of *O. volvulus* infection. Figure 1 shows for eleven villages the intensity of infection as measured by the Community Microfilarial Load (CMFL), i.e. the geometric mean mf load per skin snip among adults above the age of 20 years; an index which is theoretically proportional to the local intensity of transmission (Remme et al 1986). The CMFL is extremely high in the centrally located villages of Asubende, Faowomang and Hiampe, with values between 58 and 73 mf per skin snip (mf/s). These villages will be referred to as the holo-endemic villages. The intensity of infection rapidly declines with increasing distance from the centre and the CMFL falls to insignificant levels near the boundary of the treatment area to the north and west. The southern boundary is not so clearly demarcated. The most intense transmission evidently occurs in the centre of the focus and it was for this reason that the holo-endemic villages were selected for a detailed study of the effect of ivermectin on the mf reservoir which is the source of transmission.

Skin snip surveys in the holo-endemic villages

Four skin snip surveys were conducted in the holo-endemic villages according to the standard methodology of the OCP. This includes a full census, the taking of two skin snips from the Iliac Crest using a Holtz corneo-scleral punch, and skin snip reading after 30 minutes incubation in distilled water (Prost and Prod'hon 1978).

Standard pre-treatment surveys were done in April 1987 and September 1987. In the analysis the results from September 1987 were taken as pre-treatment data and the April result was used for a few cases who were not examined in September. The pre-treatment census population was 864.

Follow-up surveys were undertaken in December 1987 and in February 1988. In the December survey there was a deviation from the standard methodology in the sense that only the treated population was followed-up, but a complete standard survey was again done in February 1988. By that time eight persons had died or emigrated, while nine others were born or had immigrated. The census population had become 865.

Estimation of microfilarial loads in the total population

In order to assess the effect of ivermectin treatment on the reservoir of skin mf in the total population, missing skin snip data were substituted by estimates. Missing data for non-treated persons were estimated by the mean skin snip count for the same person from the other surveys. This seems justified because skin snip counts are unlikely to show any systematic changes over a short period of four months, as was also demonstrated by the fact that there was no statistically significant difference between the mean mf load for September 1987 (37.9 mf/s) and the mean for the follow-up survey in February 1988 (39.9 mf/s) in the 213 non-treated persons with skin snip data for both surveys (Paired t-test, $P=0.45$).

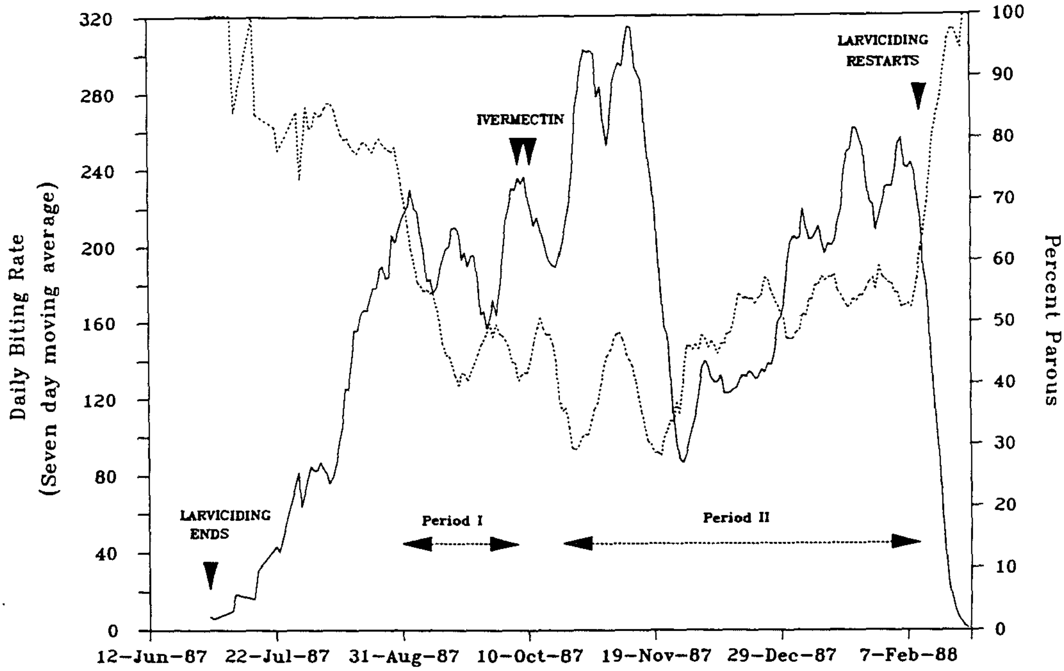
A different procedure had to be used for the 111 treated persons for whom skin snip data were not available for at least one of the surveys. One of these persons had no pre-treatment data but skin snip data for both follow-up surveys, 26 of them had no skin snip taken during the December survey but results for the other surveys, 68 had missing data for the February survey only, and for 16 persons the skin snip data were missing for two of the surveys. Each of these persons was matched using age, sex and available skin snip data to another treated person and the missing information was substituted by the corresponding values from the matched person.

Entomological evaluation of transmission

Entomological methods

Standard OCP procedures have been followed for vector collection and dissection at Asubende since 1978 (Walsh et al 1979). Flies were caught for 11 hours per day, from 7.00 a.m. to 6.00 p.m., by a team of two catchers who caught flies on the lower legs and who alternated every hour. The catching point is located in the centre of the focus near the village of Asubende. The exact location may vary during the year between two defined spots according to the height of the river and flooding of the area. In previous years the catching frequency was usually one day per fortnight. Flies were first dissected to determine parity and parous flies were further dissected to determine the presence of *O. volvulus* larvae. The number of first or second stage larvae (L1/L2), the total number of third stage larvae (L3), and the number of third stage larvae in the head of the fly (L3H) were recorded per fly.

Fig.2 Daily Biting Rate (solid line) and Parous Rate (broken line) during the study period in 1987-1988



Pre- and Post-treatment study periods

Vector control was interrupted on 30 June 1987 to allow a stable vector population to build up before ivermectin delivery. Fig. 2 shows that by 1 September the daily biting rate had begun to level out at around 200 flies per man per day and the parous rate, a good indicator of population recruitment, mortality and dispersion, had begun to stabilize at around 40% - 50%. Parous rates at this level are common near untreated breeding sites where there is little vector immigration. Ivermectin was given to the human population on 7-10 October 1987. Assuming a gonotrophic cycle of 3-4 days, no effect on vector infection could be expected before the 10 October and this date was chosen to mark the end of the pre-treatment study period.

The full effect of ivermectin treatment on transmission can only be measured after a delay of some 10-11 days to allow for the drug to have its full microfilaricidal effect and to allow two gonotrophic cycles to elapse before engorged mf can become an infective challenge to the human population. The post-treatment study period was therefore defined as starting on 22 October 1987 and lasted for 113 days until the 11 February 1988 when larvicide was re-applied to the river and the vector population was again brought under control.

In the analysis the period of 1 September to 10 October of each year since 1978 will be referred to as Period I, and the period of 22 October of that year to the 11 February of the subsequent year as Period II.

RESULTS

Effect of mass treatment on the microfilarial reservoir in the holo-endemic villages

Treatment coverage by intensity of infection

A total of 14,991 people were treated with ivermectin, which accounts for 61.5% of the census population in the total study area (De Sole et al 1989). In the villages in the core of the focus the overall coverage was about 64%. However, treatment coverage varied considerably with the presence and intensity of *O. volvulus* infection (Table 1 for details of the holo-endemic villages). The lowest coverage of 21.7% was observed in the skin snip negative group, which consisted mainly of children below the age of five years who are excluded from treatment. In contrast, a coverage of close to 80% was achieved among patients with a mf load in excess of 64 mf/s.

Table 1: Treatment coverage in the holo-endemic villages in relation to pre-treatment mf load

No. of microfilariae per skin snip	No. of persons	Treated with ivermectin	
		Number	Percentage
0	166	36	21.7
0.5 -	19	8	42.1
2 -	20	16	80.0
4 -	35	24	68.6
8 -	36	25	69.4
16 -	52	33	63.5
32 -	105	79	75.2
64 -	236	188	79.7
128 -	166	133	80.1
256 -	10	7	70.0
Unknown	19	4	21.1
Total	864	553	64.0

Reduction in skin microfilarial loads in treated patients

A complete set of skin snip data for the pre-treatment survey as well as for both follow-up surveys is available for 443 of the 553 treated persons. Table 2 shows the distribution of the skin snip loads two months after treatment and in relation to the pre-treatment intensity of infection for these 443 cases. Ivermectin treatment produced dramatic reductions in mf loads for all levels of intensity. The mean mf load fell by 96%, and the proportional reduction in mf loads was equally high in the groups which initially had a high intensity of infection. In the group with a pre-treatment load of more than 64 mf/s, as many as 40-44% had become skin snip negative and about 75% of this group had less than 2 mf/s. However, a few cases (some 3%) did not seem to have responded to the treatment and remained with high mf loads.

Table 2: Distribution of microfilarial loads two months after ivermectin treatment in relation to pre-treatment mf loads

		Mf per snip two months after treatment (Percentage distribution per pre-treatment group)										Arithmetic mean mf/s		
Mf/s pre-treatment	No. of patients	0	0.5-	2-	4-	8-	16-	32-	64-	128-	256+	pre-treatment	post-treatment	Percentage reduction in mean mf/s
0	27	92.6	3.7	3.7	0	0	0	0	0	0	0	0.00	0.09	n.a.
0.5-	7	100.0	0	0	0	0	0	0	0	0	0	1.14	0.00	100.0
2-	12	66.7	25.0	8.3	0	0	0	0	0	0	0	2.50	0.46	81.7
4-	21	76.2	19.0	0.0	4.8	0	0	0	0	0	0	5.21	0.43	91.8
8-	24	62.5	16.7	12.5	8.3	0	0	0	0	0	0	11.69	0.85	92.7
16-	23	60.9	26.1	13.0	0	0	0	0	0	0	0	23.80	0.52	97.8
32-	64	57.8	23.4	12.5	3.1	1.6	0	1.6	0	0	0	46.43	1.77	96.2
64-	152	44.1	28.9	11.8	6.6	4.6	1.3	1.3	1.3	0	0	91.68	3.48	96.2
128-	108	42.6	32.4	6.5	6.5	1.9	3.7	2.8	2.8	0.9	0	174.63	6.81	96.1
256+	5	40.0	20.0	0	20.0	20.0	0	0	0	0	0	342.00	3.50	99.0
Total	443	53.5	25.5	9.3	5.2	2.5	1.4	1.4	1.1	0.2	0	86.80	3.26	96.2

A quite different pattern was seen in February 1988, four months after ivermectin treatment (Table 3). For all groups there was a clear shift to higher mf loads compared to the survey done two months after treatment. Overall, only 20.8% of the 443 persons followed up after treatment were still skin snip negative, compared to 53.5% in December 1987. In the groups with high pre-treatment mf loads, nearly all had become skin snip positive again. However, their skin snip loads were still relatively low, generally below 8-16 mf/s, with the mean mf count still only at 10% of the pre-treatment level.

Table 3: Distribution of microfilarial loads four months after ivermectin treatment in relation to pre-treatment mf loads

		Mf per snip two months after treatment (Percentage distribution per pre-treatment group)										Arithmetic mean mf/s		
Mf/s pre-treatment	No. of patients	0	0.5-	2-	4-	8-	16-	32-	64-	128-	256+	pre-treatment	post-treatment	Percentage reduction in mean mf/s
0	27	81.5	14.8	0	0	0	4	0	0	0	0	0.00	0.70	n.a.
0.5-	7	85.7	14.3	0	0	0	0	0	0	0	0	1.14	0.14	87.5
2-	12	33.3	33.3	25.0	8	0	0	0	0	0	0	2.50	1.42	43.3
4-	21	47.6	33.3	9.5	9.5	0	0	0	0	0	0	5.21	1.05	79.9
8-	24	41.7	33.3	8.3	4.2	8.3	0	4.2	0	0	0	11.69	3.02	74.2
16-	23	26.1	30.4	13.0	21.7	4.3	4.3	0	0	0	0	23.80	3.22	86.5
32-	64	21.9	26.6	20.3	20.3	7.8	1.6	0.0	1.6	0	0	46.43	4.54	90.2
64-	152	10.5	23.0	17.1	19.7	16.4	4.6	5.3	2.6	0.7	0	91.68	10.68	88.3
128-	108	3.7	13.0	18.5	19.4	15.7	12.0	9.3	4.6	2.8	0.9	174.63	22.39	87.2
256+	5	0	0	40.0	0	0	40.0	20.0	0	0	0	342.00	18.30	94.6
Total	443	20.8	21.9	16.0	16.5	11.3	5.6	4.5	2.3	0.9	0.2	86.80	10.45	88.0

Estimated reduction in the total reservoir of skin microfilariae

For the holo-endemic villages an attempt has been made to estimate the effect of mass treatment on the reservoir of skin mf available for transmission in the total population, consisting of both treated and untreated subjects. Table 4 shows the pre- and post-treatment levels of different indices of mf availability, and the percentage reduction in these indices at two and four months after treatment. Two months after treatment the mean microfilarial load had been reduced by 77% two months but the overall prevalence of mf by only 40%. The remaining three indices in Table 4 are more consistent with the observed decrease in the mean mf load, and suggest a reduction of 68% to 78% in the availability of skin mf for transmission two months after treatment.

After four months the prevalence of mf had nearly returned to the pre-treatment level, while the prevalence of loads of more than 4 mf/s was only 35 to 40% below the initial level. Only the mean mf load and the prevalence of high loads remained about 70% below pre-treatment levels. It should be noted that an arithmetic mean and not a geometric mean has been used because the latter is not appropriate for bi-modal distributions as described here, since it gives a disproportionate weight to the zero's and very low values.

Table 4: Estimated percentage reduction in the availability of skin microfilariae for transmission in the total population (i.e. treated plus non-treated) in the holo-endemic villages following ivermectin mass treatment.

Index of availability of skin microfilariae for transmission	Pre-treatment (N=864)	December 1987 (N=864)	February 1988 (N=865)	Percentage Reduction December 1987	Percentage Reduction February 1988
Arithmetic mean mf/s	71.7	16.4	21.2	77.2	70.5
Prevalence of mf	79.5%	48.0%	69.9%	39.6	12.0
Prevalence of >4 mf/s	75.0%	24.0%	43.9%	68.1	41.4
Prevalence of >32 mf/s	60.8%	13.4%	16.2%	77.9	73.4
Prevalence of >4 mf/s in high exposure group*	100.0%	31.1%	64.8%	68.9	35.2

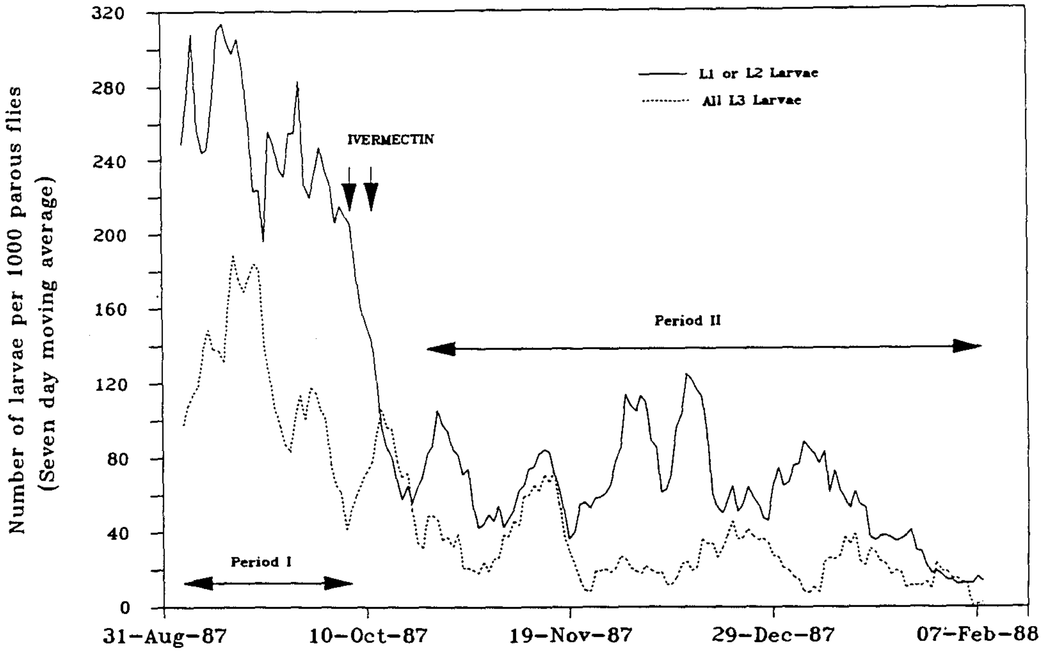
*High exposure is here defined as having a pre-treatment skin snip load > 32 mf/s

Effect of mass treatment on infection and infectivity levels in the vector

Changes during 1987-1988

During Period I in 1987 and Period II in 1987-1988, totals of 7,989 and 23,072 flies, respectively, were caught and dissected. The mean daily biting rates (200 and 204) and parous rates (48% and 46%) were very similar in the two periods. Fig.3 shows how vector infection changed during 1987-1988. A dramatic and consistent reduction in vector infection can be observed following ivermectin delivery. After 11 days, when ivermectin could have been expected to have had an effect on transmission, infection stabilized at around 60 L1/L2 larvae and 30 L3 larvae per 1000 parous flies. At the end of the study period in late January/early February there was a consistent downward trend in vector infection.

Fig.3 Changes in the mean number of *Onchocerca* larvae in parous flies following ivermectin distribution



Before ivermectin delivery, 599 flies (157 per 1000 parous) were infected and 133 (35 per 1000 parous) were infective with L3 larvae in the head (L3H). After ivermectin delivery, 450 (42 per 1000 parous flies) were infected and 100 (9 per 1000 parous) were infective. However, the mean load of L3s per infective fly head (1.87 and 1.67), and the mean number of L1/L2 per fly with L1/L2 larvae (1.99 and 1.84) did not show a statistically significant change after ivermectin treatment (Mann-Whitney U-test: $P>0.1$).

Comparison with earlier years

The 1987-1988 results were compared with the entomological results for the same periods in previous years. Extensive historical data exist for most years since 1978, with the exception of 1982, when there were very few flies because of drought conditions, and 1986, when vector control kept the biting population to very low levels. Both years have, therefore, been excluded from further analysis.

Table 5 provides biting, parous and infection rates for Period I since 1978. Although considerable variation between the years can be observed with mean daily biting rates (DBR) ranging from 38 to 121 and parous rates from 48% to 74%, the overall picture is one of reasonable stability. Examination of the eight years entomological data clearly indicates that 1987 was exceptional with the highest daily biting rate (200) and lowest parous rate (48%). L3 rates were also lower than in most previous years and this may be explained, at least partly, by the presence of a younger parous fly population.

Table 5: Biting rates, parity and infection of the vector during Period I* between 1978 and 1987

		Parous flies			Rates per 1000 flies						
Year	No. of flies dissected	No.	%	Daily Biting Rate	Infected flies	Flies with L3	Flies with L3H	No. of L3	No. of L3H	Flies with L1/L2	No. of L1/L2
1978	452	299	66.2	107	197	77	60	161	107	127	251
1979	496	239	48.2	121	188	71	46	167	92	134	310
1980	673	397	59.0	99	169	78	45	156	76	103	181
1981	526	390	74.1	60	241	151	90	379	205	118	254
1983	464	242	52.2	50	248	186	128	421	211	99	169
1984	485	254	52.4	84	142	94	59	185	118	55	134
1985	229	148	64.6	38	81	34	27	54	47	54	149
1978-1985	3325	1969	59.2	81	189	104	67	231	128	103	212
1987	7989	3805	47.6	200	157	50	35	110	65	124	246

*1 September to 10 October

Table 6 gives the biting, parity and infection rates recorded during Period II since 1978. The L3 rates for 1987-88 were dramatically lower than in all previous years, including 1979, when low parous rates were also recorded. The L1/L2 rates were also much lower in 1987-88 but the difference was not so striking.

Table 6: Biting rates, parity and infection of the vector during Period II* between 1978 and 1987

		Parous flies			Rates per 1000 flies						
Year	No. of flies dissected	No.	%	Daily Biting Rate	Infected flies	Flies with L3	Flies with L3H	No. of L3	No. of L3H	Flies with L1/L2	No. of L1/L2
1978	560	343	61.3	87	163	96	58	157	90	79	172
1979	1299	642	49.4	105	210	100	58	201	123	126	254
1980	1410	736	52.2	134	223	111	69	227	122	139	304
1981	1094	854	78.1	47	132	95	70	230	132	47	108
1983	746	528	70.8	33	165	119	74	242	129	55	102
1984	1197	826	69.0	83	131	76	51	182	104	73	176
1985	711	577	81.2	74	135	75	54	125	85	64	104
1978-1985	7017	4506	64.2	82	164	95	62	199	115	83	177
1987	23072	10656	46.2	204	42	14	9	26	16	30	55

*22 October to 11 February

Estimated reduction in O. volvulus transmission

Table 7 provides estimates of the percentage reduction in vector infection rates after ivermectin delivery. Although, strictly, only reductions in third stage larvae (especially of head L3s) can be termed transmission reductions, reductions in first and second stage larvae are also taken into account because they should be less affected by changes in vector mortality and dispersion.

When the pre and post-treatment data for 1987 are compared, similar estimates of reduction in vector infection (from 72% to 78%) are obtained for both L3 and L1/L2 rates. However, when the post-treatment data are compared directly with the historical data for Period II, there is a much greater reduction in transmission according to estimates based on the L3 rates (85%) compared to those based on the L1/L2 rates (65%).

Table 7: Estimated percentage reduction in *Onchocerca* transmission after ivermectin treatment as compared to the pre-treatment period in 1987 and to historical data from 1978-1985

	Index of *O. volvulus* infection in the vector						
Pre-treatment period	Infected flies	Flies with L3	Flies with L3H	No. of L3	No. of L3H	Flies with L1/L2	No. of L1/L2
Period I* in 1978	73.2%	72.0%	74.3%	76.4%	75.4%	75.8%	77.6%
Period II** in 1978-1985	74.4%	85.3%	85.5%	87.0%	86.5%	64.7%	68.9%

*1 September to 10 October, **22 October to 11 February

DISCUSSION

The treatment coverage of 61.1% of the census population in the total study area, and 64% in the holo-endemic villages, would appear to be rather low for the purpose of transmission control. However, crude coverage figures underestimate the extent of treatment with respect to transmission and it is more appropriate to assess treatment coverage in relation to the presence and intensity of *O. volvulus* infection in the human population. A high intensity of infection can be regarded as a result of a high level of man-vector contact and it is therefore especially important to treat highly infected people if the aim is to reduce transmission. Seen in this light, the treatment coverage is more favourable: 75.5% among skin snip positives and close to 80% among the people with a microfilarial load of more than 64 mf/s.

Two months after ivermectin treatment the microfilaricidal effect appeared to be basically the same as reported in the clinical trials (Greene et al 1985, Lariviere et al 1985, Awadzi et al 1986, Diallo et al 1986), with a 96% reduction in the mean mf load among treated cases. The drug was equally effective in people with very high intensities of infection, which is important, not only because these are the patients most at risk of developing onchocercal disease, but also because of the major role which they play in transmission.

It is more difficult to say to what extent the consistent shift in the distribution of mf loads during the next two months conforms with previous findings because published reports of the clinical trials provide only geometric means for the skin snip results. It would appear that the increase in mf loads between the second and fourth month after treatment is greater than reported in previous studies and the observed trend does not seem to support the hypothesis of long term suppression of mf counts as a result of intrauterine sequestration of microfilariae during this period (Schultz-Key et al 1986).

The assessment of the effect of mass treatment on the reservoir of skin microfilariae which are available for transmission in the total, treated plus non-treated, population, depends on the index used. The reduction in the mean mf load suggests that the total skin mf reservoir had been reduced by some 77% two months after treatment. However, this finding does not necessarily imply a similar reduction in transmission because skin mf are not randomly distributed in the population but clustered in persons who differ in their intensity of infection and in their exposure to the vector (Renz et al 1987). It is, therefore, also relevant to assess changes in the prevalence of different intensities of infection in the total population and in the high exposure group. The prevalence of mf showed only a 40% reduction two months after treatment but at that time there was a large group of treated patients with very low mf loads. Vector feeding and transmission experiments (Duke et al 1962; OCP unpublished data) indicate that the contribution to transmission by persons with low intensities of infection is very limited, especially when ivermectin treatment is the cause of the low mf density (Bissan et al 1986). If the lowest loads, of less than 4 mf/s, are excluded, or if the mean mf load in the total population is considered, then for the middle of the post-treatment study period an estimated reduction in the order of 68-78% in the availability of skin microfilariae for transmission is obtained.

These estimates agree very well with the entomological results which indicate reductions in vector infection levels of 72% to 77% when using the 1987-88 data, and of 65% to 85% when the post-treatment data are compared with the historical data. The comparison with historical data shows a disparity between the estimates based on L1/L2 rates and the L3 rates. There was clearly a younger age composition of the vector population in 1987-88 and a reduction of 85% in L3 infections therefore must be an exaggeration of the effect of ivermectin treatment. In contrast the 65% reduction of L1/L2 infections is the minimum that could have been achieved as it is probable that there was some undercounting of L1/L2 larvae during routine dissections, which is known to have occurred in other routine work (OCP, unpublished data).

The increase in mf loads between December 1987 and February 1988 was not accompanied by a corresponding rise in vector infection levels and there was even a marked decrease in vector infection towards the end of January 1988. At Asubende Walsh (1984) has shown that infection levels in the fly are, at the height of the dry season, only half of that recorded in the wet season. The reasons for the difference are not understood.

The reduction in vector infection levels was substantial and suggests that regular mass treatment with ivermectin may also benefit the non-treated population and reduce their levels of infection and disease considerably over time. However, it should be noted that a reduction in transmission of this magnitude would, during an average year without vector control, bring the Annual Transmission Potential only down to a level of about 600-700 infective larvae per person per year, a level which is still unacceptably high (Thylefors et al 1978).

The present study has demonstrated for the first time that mass treatment with ivermectin can considerably reduce *O. volvulus* transmission. The data are not yet sufficient to design definite strategies for the use of ivermectin in onchocerciasis transmission control. The main remaining question is whether it will be possible to progressively eliminate the parasite reservoir with regular ivermectin mass treatment, or whether treatment will need to be continued indefinitely. This question is currently the focus of several OCP research activities.

REFERENCES

Awadzi,K., K.Y.Dadzie, H.Schulz-Key, H.M.Gilles, A.J.Fulford, M.A.Aziz. The chemotherapy of onchocerciasis XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Annals of Tropical Medicine and Parasitology*, 80 (1986) 433-442.

Aziz,M.A., S.Diallo, I.M.Diop, M.Lariviere, M.Porta. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet*, ii (1982) 171-173.

Bissan,Y., P.Vingtain, K.Doucoure, O.Doumbo, D.Dembele, J.Ginoux, P.Cozettes, Ph.Ranque. L'ivermectine (MK-933) dans le traitement de l'onchocercose, son incidence sur la transmission d'*Onchocerca volvulus* en savane soudanienne au Mali. *Médecine d'Afrique Noire*, 33 (1986) 81-93.

Cupp,E.W., M.J.Bernardo, A.E.Kiszewski, R.C.Collins, H.R.Taylor, M.A.Aziz, B.M.Greene. The effects of Ivermectin on Transmission of *Onchocerca volvulus*. *Science* 231 (1986) 740-742.

Diallo,S., M.A.Aziz, M.Lariviere, J.S.Diallo, I.Diop, O.N'Dir, S.Bandiane, D.Py, H.Schulz-Key, P.Gaxote, A.Victorius. A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 80 (1986) 927-934.

Duke,B.O.L. Studies on factors influencing the transmission of onchocerciasis. II. The intake of *Onchocerca volvulus* microfilariae by *Simulium damnosum* and the survival of the parasites in the fly under laboratory conditions. *Annals of Tropical Medicine and Parasitology*, 56 (1962) 255-263.

Greene,B.M., H.R.Taylor, E.W.Cupp, R.P.Murphy, A.T.White, M.A.Aziz, H.Schulz-Key, S.A.D'Anna, H.S.Newland, L.P.Goldschmidt, A.Auer, A.P.Hanson, V.Freeman, E.W.Reber, P.N.Williams. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *New England Journal of Medicine*, 313 (1985) 133-138.

Lariviere,M., P.Vingtain, M.A.Aziz, B.Beauvais, D.Weimann, F.Derouin, J.Ginoux, H.Schulz-Key, P.Gaxote, D.Basset, C.Sarfati. Double-blind study of ivermectin and diethylcarbamazine in african onchocerciasis patients with ocular involvement. *Lancet*, ii (1985) 174-177.

Prod'hon,J., F.Lardeux, O.Bain, G.Hébrard, J.M.Prud'hom: Ivermectine et modalités de la réduction de l'infection des simulies dans un foyer forestier d'onchocercose humaine. *Annales de Parasitologie Humaine Comparée*. 62 (1987) 590-598.

Prost,A., J.Prod'hon. Le diagnostique parasitologique de l'onchocercose, revue critique des méthodes en usage. *Médecine Tropicale*, 38 (1978) 519-532.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Renz,A., H.Fuglsang, J.Anderson. Studies on the dynamics of transmission of onchocerciasis in a Sudan-savanna area of North-Cameroon IV. The different exposure to *Simulium* bites and transmission of boys and girls and men and women, and the resulting manifestations of onchocerciasis. *Annals of Tropical Medicine and Parasitology*, 81 (1987) 253-262.

Schultz-Key,H., B.M.Greene, K.Awadzi, M.Lariviere, S.Klaeger, K.Y.Dadzie, M.A.Aziz. Efficacy of ivermectin on the reproductivity of female *Onchocerca volvulus*. *Tropical Medicine and Parasitology*, 37 (1986) 89.

Thylefors,B., B.Philippon, A.Prost: Transmission potentials of *Onchocerca volvulus* and the associated intensity of Onchocerciasis in a Sudan savanna area. *Tropical Medicine and Parasitology*, 29 (1978) 346-354.

Walsh,J.F. Aspects of the biology and control of *Simulium damnosum* s.l. (Diptera: Simuliidae) in West Africa. Ph.D. Thesis, Salford University, England (1984)

Walsh,J.F., J.B.Davies, R.L.Le Berre. Entomological aspects of the first five years of the Onchocerciasis Control Programme in the Volta River Basin. *Tropical Medicine and Parasitology*, 30 (1979) 328-344.

Chapter 5.2

Adverse reactions after mass treatment of onchocerciasis with ivermectin: Combined results from eight community trials

Bulletin of the World Health Organization, 67, no.6 (1989)

INTRODUCTION

Ivermectin is a new microfilaricide for the treatment of human onchocerciasis (Aziz et al 1982) which has been shown to be highly effective and relatively well-tolerated in a series of clinical trials (Greene et al 1985, Lariviere et al 1985, Awadzi et al 1986, Diallo et al 1986, White et al 1987). The drug was registered for human use in October 1987 in France. This development was of major significance for the Onchocerciasis Control Programme in West Africa (OCP) which has had to rely on vector control through larviciding as the sole available method of control since the start of its operations in 1975 (WHO 1976). However, only 1,209 selected volunteers had been treated with ivermectin during the clinical trials (Merck, Sharp and Dohme 1988). Before ivermectin could qualify as an effective tool for control in the OCP, further evidence was needed that the drug was sufficiently safe to be used in mass treatment in endemic areas where there are often insufficient health care facilities to deal with possible severe adverse reactions. It was therefore necessary to determine in community trials the risk of rare but severe adverse reactions following ivermectin treatment.

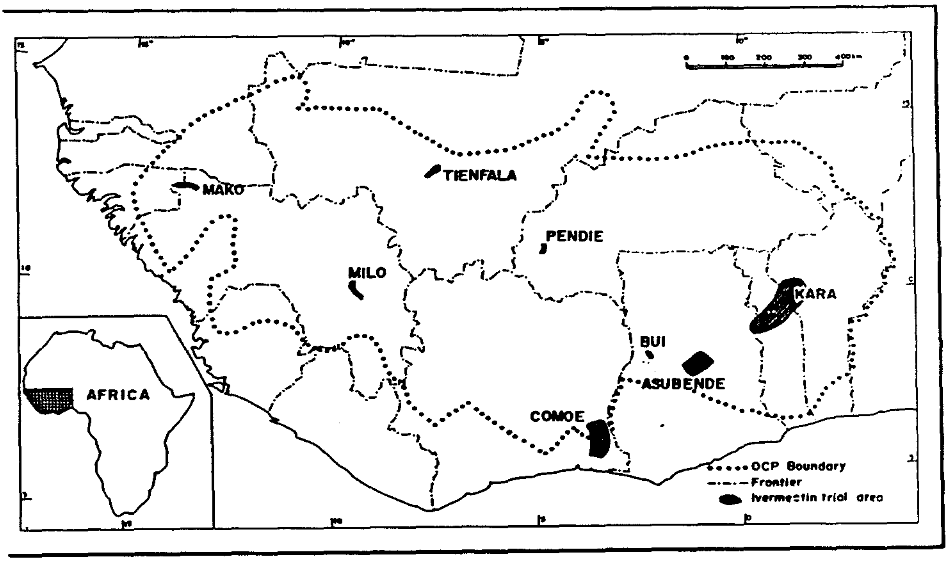
The Onchocerciasis Control Programme (OCP) undertook between August 1987 and May 1988 eight community trials of ivermectin. The two main objectives were to determine the safety of ivermectin for mass treatment and its potential as a tool in transmission control (De Sole et al 1989, Remme et al 1989). The combined results on adverse reactions encountered during these eight trials are reported here.

MATERIALS AND METHODS

The trial areas

The trial areas represent the different epidemiological situations of operational importance for the OCP and range from non-controlled hyperendemic foci in the extension areas to foci with incomplete control in the original Programme area. For the purpose of the transmission component of the study, relatively isolated onchocerciasis foci with a local transmission cycle were selected. Figure 1 shows the location of the selected trial areas.

Fig.1 Location of the trial areas in West Africa



The main characteristics of the different trial areas are summarized in Table 1 which list the trials in chronological order of ivermectin treatment. Four of trials, i.e. Asubende, Milo, Tienfala and Mako, are hyperendemic onchocerciasis foci in the extension areas of the OCP where the epidemiological situation has not yet been affected by vector control. The Comoe trial is located in the pre-forest area on the southern Programme boundary where transmission is mainly due to the forest vector *Simulium Sanctipauli* s.n. The other three trials are located within the original programme area and are foci where an insufficient level of control has been achieved, either because of reinvasion by infective flies from elsewhere (Kara), or because of the difficulty of local larviciding (Bui), or because of undetected local vector breeding and a subsequent relapse in transmission (Pendie).

Table 1: Description of the trial areas.

				Population distribution by village CMFL			
Trial name	Country	River	Vector control	<10 mf/s	10-35 mf/s	>35 mf/s	Census population
Bui	Ghana	Black Volta	Control since 1975. Incomplete interruption of transmission	90%	10%	0%	1,573
Asubende	Ghana	Pru	No control till 1986	49%	42%	9%	26,117
Kara	Togo, Benin	Kéran/ Kara/Mô	Control since 1977. Reinvaded by infective flies.	90%	6%	4%	21,437
Comoe	Côte d'Ivoire	Comoe	Selective control savanna flies. No control forest flies.	100%	0%	0%	22,575
Pendie	Burkina Faso	Dienkoa	Control since 1975. Localized relapse in transmission	100%	0%	0%	2,965
Milo	Guinea	Milo	No control till 1987	26%	64%	9%	3,659
Tienfala	Mali	Niger	No control	65%	27%	8%	4,435
Mako	Senegal	Gambia	No control	74%	17%	9%	4,802

Epidemiological mapping and endemicity levels.

Skin snip surveys were done in a sample of villages in each trial area. This involved a complete village census, the taking of two skin snips from the Iliac Crest of each person using a Holtz corneo-scleral punch, and the microscopic examination of the skin snips for *O.volvulus* microfilariae after 30 minutes incubation in distilled water (Prost and Prod'hon 1978). The skin snip data were used to determine the endemicity level of the village as expressed by the Community Microfilarial Load (CMFL), i.e. the geometric mean number of microfilariae per snip (mf/s) in persons with an age of 20 years or above (Remme et al 1986). A map was made for each trial which showed the geographical distribution of onchocerciasis endemicity and the CMFL values for non-surveyed villages were estimated by extrapolation. Table 1 shows the approximate distribution of the population by endemicity level of the village. The endemicity level was lowest for the Comoe and Pendie trials where the total population lived in villages with CMFL's below 10 mf/s. The most endemic trials were the populous Asubende trial where over 50% of the population lived in villages with a CMFL in excess of 10 mf/s, and the Milo trial where nearly three quarters of the population fell in this category.

Organization of ivermectin delivery

The community trials were undertaken in collaboration with the Ministries Health of the eight participating countries who provided additional medical personnel. Guidelines for drug distribution and monitoring together with specially designed data collection forms were prepared and all personnel were briefed before the start of field activities in each trial. A major effort was made to ensure maximum, voluntary, community participation. Local authorities were informed in advance of the purpose and nature of the trials and of the need for informed consent. The trial areas were divided in sectors, each assigned to a medical officer in charge of ivermectin distribution and monitoring of adverse reactions.

Drug administration

Following a census taking by a trained census clerk, the community members were requested to present themselves as family units to the treatment post. Enquiry was made as to the presence of pregnancy, the duration of lactation and the existence of epilepsy in the family. A rapid examination of each patient was conducted for presence of general ill health, anaemia, jaundice, oedema, high fever (by touch) and multiple facial injuries that may suggest epilepsy. Selected patients were examined for neck stiffness. Local officials assisted in obtaining informed consent to treatment. Ivermectin was administered as a single oral dose, based on body weight, to all those who agreed to treatment and did not fall under the exclusion criteria, i.e. an age of less than 5 years, a body weight of less than 15 kg, pregnancy, first three months of lactation (in Bui and Asubende only the first month of lactation was used), jaundice, severe anaemia, disease of the central nervous system and severe illness. The patients were advised to avoid undue physical activity and to refrain from the consumption of alcoholic drinks for the ensuing 72 hours.

Monitoring of adverse reactions

Monitoring was carried out for at least 72 hours after treatment and was usually effected by resident nurses living in the villages during this period. Only in the three largest trials was a section of the population, who lived in very dispersed settlements, monitored by mobile nurses who visited each settlement at least once per day. Patients were requested to report with any complaint to the monitoring nurse. After the second trial in Asubende, patients were advised to stay at home in case of dizziness and general weakness, and to send a relative to fetch the nurse. Symptoms were always volunteered by the patient and not sought by questioning.

Quantification of adverse reactions

In order to classify the severity of the various type of reactions a system of quantifying reactions, principally addressed to nurses as the primary personnel involved in monitoring, was developed (see Table 2). This was a simplification of the protocol used by the Onchocerciasis Chemotherapy Research Center (Awadzi 1980). Four grades of reactions were recognised: no reaction, mild, moderate and severe reaction. The grading of reactions was based on the functional disability experienced by the patient at the time of the medical examination. Thus, mild reactions involved symptoms but not disability, moderate reactions symptoms with partial disability and severe reactions symptoms with complete functional disability. Exceptions to the general rule included:

a) fever in which an arbitrary age depended scale was used irrespective of disability. The cut off point between children and adult was the age of 12 years. In children an axillar temperature of 38.5° - 39.4° was defined as moderate fever and 39.5° or more as severe fever. In adults these two definitions were a temperature of 39.5° - 40.4° and of 40.5° or more.

b) rash was graded as mild when it covered less than 1/3 of the body surface and moderate when it was more extensive. A severe rash was considered inappropriate since it did not carry any element of disability.

Table 2: Grading of common reactions

	SEVERITY		
SYMPTOM	MILD	MODERATE	SEVERE
Itching*	Not obviously scratching. No scratch marks	Obviously recent scratch marks or excoriations. Insomnia, but remained in bed. Able to carry out normal activity but at reduced level.	Vigorous continuous scratching. Restlessness. Insomnia with abandonment of bed and pacing up and down.
Joint Pain Muscle Ache Gland Pain Backache	No discomfort Normal gait	Obvious marked limp or difficulty in moving about	Rooted to the spot (pillar of salt). Bedridden on account of any of these symptoms
Headache**	Comfortable	In distress, holding head stiffly	Restless, bedridden
Swollen Limb	Part of limb only. No pain or mild pain only	Involvement of whole limb ±pain plus some impairment of normal use	Involvement of whole limb with extension into adjacent area plus loss of limb ±pain.

*For rash: note location and approximate extent; **Check for neck stiffness, fever or altered mentation.

Data processing and analysis

Data entry and validation of treatment and adverse reaction data was done on microcomputers equipped with removable mass storage devices and by using computer programmes developed under CLIPPER. Data analysis was done using SPSS/PC+ and with BMDPC for logistic regression analysis. The results from the skin snip surveys were processed using routine OCP computer programmes.

In order to facilitate the presentation of results on adverse reactions, a number of reaction types with common features have been posted together to form the following reaction groups:

painful conditions : headache, joint pain, muscle aches, general aches, backache
gland reaction : gland pain, swelling
fever : fever, chills
swelling : limbs, face, other sites
cutaneous reaction : itching, rash
ocular reaction : pain, redness, watering
SSPH : Severe Symptomatic Postural Hypotension
dyspnoea : asthma, laryngeal oedema
other complaints : anorexia, nausea, vomiting, dizziness, insomnia.

SSPH was defined by the inability of a patient to stand for at least two minutes due to severe dizziness or weakness attributable to a marked drop in the blood pressure.

RESULTS

Treatment coverage

Table 3 shows the treatment coverage by trial area. The coverage was fairly uniform and varied from 59.3% to 67.7% in seven of the trials. The lowest coverage of 55% was obtained in the Comoe trial where the population is very dispersed and highly mobile. The coverage was higher in the smaller trials with a population of less than 5000 than in the three large trials with populations over 20,000. The only exception was the Tienfala trial where there was much mobility as a result of the proximity of the national capital. The most frequent cause of non-treatment was an age of less than 5 years (43.6%) followed by failure to present at the treatment post (38.5%) mainly because of absenteeism from the village. Pregnancy and first three months of lactation accounted for 6.4% of non-treatment, and severe illness and epilepsy for 1.8%.

Table 3: Treatment coverage by trial area.

Trial	Census population	Treated with ivermectin No.	%
Bui	1,573	1,065	67.7
Asubende	26,117	14,991	61.5*
Kara	21,437	12,924	60.3
Comoe	22,575	12,436	55.1
Pendie	2,965	1,390	63.4*
Milo	3,659	2,327	63.6
Tienfala	4,435	2,632	59.3
Mako	4,802	3,164	65.9
Total	87,563	50,929	59.9*

*Excluding villages where only skin snip positives have been treated

Severe adverse reactions in the total treated population

The incidence of severe adverse reactions by trial area is shown in Table 4. The most frequent severe reaction encountered was SSPH which was diagnosed in 49 patients. However, three of the five cases from the Kara trial were not confirmed by the supervising medical officer. The majority of SSPH cases (37) were diagnosed in Asubende but no case of SSPH was detected during the last four trials where, instead, four cases of severe dizziness were reported. These differences between the trials are partially a result of changes in the monitoring procedure for SSPH. In the first two trials all treated persons were asked to report with any complaint at the monitoring station at a central location in the village. Following the unexpectedly high incidence of SSPH in Asubende, where several cases actually collapsed at the monitoring post, all treated persons were advised in the subsequent trials to lie down in case of dizziness or general weakness and to send somebody to fetch the nurse. It is most likely that this change in procedure reduced the incidence of SSPH by eliminating the physical stress of walking to the monitoring station in patients who were already dizzy and weak. Furthermore, the operational definition of SSPH requires that a patient should attempt to stand for more than two minutes while the blood pressure is being taken. However, because of the accumulated experience with SSPH, it was decided for the last four trials not to request patients who felt very dizzy to stand up and a possible SSPH could therefore no longer be diagnosed.

Treatment in the form of a single dose of 200mg of hydrocortisone sodium succinate was given in nine SSPH cases. These included a lightly infected (25 mfs/snip) woman of 27 years of age for whom no blood pressure nor pulse could be detected by the examining nurse. Another woman of the same age had an unperceptible pulse and a blood pressure of 70/40, but she remained alert all the time. The other seven patients were either "toxic" or the SSPH had recurred on retesting 5-12 hours later. All nine patients improved, usually within 2-4 hours, with the ability to sustain an adequate standing blood pressure.

Table 4: Severe adverse reactions by trial area.

		All severe reactions		SSPH		SSPH or severe dizziness		Severe fever		Severe dys-pnoea		Severe pain	
Trial name	Number treated	No	per 1000	No	per 1000	No	per 1000	No	per 1000	No	per 1000	No	per 1000
Bui	1,065	1	0.94	1	0.94	1	0.94	0	0.00	0	0.00	0	0.00
Asubende	14,991	52	3.47	37	2.47	37	2.47	13	0.87	2	0.13	0	0.00
Kara	12,924	10	0.77	5	0.39	5	0.39	5	0.39	0	0.00	0	0.00
Comoe	12,436	20	1.61	6	0.48	6	0.48	11	0.88	1	0.08	2	0.16
Pendie	1,390	3	2.16	0	0.00	0	0.00	3	2.16	0	0.00	0	0.00
Milo	2,327	4	1.72	0	0.00	3	1.29	1	0.43	0	0.00	0	0.00
Tienfala	2,632	2	0.76	0	0.00	1	0.38	1	0.38	0	0.00	0	0.00
Mako	3,164	1	0.32	0	0.00	0	0.00	0	0.00	0	0.00	1	0.32
Total	50,929	93	1.83	49	0.96	53	1.04	34	0.66	3	0.06	3	0.06

There were three cases of severe dyspnoea, one of laringeal oedema and two cases of severe asthma in known asthmatics. All three cases occurred within 24 hours after ivermectin treatment and they required prompt and intense medical intervention. A pre-treatment skin biopsy was taken only in one of the severe asthma cases and the snips were negative. Severe fever was more frequent in children in part because of the lower cut-off point used in this age group. All cases of severe fever and severe pain responded to treatment with paracetamol or paracetamol and chloroquine.

Adverse reactions in villages with resident monitoring

The incidence of adverse reactions of all grades of severity has been analysed for villages with resident monitoring only because mild and moderate reactions are likely to be under-reported in villages with mobile monitoring in which a nurse visits a village only shortly one or more times per day.

Table 5: Incidence of different types of adverse reactions in villages with resident monitoring (number treated = 31,260).

	Incidence of adverse reaction					
	Any reaction		Moderate reaction		Severe reaction	
Type of reaction	No.	%	No.	%	No.	%
Pain conditions	1746	5.59	253	0.81	2	0.006
Cutaneous reactions	945	3.02	218	0.70	0	0.000
Fever and chills	824	2.64	209	0.67	28	0.090
Swelling	809	2.59	118	0.38	0	0.000
Gland reactions	354	1.13	146	0.47	0	0.000
Eye reactions	116	0.37	5	0.02	0	0.000
SSPH or severe dizziness	46	0.15	0	0.00	46	0.147
Dyspnoea	11	0.04	0	0.00	1	0.003
Other complaints	464	1.48	21	0.07	0	0.000
Most severe reaction	2815	9.01	745	2.38	76	0.243

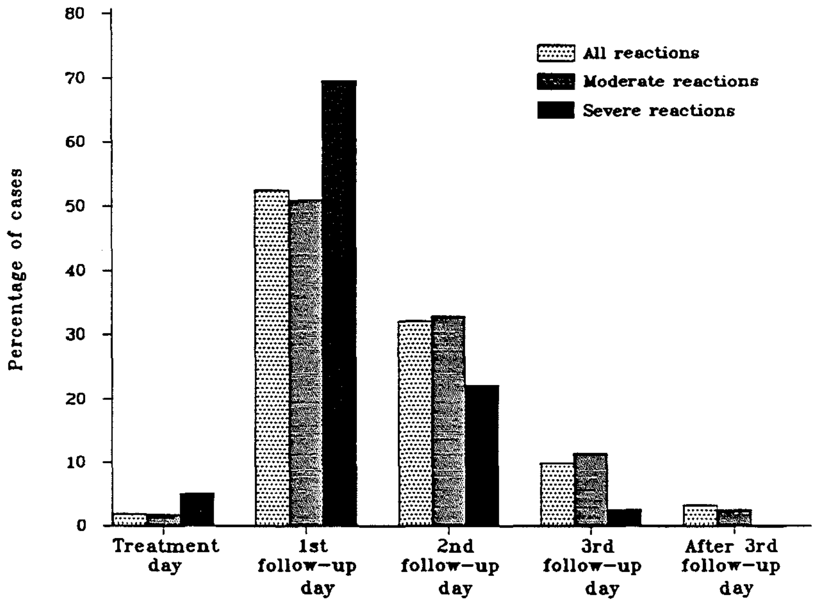
Type of reactions.

In the villages with resident monitoring a total of 31,260 people were treated with ivermectin and 2,815 of them (9.0%) reported with one or more adverse reactions (see Table 5). The most frequent reactions were pain conditions, followed by cutaneous reactions, fever, swelling and gland reactions. Most of these reactions were classified as mild. The proportion of reactions classified as moderate was higher for gland reactions than for the other types of reactions. The group of 'other complaints' covers a variety of reactions of which dizziness was the most common one.

Hardly any adverse reactions occurred during the day of treatment itself, but more than half of all reactions were reported during the first day after treatment and the incidence of reactions decreased progressively during the subsequent days of monitoring (see Fig.2). The proportion of reactions reported during the first day of follow-up was much higher for severe reactions, mainly because 80% of the SSPH cases and all severe dyspnoea cases were reported during the first follow-up day. There was not much difference in the time of reporting between the other type of reactions even though gland reactions and swelling appeared to be slightly delayed.

Fig.2: Day of first reporting of adverse reactions.

Villages with resident monitoring only (N=2,815 cases with reaction)

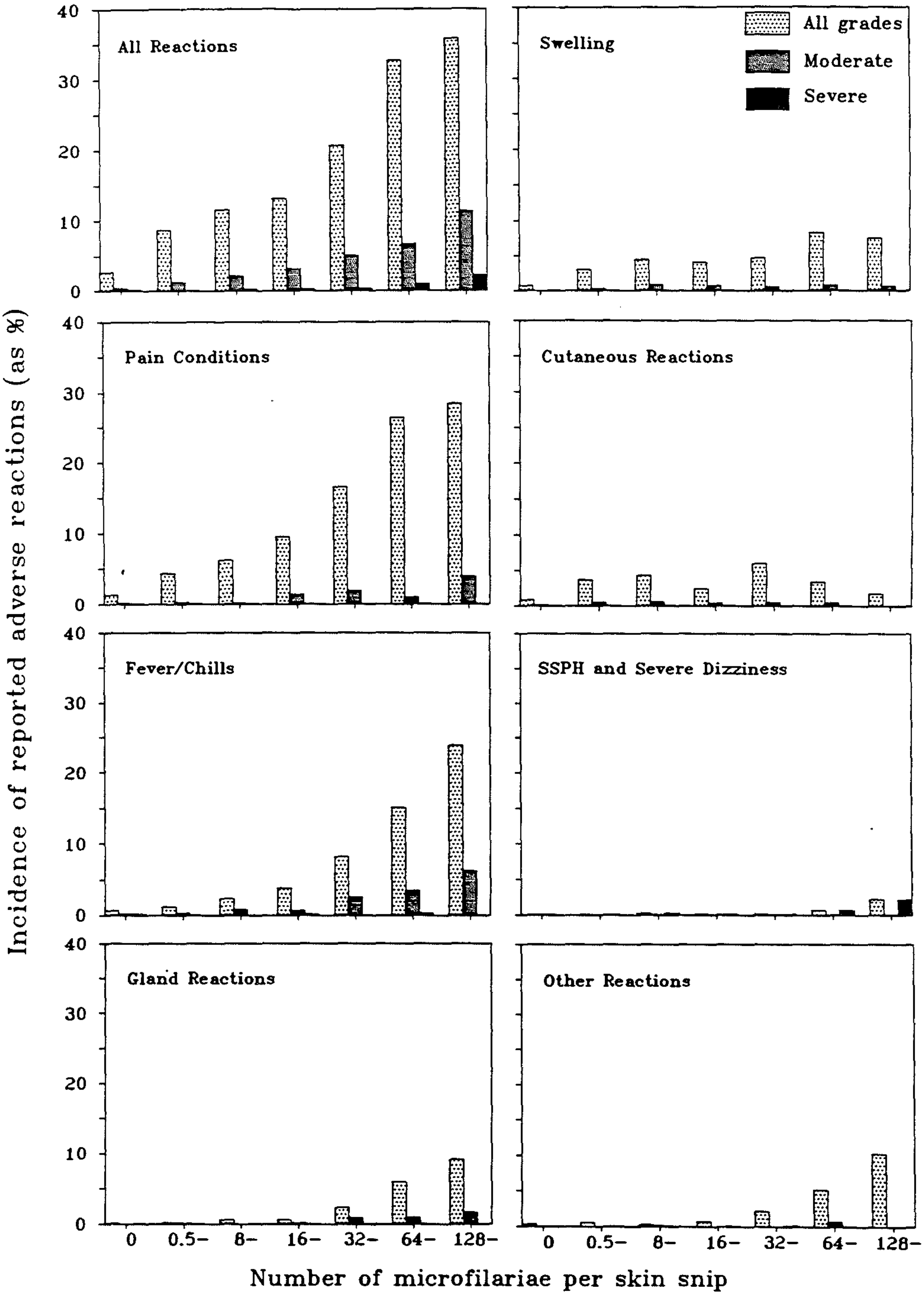


Relationship with intensity of infection.

The relationship between the incidence of adverse reactions and the intensity of infection was studied for 7,239 treated patients from six trials for whom pre-treatment skin snip results were available. Figure 3 shows that the incidence of reactions was directly related to the mf load in the skin. The incidence of severe, moderate and all reactions increased from 0.1%, 0.3% and 2.7% in the skin snip negative group to 2.3%, 11.4% and 35.8% respectively in people with more than 128 mf/s and the relationship is highly significant for all three grades of severity (logistic regression analysis: $P<0.001$ in each case).

Fig.3: Incidence of different types of adverse reactions in relation to skin microfilarial load.

Villages with resident monitoring only (N=7,239)



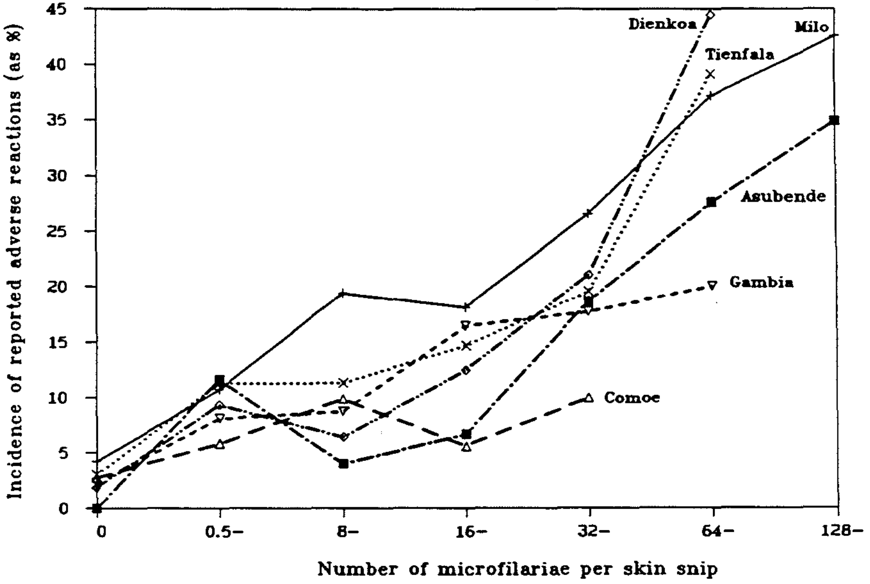
It may be noted that the severe reactions in the skin snip negative group concerned four cases of severe fever. An equally clear relationship was observed for pain conditions, fever, gland reactions, other reactions and to a lesser extent for swelling (P<0.001 in each case). However, cutaneous reactions showed a quite different pattern. They were significantly more frequent in skin snip positives compared to skin snip negatives (P<0.001), but within the skin snip positive group there was no increase in cutaneous reactions with increasing mf load (P=0.83) and the lowest incidence was actually observed in the group with the highest intensity of infection. SSPH and severe dizziness are shown together in Figure 3 and, even though the number of cases involved is small, their combined incidence as well as the incidence of SSPH alone were also significantly related to the intensity of infection (P<0.001).

Variations between trial areas.

The incidence of adverse reactions ranged from the lowest rates of 4.8%, 5% and 6% for the Kara, Pendie and Comoe trials, via intermediate values of 7.9% for Mako and 9.5% for Tienfala to maxima of 14.9% for Asubende and 15.7% for the Milo trial. This variation correlates well with the ranking of the endemicity levels of the trials (see Table 1) and this suggests that the differences may be due to variations in intensity of infection between trials. The results on adverse reactions were therefore also compared between trials after correction for intensity of infection and the results are shown in Figure 4. In each trial area there was a statistically significant relationship between the incidence of adverse reactions and skin mf load (P<0.001). The relationships were similar but the incidence of adverse reactions in the Milo trial was systematically higher than in the other trials (P<0.001). In the Comoe trial there appeared to be a slower increase in adverse reactions with intensity of infection but the mf loads in this trial were low and the difference was only of borderline significance (P=0.032). There was no difference between the other trials (P=0.83).

Fig.4: Incidence of adverse reactions in different trial areas in relation to skin microfilarial load.

Villages with resident monitoring only (N=7,239)

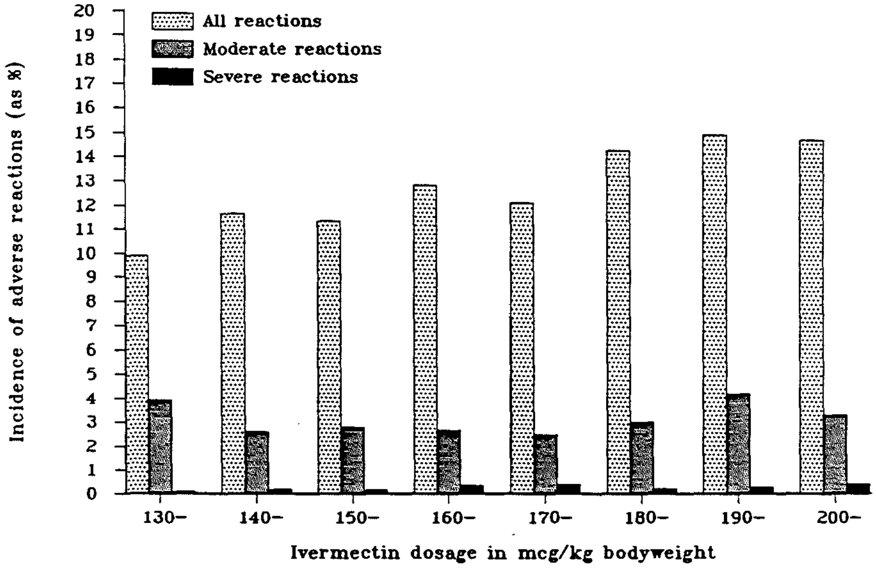


Ivermectin dosage.

The bodyweight and the number of ivermectin tablets had been recorded per person and the exact ivermectin dosage taken could be calculated. The dosage ranged from 100 to 200 mcg/kg in children and from 130 to 200 mcg/kg in adults. After correction for mf load there was a statistically significant relationship between the incidence of all reactions and ivermectin dosage ($P<0.001$), but no such relationship existed for moderate reactions ($P=0.84$) nor for severe reactions ($P=0.63$). The implication of this finding is illustrated in Figure 5 which shows the incidence of adverse reactions by dosage in 15,601 persons with an age of more than 20 years. This age limit was introduced to eliminate the confounding effect of intensity of infection (Remme et al 1986). The figure shows that there is indeed an increase in the total incidence of adverse reactions with ivermectin dosage but the difference in incidence between the lowest and highest dosage group is very small.

Fig.5: Incidence of adverse reactions in relation to ivermectin dosage

Adults with an age of 20 years or above
in villages with resident monitoring only (N=15,601)



Delayed reactions and mortality

Delayed reactions refer to reactions which occurred after the 72 hours monitoring period and the departure of the monitoring team. During a 4-week follow up visit in the Asubende trial area a total of 13 people reported delayed reactions. Because of this finding a follow-up visit was undertaken in each of the six remaining trials two weeks after ivermectin distribution. The most frequent delayed reaction was swelling (19 cases) and this was reported in five trials. In Asubende five cases with abscesses and one pyoarthrosis were seen but none was reported for the other trials. A case of delayed gland reaction was reported in three of the trials. Two patients were hospitalized for pulmonary infections. Two cases of joint pain, one paresthesia, one fever and one abortion were also reported.

None of the 50,929 persons treated with ivermectin was reported to have died during the 72 hours monitoring period and only one death was reported during the follow-up visit. This concerned a 38 year old male who according to his wife had had an episode of generalized pain, perspiration and marked weight loss two weeks before ivermectin distribution. During the treatment day he had walked to the treatment post where he received ivermectin on 14 April 1988. Two days later he reported with chest pain to the monitoring nurse and he was treated with paracetamol. Fever started on 18 April after the departure of the monitoring team and lasted until his death the 23rd of April. His relative attributed his death to a condition called "white jaundice" which according to the local nurses refers to acute anaemia caused by malaria or another infective disease.

Microfilaricidal effect by endemicity level.

Follow-up skin snip surveys were done in selected villages from three of the trial areas in order to study the microfilaricidal effect of ivermectin for different endemicity levels, and the results are shown in Table 6. Three villages were selected from the Asubende trial and these were the most endemic villages from all the eight trials. The CMFL, which is based on skin snip counts for adults, was as high as 64.4 mf/s and the pre-treatment geometric mean mf/s in treated patients from all age groups was equal to 45.4 mf/s. A sample of less infected but still hyper endemic villages was taken for the Milo trial. Finally, several villages with a very low endemicity level were included from the Pendie trial. Table 6 shows the changes in skin microfilarial loads which were seen in treated patients two weeks after treatment in the Milo trial and two months after treatment in the Asubende and Pendie trial. In the Asubende trial more than half of the skin snip positives had turned skin snip negative after treatment, while in the Pendie trial more than 90% of skin snip positives had reverted. On the average there was a reduction of about 98% in skin mf loads. The percentage reduction was similar for the different endemicity levels and certainly not less pronounced in the most endemic villages. In each of the three trials there were a few cases, representing some 2-3% of patients with high mf loads, who responded poorly or not at all to ivermectin treatment.

Table 6: Reductions in skin mf loads in treated patients from follow-up villages with different endemicity levels.

			Prevalence of mf in treated persons		Geometric mean mf/s in treated persons (95% confidence interval)		
Trial	Endemicity level as measured by CMFL	Number treated and followed up	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Percentage reduction in mean mf/s
Asubende	64.4	497	93.0%	44.3%	45.43 (39.64-52.05)	0.70 (0.58-0.84)	98.5
Milo	18.3	549	83.2%	22.6%	11.90 (10.26-13.79)	0.25 (0.20-0.31)	97.9
Pendie	3.2	416	43.8%	4.1%	1.42 (1.13-1.73)	0.04 (0.02-0.06)	97.3

DISCUSSION

Rarely, if ever, has the safety of a new drug for mass treatment been tested as extensively as has been done for ivermectin, and the community trials of this drug were an exceptional effort. The OCP has completed eight community trials in eight of the participating countries and has managed to treat and monitor more than 50,000 people within a period of less than a year. Furthermore, another five community trials are being undertaken by investigators from outside the OCP area.

The overall treatment coverage in the OCP trials was 60% of the census population. The lowest coverages were obtained in trials with the most mobile populations where there was a high rate of absenteeism at the time of treatment. The main reasons for non-treatment were the exclusion criteria, and particularly the minimum age limit of 5 years. In our opinion it is unlikely that mass treatment coverage can be greatly increased without major changes in the existing exclusion criteria.

Ivermectin treatment had an equally dramatic microfilaricidal effect as in the clinical trials (Aziz et al 1982, Greene et al 1985, Lariviere et al 1985, Awadzi et al 1986, Diallo et al 1986, White et al 1987) and reduced skin microfilarial loads by some 98%. The percentage reduction was the same over a wide range of endemicity levels. It was particularly gratifying to see that the drug was equally effective in the villages with the highest endemicity levels where ivermectin mass treatment is most indicated because of the high risk of developing onchocercal eye lesions and blindness. A few people did not respond to ivermectin treatment. It is possible that this was only due to malabsorption of the drug but these cases will nevertheless be studied in detail during the second round of treatment.

The total incidence of adverse reactions was much lower in the community trials than in the clinical trials (WHO 1976). This is not surprising given the differences in the treated populations and monitoring procedures, i.e. passive field monitoring in communities where treatment was given irrespective of infection versus regular clinical examinations of hospitalized patients who all had moderate to severe infections. However, the type of reactions were generally similar and included various pain conditions, fever, itching, rash, lymph node enlargement and oedema. Not reported previously were inguinal gland pain and brawny oedema of the limbs which were fairly common in the most endemic trial areas where gland pain could be a significant cause of morbidity and last for several days.

The incidence of adverse reactions was directly related to the skin mf load. This strongly suggests that the observed reactions were due to the microfilaricidal effect of ivermectin and not a result of intrinsic toxicity of the drug or completely unrelated morbidity for which the population was seeking medical help. The relationship with skin mf load was significant for all the different types of adverse reactions with the exception of cutaneous reactions which were more frequent in skin snip positives but for which there was no increase in incidence with increasing mf load. The relationship with intensity of infection explains why adverse reactions were much more common in the most endemic trial areas. After correction for intensity of infection there was a similar incidence of adverse reactions in all trials. Only in the Milo trial remained the incidence of reactions somewhat higher. The differences between types of reactions in their relationship with mf load explain differences in the pattern of reactions between trials. Cutaneous reactions did not increase with mf load and they were therefore relatively common in trials with the lowest endemicity but ranked only fifth in the most endemic trials. On the other hand, the incidence of gland reactions started only to increase for high mf loads and these reactions were nearly exclusively found in foci of high endemicity. Within the observed ivermectin dosage range of 100 to 200 mcg/kg there was no relation between moderate or severe reactions and dosage, but mild reactions were less common in the lower dosage range. However, the difference was very small and it seems unlikely that a major reduction in adverse reactions can be achieved by reducing the dosage without severely limiting the microfilaricidal effect of the drug.

The majority of the reported adverse reactions were mild, transient and required no treatment. All moderate reactions, with the exception of gland reactions, responded well to simple treatment with paracetamol, phenergan and chloroquine. A total of 97 severe adverse reactions were reported. The most common was SSPH which was diagnosed in 49 cases. Nine of these were given treatment in the form of intravenous injection of hydrocortisone and they all improved promptly, usually within two to four hours. The other SSPH cases recovered without treatment after several hours of rest in the supine position. Severe fever was the second most common severe reaction and all cases were successfully managed by treatment with paracetamol or paracetamol with chloroquine. SSPH and severe fever showed both a statistically significant relationship with the intensity of infection which indicates that SSPH and most of the severe fevers were definite adverse reactions to ivermectin treatment.

The three cases of severe dyspnoea were life threatening events which occurred within 24 hours after ivermectin intake in three villages with relatively low endemicity levels. This condition had not been reported in the clinical trials. One patient with laryngeal oedema had an upper respiratory tract infection which preceded ivermectin treatment and may have led to the severe episode. He was found to have a lobar pneumonia subsequently. It was the only reported case of oedema of the upper respiratory tract of any degree of severity and a causal relation with ivermectin treatment is doubtful. Two episodes of severe asthma occurred in known asthmatic patients. A pre-treatment skin snip was taken for one of them and no microfilariae had been detected. Two mild attacks of asthma were also reported. All asthmatic attacks occurred in known asthmatics. The possibility that ivermectin treatment precipitates asthmatic attacks in known asthmatics cannot be excluded and this question should receive further attention during future mass treatments with ivermectin.

Virtually no adverse reactions were reported during the day of treatment itself. However, more than half of all reactions, two third of severe reactions, 80% of SSPH cases and all three severe dyspnoea cases were reported during the first day after treatment. Only a limited number of cases who had mainly mild reactions reported during the third follow-up day and it would appear that the monitoring period of 72 hours may be reduced during future mass treatments with ivermectin. A few delayed reactions were reported during follow-up visits after two to four weeks. Most of these were mild and their relation with ivermectin treatment was doubtful. Only for swelling, which was the most common delayed reaction, is it likely that such a relationship exists because it was reported for several trials.

No deaths were reported among treated persons during the 72 hours monitoring period and only one death, for which there was no indication of a relationship with ivermectin treatment, was reported during the follow-up visits. This number of deaths is far below the number which would be expected normally in a population of this size during a two week period. One explanation for this discrepancy is that most deaths occurred in people who were already severely ill at the time of ivermectin distribution and who were therefore excluded from ivermectin treatment. However, it is also quite possible that a number of deaths were not reported during the follow-up visits.

The combined results on adverse reactions in more than 50,000 treated persons from endemic onchocerciasis foci indicate that ivermectin is sufficiently safe to be used for mass treatment of onchocerciasis. Adverse reactions did occur, but all were transient and they were managed successfully by the monitoring teams. The discomfort, which was experienced by part of the treated population as a result of adverse reactions, was more than compensated by the massive reductions in mf loads in treated patients and by the associated decrease in the risk of developing onchocercal pathology which is a function of the intensity of infection (WHO 1976). It has been shown above that the incidence of adverse reactions is also related to the intensity of infection. This implies that the benefit of ivermectin mass treatment will be greatest in those communities where adverse reactions are most frequent. The incidence and severity of adverse reactions will be much lower in less endemic areas and during retreatment of hyperendemic areas after six to twelve months when the mf loads in treated patients will not yet have returned to the pre-treatment levels. Nevertheless, a few medical emergencies did occur and these were in patients from villages with relatively low levels of endemicity. It is, therefore, recommended that mass treatment with ivermectin should involve monitoring by resident nurses for a period of at least 36 hours after treatment in any onchocerciasis focus, irrespective of the level of endemicity.

REFERENCES

Awadzi,K. The chemotherapy of onchocerciasis II. Quantitation of the clinical reaction to microfilaricides. *Annals of Tropical Medicine and Parasitology*, 74 (1980) 189-197.

Awadzi,K., K.Y.Dadzie, H.Schulz-Key, H.M.Gilles, A.J.Fulford, M.A.Aziz. The chemotherapy of onchocerciasis XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Annals of Tropical Medicine and Parasitology*, 80 (1986) 433-442.

Aziz,M.A., S.Diallo, I.M.Diop, M.Lariviere, M.Porta. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet*, ii (1982) 171-173.

De Sole,G., K.Awadzi, J.Remme, K.Y.Dadzie, O.Ba, J.Giese, M.Karam, F.M.Keita, N.O.Opoku. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. II. Adverse reactions. *Tropical Medicine and Parasitology*, 40 (1989) 375-382.

Diallo,S., M.A.Aziz, M.Lariviere, J.S.Diallo, I.Diop, O.N'Dir, S.Bandiane, D.Py, H.Schulz-Key, P.Gaxote, A.Victorius. A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 80 (1986) 927-934.

Greene,B.M., H.R.Taylor, E.W.Cupp, R.P.Murphy, A.T.White, M.A.Aziz, H.Schulz-Key, S.A.D'Anna, H.S.Newland, L.P.Goldschmidt, A.Auer, A.P.Hanson, V.Freeman, E.W.Reber, P.N.Williams. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *New England Journal of Medicine*, 313 (1985) 133-138.

Lariviere,M., P.Vingtain, M.A.Aziz, B.Beauvais, D.Weimann, F.Derouin, J.Ginoux, H.Schulz-Key, P.Gaxote, D.Basset, C.Sarfati. Double-blind study of ivermectin and diethylcarbamazine in african onchocerciasis patients with ocular involvement. *Lancet*, ii (1985) 174-177.

Merck, Sharp and Dohme. *Mectizan™, Product monograph*. Merck & Co. Inc. Rahway N.J. (1988)

Prost,A., J.Prod'hon. Le diagnostique parasitologique de l'onchocercose, revue critique des méthodes en usage. *Médecine Tropicale*, 38 (1978) 519-532.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Remme,J., R.H.A.Baker, G.De Sole, K.Y.Dadzie, M.A.Adams, E.S.Alley, H.S.K.Avissey and J.F.Walsh. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect on the microfilarial reservoir and the transmission of *Onchocerca volvulus*. *Tropical Medicine and Parasitology*, 40 (1989) 367-374.

White,A.T., H.S.Newland, H.R.Taylor, C.D.Erttmann, E.Keyvan-Larijani, A.Nara, M.A.Aziz, S.A.D'Anna, P.N.Williams and B.M.Greene Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *Journal of Infectious Diseases*, 156 (1987) 463-470.

World Health Organization. *Epidemiology of onchocerciasis:* report of a WHO Expert Committee. WHO Technical Report Series, No. 597 (1976)

Chapter 5.3

Changes in ocular onchocerciasis four and twelve months after community-based treatment with ivermectin in an holo-endemic onchocerciasis focus

Transactions of the Royal Society for Tropical Medicine and Hygiene (in press)

INTRODUCTION

Ivermectin has been shown in clinical trials to be an effective, long acting microfilaricide with little adverse reactions, easy to apply as a single oral dose, and has been esteemed to be suitable for mass treatment, (Aziz et al 1982, Coulaud et al 1983, Coulaud et al 1984, Awadzi et al 1985, Greene et al 1985, Lariviere et al 1985, Awadzi et al 1986, Diallo et al 1986, White et al 1987, Awadzi et al 1989). Ophthalmological studies have also shown the drug to be safe to the eye but the studies have involved few patients and hardly any candidates with heavy ocular microfilarial load in the eye, (Taylor et al 1986, Dadzie et al 1987, Newland et al 1988, Dadzie et al 1989). One study has reported disc leak in fluorescein angiography unassociated with functional deficit and has stressed the need for further studies in heavily infected patients to ensure the safety of ivermectin to the eye in such patients (Dadzie et al 1987).

Consequently at its registration in 1987, there was a need for ophthalmological studies to be incorporated in the community trials which were started in the same year, (De Sole et al 1989, Remme et al 1989), with the view to confirm the clinical results with regard to the efficacy and safety in the treatment of unselected population with ivermectin, as well as to show the long term benefit to be derived from repeated ivermectin mass treatment in the prevention of eye morbidity and blindness.

This paper reports on the ophthalmological changes in an extremely highly endemic savanna onchocerciasis focus, four and twelve months after community-based treatment with ivermectin.

PATIENTS AND METHODS

Study population:

A community trial with ivermectin was started in an isolated savanna onchocerciasis focus in Ghana with a census population of about 25,000 in October 1987, (Remme et al 1989, De Sole et al 1989). The population living in three settlements with the highest endemicity of onchocerciasis were selected for the ophthalmological study. In these communities the Community Microfilarial Load (CMFL, Remme et al 1986) ranged from 58 to 73 mf per skin snip. Five hundred and eighty six persons aged 5 years and over, out of the total census of 864 from the three communities, were examined ophthalmologically before the mass treatment. The ophthalmological examination was repeated four and twelve months thereafter by the same observer. All persons present at the villages at the time of the follow-up examinations, including those not examined before ivermectin treatment, were examined to encourage participation by the entire population.

Drug administration

Ivermectin tablets were given as a single oral dose at approximately 150 mcg/kg body weight to the population in the study area who qualified for treatment under the direct supervision of a nurse or a medical officer. Excluded from treatment were children under the age of 5 years or with a weight of less than 15 kg, women who were pregnant or breastfeeding a baby less than 1 month old, and people with jaundice, severe anaemia, a disease of the central nervous system or severe illness. The details of the organisation of the treatment has been reported elsewhere (De Sole et al 1989).

Methods:

Detailed ophthalmological examination was done in all subjects aged 5 years or more. Visual acuity test with Sjogren's hand test type was undertaken in broad daylight and all other examinations in an ophthalmic mobile clinic. Slit lamp examination of the anterior segment started with the counting of microfilariae in the anterior chamber of each eye after the patients had bent down their heads between their knees for at least two minutes (Dadzie et al 1986). This was followed by the counting of live and dead microfilariae in the cornea as well as punctate opacities. Contrary to past practice the exact microfilarial count was recorded. Signs of sclerosing keratitis and other corneal pathology and iridocyclitis were then looked for. Fundus examination with the direct and indirect ophthalmoscope was carried out after dilatation of the pupil with mydriacil 1% to elicit signs of onchocercal choroido-retinitis, optic nerve disease and other fundus pathology. The results of the examination were recorded on a standard OCP form for each individual on each occasion without consulting the records of previous examinations.

Analytical indices used:

For the analysis of the results of this study the four typical onchocercal eye lesions were classified into three grades, viz. no lesion, (being absence of signs of any lesion), early lesion and advanced lesion which were defined as follows:

i. Sclerosing keratitis.

- a) An early sclerosing keratitis was a corneal opacity limited to the nasal or temporal periphery or both.
- b) An advanced sclerosing keratitis was a corneal opacity more extensive than the former, presenting as an inferior semi-lunar opacity but which could extend to cover the pupil area.

ii. Iridocyclitis

- a) An early iridocyclitis was the condition in the acute or chronic stage but without synechiae.
- b) An advanced iridocyclitis existed when in addition to the signs of the early stage either anterior or posterior synechiae had developed.

iii. Choroido-retinitis

- a) An early choroido-retinitis was the presence of retinal pigment epithelial atrophy, typically located temporal to the macular area.
- b) An advanced choroido-retinitis existed when atrophy of chorio-capillaris, choroido-retinal scarring or sub-retinal fibrosis could be seen in addition to the atrophy of retinal pigment epithelium.

iv. Optic atrophy

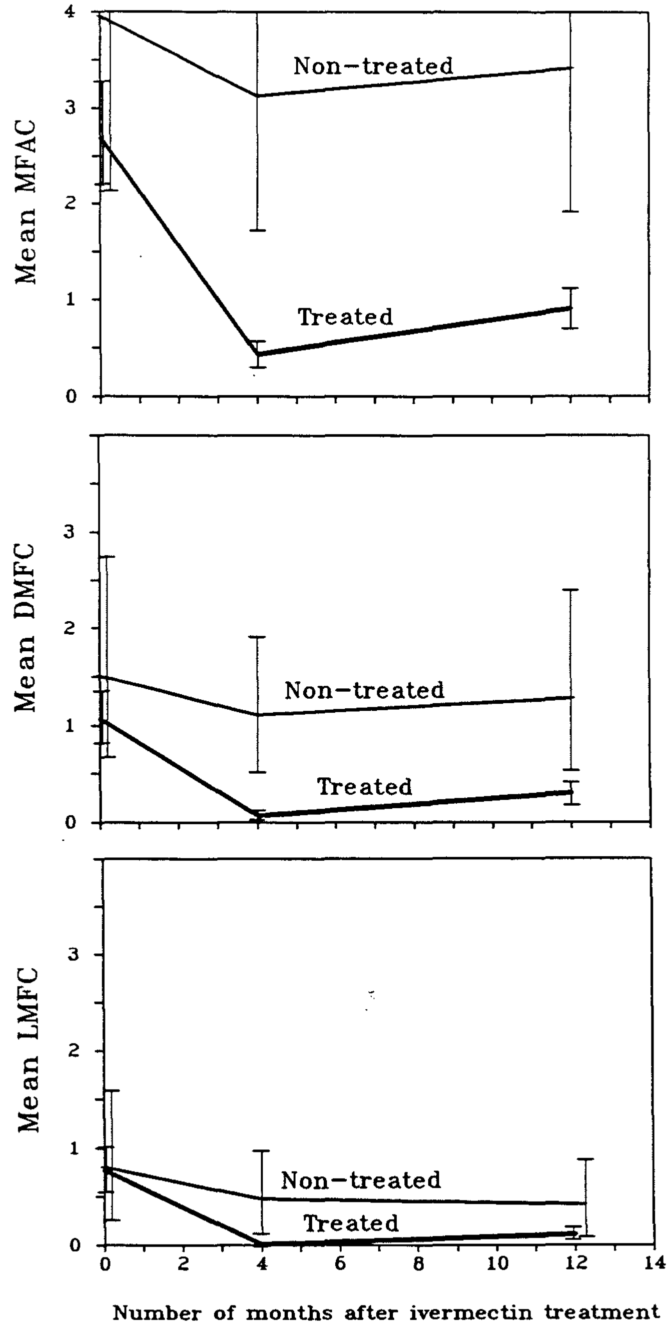
- a) An early optic atrophy comprised the early pallor of the disc or the acute or chronic optic neuritis.
- b) An advanced optic atrophy was the frank optic atrophy, presenting as post-neuritic optic atrophy, often associated with sheathing of the central retinal vessels and increased peri-papillary pigmentation or the secondary optic atrophy consecutive to retinal disease.

Statistical analysis:

Data processing was done on microcomputers running under MS-DOS using routine computer programmes developed in the OCP. SPSS/PC was applied for the final analysis. Only data from the right eye of 417 patients who had had a complete ophthalmological examination at all three surveys were considered for the analysis. Of those, 369 patients were treated with ivermectin and 48 had been excluded from treatment. Geometric mean microfilarial loads were calculated using the log(x+1) transformation. Differences in microfilarial loads were tested for statistical significance using the Wilcoxon signed rank sum test for comparisons between surveys and the Mann-Whitney U test for comparisons between the treated and non-treated group. Relative trends in mean loads in the treated group were corrected for possible systematic differences in counting between surveys by multiplication with the ratio between the pre- and post-treatment mean counts in the non-treated group.

Fig.1: Changes in geometric mean microfilarial counts in the eye following mass treatment with ivermectin

(Vertical lines represent 95% confidence limits)



The four typical onchocercal eye lesions were allocated a score of 0 for no lesion, 1 for early lesion and 2 for advanced lesion. The significance of changes in ocular lesions within the treated and non-treated group were tested using the Wilcoxon signed rank sum test on pre- and post-treatment scores for each lesion. For the comparison of the changes between the two groups the Mann-Whitney U test was applied to the difference between pre- and post-treatment scores in cases with a change in score. In 21 persons it was not possible to arrive at a classification for all lesions because of a partial obstruction of view during examination, usually as a result of other onchocercal pathology. This affected in particular posterior segment lesions. In 16 cases the view of the posterior segment was completely blocked during at least one examination, and in 10 of them during all three examinations. For similar reasons it was not possible to obtain counts of microfilariae in the anterior chamber of the eye for five persons, four of whom were treated, and of living microfilariae in the cornea in three treated persons. These cases with missing data were excluded from the analysis for the respective lesion or microfilarial load.

RESULTS

Figure 1 shows the trend in the intensity of onchocercal ocular infection as expressed by the geometric mean microfilarial count in the anterior chamber of the eye (MFAC), of the dead microfilarial count in the cornea (DMFC) and of the living microfilarial count in the cornea (LMFC). In the non-treated group there was no statistically significant change in the mean microfilarial loads during the 12 months follow-up period, though the loads were slightly lower at month 4 review. In the group treated with ivermectin, the mean ocular microfilarial loads fell to very low levels 4 months after treatment. Between the 4 and 12 months follow-up, however, there was an increase in microfilarial count which was statistically significant for all three indices used ($P<0.001$ for each index). Figure 2 shows for the treated group the relative trends in the mean microfilarial loads after correction for systematic differences between surveys as seen in the non-treated group. Four months after treatment the mean microfilarial load in the anterior chamber of the eye had reduced to 20% of the pre-treatment value and the mean number of dead and living microfilariae in the cornea to 9% and 2% respectively. At 12 month follow-up, the levels had risen to 39% of the pre-treatment value in the anterior chamber and to 33% and 27% respectively for the dead and living microfilariae in the cornea.

Fig.2: Trend in ocular microfilarial loads after ivermectin treatment (Asubende, Ghana)

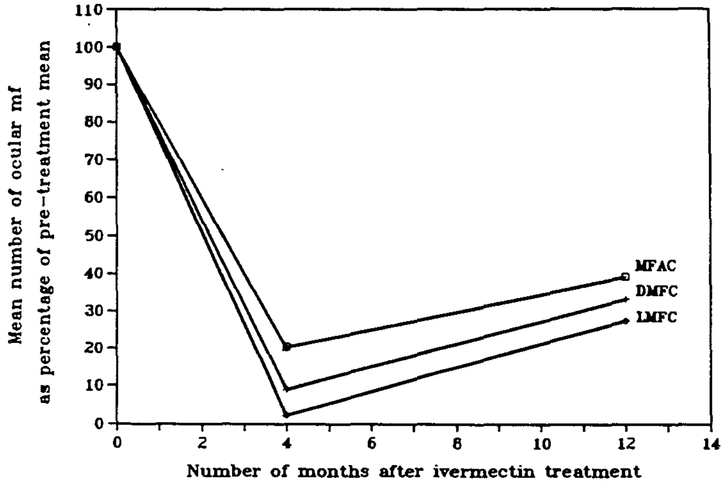


Table 1: The post-treatment distribution of microfilarial loads in the anterior chamber of the eye (MFAC) of 365 treated persons in relation to pre-treatment loads (percentage per pre-treatment group between brackets)

MFAC pre-treatment	No. of persons	MFAC 4 months post-treatment					MFAC 12 months post-treatment				
		0	1-	4-	10-	32-	0	1-	4-	10-	32-
0	167	164	2	0	1	0	154	12	0	1	0
		(98.2)	(1.2)	(0.0)	(0.6)	(0.0)	(92.2)	(7.2)	(0.0)	(0.6)	(0.0)
1-	48	45	1	1	1	0	32	14	1	1	0
		(93.8)	(2.1)	(2.1)	(2.1)	(0.0)	(66.7)	(29.2)	(2.1)	(2.1)	(0.0)
4-	32	29	2	1	0	0	15	9	5	2	1
		(90.6)	(6.3)	(3.1)	(0.0)	(0.0)	(46.9)	(28.1)	(15.6)	(6.3)	(3.1)
10-	92	61	9	14	7	1	30	27	20	14	1
		(66.3)	(9.8)	(15.2)	(7.6)	(1.1)	(32.6)	(29.3)	(21.7)	(15.2)	(1.1)
32-	26	2	5	6	8	5	0	4	5	8	9
		(7.7)	(19.2)	(23.1)	(30.8)	(19.2)	(0.0)	(15.4)	(19.2)	(30.8)	(34.6)
Total	365	301	19	22	17	6	231	66	31	26	11
		(82.5)	(5.2)	(6.0)	(4.7)	(1.6)	(63.6)	(18.1)	(8.5)	(7.1)	(3.0)

Table 1 shows the post-treatment distribution of microfilarial loads in the anterior chamber of the eye in relation to the pre-treatment loads. The majority of the people with pre-treatment microfilarial counts of less than 10 had lost their microfilariae at the 4 month follow-up and only a few of them remained with counts of more than 4 in their anterior chamber. However, half of the people who had initially 32 microfilariae or more in their anterior chamber still had loads of 10 or more. At 12 months the microfilarial counts of the anterior chamber of the eye had increased generally and those who attained high counts were those who originally had high counts. In particular, one third of those who originally had more than 32 microfilariae, presented again with counts in excess of this level. In the cornea, similar changes were recorded for the counts of dead microfilariae.

Tables 2 and 3 summarize the changes with respect to the onchocercal lesions of the anterior and posterior segment of the eye respectively. The post-treatment classification of the presence and severity of each lesion is shown in relation to the pre-treatment classification of the same eye in order to allow the assessment of both random variation and systematic changes. The results for the treated and non-treated group are presented separately to enable the comparison of the changes in the two groups and the appraisal of a possible impact of ivermectin treatment on ocular lesions.

Table 2: The classification of onchocercal lesions of the anterior segment of the eye four and twelve months after ivermectin mass treatment in relation to the pre-treatment classification.

		Post treatment lesions						
		Non-treated group			Treated group			
Type of lesion	Pre-treatment lesion	None	Early	Adv	None	Early	Adv	Significance of change*
		Four months follow-up						
Sclerosing Keratitis	None	38	4	-	296	9	-	a) P=0.22
	Early	1	2	-	19	24	2	b) P=0.16
	Advanced	-	-	3	-	1	18	c) P=0.06
Iridocyclitis	None	34	2	-	313	-	-	a) P=0.74
	Early	2	5	1	25	10	1	b) P<0.001
	Advanced	-	2	2	1	1	16	c) P<0.01
		Twelve months follow-up						
Sclerosing Keratitis	None	40	2	-	295	10	-	a) P=0.36
	Early	1	1	1	23	20	2	b) P=0.04
	Advanced	-	-	3	-	4	15	c) P=0.08
Iridocyclitis	None	33	3	-	307	6	-	a) P=1.0
	Early	2	5	1	23	11	3	b) P<0.005
	Advanced	-	2	2	4	2	12	c) P=0.10

* a) Within non-treated group, b) within treated group, c) between the two groups

At the four month follow-up there was no significant change in the pattern of sclerosing keratitis in the non-treated group (Table 2). Four persons, who were initially negative, were classified as having an early sclerosing keratitis, compared to one person who went from early lesion to negative. Such changes can partly be explained by random variation in the classification of borderline lesions. However, in the treated group there was a different trend: 19 cases with early sclerosing keratitis before treatment (i.e. 42% of cases with this lesion) were reclassified as negative post-treatment compared to 9 cases who went from negative to early sclerosing keratitis. The tendency of regression of early sclerosing keratitis in the treatment group was of borderline statistical significance when compared with the changes in the non-treated group ($P=0.06$). The results for the 12 month follow-up were very similar and showed the same tendency of regression of the early sclerosing keratitis and stability in the advanced sclerosing keratitis.

The findings for iridocyclitis were even more striking. In the non-treated group there was no systematic change both at the 4 and 12 month follow-up. However, in the treated group there were 25 cases with early iridocyclitis (70% of all pre-treatment cases) who were classified as having no lesion at the four months follow-up while no change from negative to early iridocyclitis was recorded. At 12 months a small number of new iridocyclitis was diagnosed, but the number of cases who had apparently lost their early iridocyclitis still predominated. Four cases of advanced iridocyclitis were also classified as having no iridocyclitis at the 12 month review. The tendency of regression of iridocyclitis after ivermectin treatment was highly statistically significant.

No statistically significant changes were noted in the lesions of the posterior segment of the eye at the 12 month follow-up period (Table 3). In the non-treated group there was virtually no change in the posterior segment lesions. In the treated group also there were no changes which could not be explained by random variation except one case which was classified as having no optic nerve disease before treatment and as an advanced optic atrophy at the 12 month review.

No significant changes occurred in the visual acuities which remained perfectly stable in the two treatment groups both at 4 and at 12 month follow-up.

Table 3: The classification of onchocercal lesions of the posterior segment of the eye twelve months after ivermectin mass treatment in relation to the pre-treatment classification.

		Post treatment lesions						
		Non-treated group			Treated group			
Type of lesion	Pretreatment lesion	None	Early	Adv	None	Early	Adv	Significance of change*
Choroido-retinitis	None	33	-	-	309	9	-	a) $P=0.18$
	Early	1	4	-	2	9	4	b) $P=0.46$
	Advanced	-	1	4	-	7	14	c) $P=0.12$
Optic Atrophy	None	33	1	-	306	6	1	a) $P=0.59$
	Early	1	4	1	5	14	4	b) $P=0.33$
	Advanced	-	-	5	-	2	19	c) $P=0.95$

* a) Within non-treated group, b) within treated group, c) between the two groups

DISCUSSION

The protocol of the ophthalmological examination applied in this study did not include fluorescein angiography and the observation of patients was limited to the review 4 and 12 months after treatment only. This differed from the detailed protocol used in the clinical trials and the frequent observations which were carried out during the initial few days to two weeks of the follow-up period of up to 1 year (Taylor et al, 1986, Dadzie et al, 1987). Thus neither the observation of the rare if any acute inflammatory reaction which could have occurred in the first few days after treatment nor any fine anatomical changes demonstrable only by fluorescein angiography, could have been made. However, changes in the microfilarial distribution in the eyes, in the distribution of onchocercal eye lesions as well as changes occurring in the visual function as elicited by the test of visual acuity at 4 and 12 months after treatment can be described in all sections of the population present in the so-called holo-endemic onchocerciasis focus.

In the present study the mean ocular microfilarial loads in a population of 369 treated with ivermectin, some of whom had very high loads, fell to very low levels at the 4 month follow-up. However, the levels attained were not as low as those reported in the clinical trials, (Taylor et al,1986, Dadzie et al, 1987, Newland et al,1988, Dadzie et al, 1989)

Important changes occurred in the distribution of early onchocercal lesions of the anterior segment of the eye in the group of patients who were treated with ivermectin. Forty to seventy percent of these lesions were not seen at 4 months and the majority remained so up till 12 months after treatment. Some of these changes can certainly be attributed to biological variation or to intra-observer variation due to the inherent difficulty in the diagnosis of early onchocercal eye lesions (Dadzie et al, 1986). However, the pattern in the treated group was significantly different from that in the non-treated group among which there was no tendency for early eye lesions to regress. Hence, most of the changes in the early lesions of the anterior segment of the eye are likely to be real regressions resulting from the treatment with ivermectin. This finding is particularly remarkable for iridocyclitis which showed 70% regression and no new positive cases in the treated group at 4 months. Though some incidence of early iridocyclitis occurred at 12 months, the regression of early iridocyclitis still predominated and 60% of early iridocyclitis pre-treatment had remained regressed at the 12 month follow-up.

The advanced lesions of the anterior segment of the eye remained generally stable and no significant changes in the pattern of lesions of the posterior segment of the eye was registered during the 12 month follow-up. This stability was reflected in the visual function as elicited by the visual acuity test which remained unchanged both in the treated and non-treated groups.

Extreme changes, although few, were however observed. Four cases of advanced iridocyclitis were reclassified to no lesion; one case at 4 month follow-up and 3 further cases at 12 months. These lesions probably got their posterior synechiae broken by diagnostic dilatation. Thus the lesions ceased to be advanced iridocyclitis and since no signs of active iridocyclitis could be elicited also, they were reclassified as negative. On the other hand, one case of optic nerve disease turned from negative to advanced. This was a case which was diagnosed negative pre-treatment, an early optic neuritis at 4 months and finally a full blown optic atrophy at 12 months. This appears therefore to be a case of a progressive optic neuritis whose diagnosis was not clearly apparent at the pre-treatment examination but which had got to its inevitable end of optic atrophy despite ivermectin treatment.

Clinical trials have reported that ocular microfilarial loads reach their lowest levels at six months and remain low up to 12 months after ivermectin treatment (Taylor et al, 1986, Dadzie et al, 1987, Newland et al, 1988, Dadzie et al, 1989). In the present study, an unprecedented, marked increase in the ocular microfilarial load at 12 month follow-up was observed. This increase could be a cause for concern because an important part of the population with the higher ocular microfilarial loads had a repopulation of their eyes close to the pre-treatment level at 12 month follow-up. It may be noted that people with high ocular microfilarial loads run a high risk of developing onchocercal eye lesions, particularly lesions of the anterior segment of the eye (Thylefors and Brinkman, 1977). The important regression of early lesions of the anterior segment of the eye and the stability of the other ocular lesions, observed in this study, suggests that these high ocular loads did not yet have any deteriorating effect on the eye. It is, however, to be considered that the development of new eye lesions and the deterioration of existing lesions would take some time. A longer follow-up period is therefore necessary to determine the clinical significance of the observed microfilarial repopulation of the eye. In the mean time it may be prudent to treat such heavily infected patients at a shorter interval than one year.

It may therefore be concluded that mass treatment with ivermectin offers great benefits to people living in highly endemic onchocerciasis foci by causing not only a major reduction of ocular microfilarial loads, but also an immediate regression of early lesions of the anterior segment of the eyes. The estimation of the full extent of the benefit will require a long term study. However, in highly hyperendemic areas, treatment with ivermectin at yearly intervals might not be adequate to prevent ocular pathology in a section of the population who are very highly infected and 6-monthly treatment in such situations may be recommended, at least in the initial years.

REFERENCES

Awadzi,K., K.Y.Dadzie, H.Schulz-Key, D.R.W.Haddock, H.M.Gilles, M.A.Aziz. The chemotherapy of onchocerciasis X. An assessment of four single dose treatment regimes of MK-933 (Ivermectin) in human onchocerciasis. *Annals of Tropical Medicine and Parasitology*, 79 (1985) 63-78.

Awadzi,K., K.Y.Dadzie, H.Schulz-Key, H.M.Gilles, A.J.Fulford, M.A.Aziz. The chemotherapy of onchocerciasis XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana. *Annals of Tropical Medicine and Parasitology*, 80 (1986) 433-442.

Awadzi,K., K.Y.Dadzie, H.Schulz-Key, H.M.Gilles. The chemotherapy of onchocerciasis XIII. Further studies with ivermectin in onchocerciasis patients in Northern Ghana. *Tropical Medicine and Parasitology*, 40 (1989) 361-366

Aziz,M.A., S.Diallo, I.M.Diop, M.Lariviere, M.Porta. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet*, ii (1982) 171-173.

Coulaud,J.P., M.Lariviere, M.C.Gervais, P.Gaxote, A.Aziz, A.M.Deloul, J.Cerac. Traitement de l'onchocercose humaine par l'ivermectine. *Bulletin de la Societé de Pathologie Exotique*, 76 (1983) 681-688.

Coulaud,J.P., M.Lariviere, M.A.Aziz, M.C.Gervais, P.Gaxote, A.M.Deloul, J.Cerac. Ivermectin in onchocerciasis. *Lancet*, ii (1984) 526-527.

Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna. *Tropical Medicine and Parasitology*, 37 (1986) 263-270.

Dadzie,K.Y., A.C.Bird, K.Awadzi, H.Schulz-Key, H.M.Gilles, M.A.Aziz. Ocular findings in a double-blind study of ivermectin versus diethylcarbamazine versus placebo in the treatment of onchocerciasis. *British Journal of Ophthalmology*, 71 (1987) 78-85.

Dadzie,K.Y., K.Awadzi, A.C.Bird. H.Schulz-Key. Ophthalmological results from a placebo controlled comparative 3-dose ivermectin study in the treatment of onchocerciasis. *Tropical Medicine and Parasitology*, 40 (1989) 355-360.

De Sole,G., K.Awadzi, J.Remme, K.Y.Dadzie, O.Ba, J.Giese, M.Karam, F.M.Keita, N.O.Opoku. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. II. Adverse reactions. *Tropical Medicine and Parasitology*, 40 (1989) 375-382.

Diallo,S., M.A.Aziz, M.Lariviere, J.S.Diallo, I.Diop, O.N'Dir, S.Bandiane, D.Py, H.Schulz-Key, P.Gaxote, A.Victorius. A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 80 (1986) 927-934.

Greene,B.M., H.R.Taylor, E.W.Cupp, R.P.Murphy, A.T.White, M.A.Aziz, H.Schulz-Key, S.A.D'Anna, H.S.Newland, L.P.Goldschmidt, A.Auer, A.P.Hanson, V.Freeman, E.W.Reber, P.N.Williams. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *New England Journal of Medicine*, 313 (1985) 133-138.

Lariviere,M., P.Vingtain, M.A.Aziz, B.Beauvais, D.Weimann, F.Derouin, J.Ginoux, H.Schulz-Key, P.Gaxote, D.Basset, C.Sarfati. Double-blind study of ivermectin and diethylcarbamazine in african onchocerciasis patients with ocular involvement. *Lancet*, ii (1985) 174-177.

Newland,H.S., A.T.Whyte, B.M.Greene, S.A.D'Anna, E.Keyvan-Larijani, M.A.Aziz, P.N.Williams, H.R.Taylor. Effect of single-dose ivermectin on human *Onchocerca volvulus* infection with onchocercal ocular involvement. *British Journal of Ophthalmology*, 72 (1988) 561-569.

Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

Remme,J., R.H.A.Baker, G.De Sole, K.Y.Dadzie, M.A.Adams, E.S.Alley, H.S.K.Avissey and J.F.Walsh. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect on the microfilarial reservoir and the transmission of *Onchocerca volvulus*. *Tropical Medicine and Parasitology*, 40 (1989) 367-374.

Taylor,H.R., R.P.Murphy, H.S.Newland, A.T.White, S.A.D'Anna, E.Keyvan-Larijani, M.A.Aziz, E.W.Cupp, B.M.Greene. Treatment of onchocerciasis. The ocular effects of ivermectin and diethylcarbamazine. *Archives of Ophthalmology*, 104 (1986) 863-870.

Thylefors,B., U.K.Brinkmann. The microfilarial load in the anterior segment of the eye. A parameter of the intensity of infection of onchocerciasis. *Bulletin of the World Health Organization*, 55 (1977) 731-737.

White,A.T., H.S.Newland, H.R.Taylor, C.D.Erttmann, E.Keyvan-Larijani, A.Nara, M.A.Aziz, S.A.D'Anna, P.N.Williams and B.M.Greene Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *Journal of Infectious Diseases*, 156 (1987) 463-470.

Chapter 6

GENERAL CONCLUSIONS

GENERAL CONCLUSIONS

The research in this thesis has produced some important results and conclusions concerning the epidemiology and control of onchocerciasis in West Africa. Progress has been made in the description of epidemiological patterns of ocular onchocerciasis in different bio-climatic zones, in the understanding of the population dynamics of *O. volvulus*, in the evaluation and prediction of epidemiological trends during a vector control period, in the investigation of the potential of ivermectin as a tool for onchocerciasis control and in the development of new statistical and epidemiological methods, including epidemiological modelling. Many of the findings and conclusions have had direct operational and strategic implications for the Onchocerciasis Control Programme in West Africa and should also be relevant for the planning of onchocerciasis control in other areas.

Onchocerciasis is very much a community problem. Its severity is determined by the local intensity of transmission and the resulting level of endemicity. The different chapters have clearly demonstrated that the concept of endemicity is the central issue in onchocerciasis epidemiology. The importance of endemicity has been realized previously, but its description has been mainly qualitative using three groupings based on the prevalence of infection. The present work starts with a deviation from the classical approach by using information on the intensity of infection in the community for the quantitative description of onchocerciasis endemicity.

The force-of-infection model has shown that this approach makes epidemiological sense because it reflects the dynamics of onchocerciasis infection. The intensity of infection in man depends on the age-specific force-of-infection, the productive life-span of the adult *O. volvulus* and the productivity per worm. From the age of 10 years onward, the force-of-infection is independent of age and this results in a levelling-off of the intensity of infection above the age of 20 years. This is the reason for the introduction of the Community Microfilarial Load (CMFL), i.e. the mean microfilarial load per skin snip in adults above the age of 20 years, as a more relevant measure of endemicity. The CMFL is directly related to the force-of-infection in adults, and, therefore, to the local intensity of transmission. Furthermore, the CMFL determines the severity of ocular disease in the community, the epidemiological trends during the vector control period and the beneficial and adverse effects of ivermectin treatment.

A description is given of the relationship between the severity of ocular disease in the community and the CMFL in the savanna. A special effort has been made to develop an objective and appropriate methodology for the description of onchocercal ocular disease and onchocercal blindness. The results show a clear linear relationship between the mean ocular microfilarial loads, prevalences of ocular lesions and blindness, and the CMFL. These findings seem to support the validity of the methodology and they underline once more the importance of the concept of endemicity as measured by the CMFL. The results have also a very practical implication: in non-controlled savanna areas it will be possible to use information from simple parasitological examinations to give an adequate estimate of the risk of onchocercal ocular disease and blindness in the community.

The new methodology has allowed an unequivocal description of the difference in ocular disease patterns between the savanna and forest foci where the only vector was the forest vector *S. yahense*. For comparative levels of the CMFL there were very little ocular manifestations in the Yahense foci. This supports the hypothesis of differences in *O. volvulus* strains. The results indicate that microfilariae from the Yahense forest are both less eye invasive and less pathogenic to the eye than microfilariae from the savanna. The methodology has also been applied in other zones, notably in the south of the Ivory Coast. Because of the finding that the ocular disease pattern there is also of the more benign forest type, the expensive larviciding operations have been ceased in areas where the sole vectors belong to the

S.sanctipauli/soubrense subcomplex. The methodology is currently being used to clarify the situation in other areas where there is doubt as to the location of the southern boundary of the 'blinding' form of onchocerciasis.

The clear relationship between the severity of ocular disease and intensity of infection in the community suggests that the control of onchocerciasis as a problem of public health importance may be achieved by ensuring that the intensity of infection remains below a certain level. With vector control this would mean keeping the level of transmission below an 'acceptable' or 'tolerable' level, and such an approach has indeed often been advocated. However, when the OCP started in 1975, it opted for complete interruption of transmission until the parasite reservoir would be reduced to insignificant levels. The reason for this radical approach was simple: vector control through aerial larviciding is very expensive and, therefore, a time limit to the effort was a must.

In the original OCP area, control has been very effective as was initially illustrated by the entomological evaluation data which showed that the Annual Biting Rates and Annual Transmission Potentials had been reduced to very low levels throughout the area with the exception of the border areas in the west and the east which were reinvaded by infective flies originating from outside the Programme. These results were later confirmed by the epidemiological evaluation data, after re-analysis using the analytical methodology which was developed with the force-of-infection model. In the Central OCP Area, there had been a great reduction in the CMFL, and the reduction was in accordance with what would have been expected with complete interruption of transmission. There were even greater reductions in ocular microfilarial loads. Furthermore, the incidence of ocular lesions, notably those of the anterior segment of the eye, was considerably reduced compared to non-controlled areas. On the other hand, the decrease in CMFL and ocular loads was distinctly unsatisfactory in the reinvasion areas in the west and south-east. Even though there had been an improvement in the epidemiological situation in most of the reinvaded areas, onchocerciasis still remained a public health problem. These results provided therefore the epidemiological evidence that vector control needed to be extended to the west and south-east, and these extensions came into operation in 1987.

Once the effectiveness of vector control in the Central OCP Area had been proven, the attention shifted to the study of the decline in the parasite reservoir. Nodulectomy surveys provided important information showing that the worm population was rapidly ageing and dying out. The reduction in the Productivity Index for the adult *O. volvulus* correlated well with the observed decline in the CMFL. The studies also indicated that it was not just the worm death but to a large extent also the reduced worm productivity which determined the epidemiological trends. However, the cross-sectional nature of these nodulectomy surveys did not allow the estimation of the reproductive longevity of *O. volvulus*. This had to come from the analysis of the trends in the prevalence and intensity of skin microfilariae.

In order to improve the analysis and prediction of epidemiological trends in the Central OCP Area, the so-called 'host-parasite' model, which was far more sophisticated than the force-of-infection model, was developed. The host-parasite model used the flexible technique of microsimulation which involved the computer simulation of the life histories of individual hosts and adult parasites. This enabled the simulation of the population of follow-up villages and the fitting of the model to the observed trends in skin snip counts in the Central OCP Area. As a result of this fitting, the average reproductive lifespan of *O. volvulus* was estimated at 9-9.5 years and the average longevity of infection at 10.4 years with an upper limit of 15 years for 95% of infections.

The use of modelling has made it possible to make credible predictions of the expected epidemiological trends during the remainder of the vector control period, and this has been important both for planning purposes and for political reasons. The basic predictions were that the interruption of transmission would first result in a virtually linear decrease in the CMFL after a delay of about one year which is equal to the pre-patent period. The absolute decrease would depend on the initial endemicity level, but the relative decrease would be the same for all endemicity levels and depend on the longevity of *O. volvulus*. This decrease in the CMFL had already been observed during the first 8 years of control. The prevalence of infection, however, would start to decrease much later, but would then show an accelerated decline. The higher the initial endemicity, the longer it would take for the prevalence to begin its decline, but the faster would be its final descent. For all endemicity levels the prevalence was predicted to fall to insignificant levels after 15 years of interruption of transmission. It was this prediction in particular which formed the basis for the chronology of the current long term strategy of the OCP. The most recent field observations, after 14 years of vector control, have confirmed the predicted collapse in the prevalence of infection. In some areas the observed trend was even faster than predicted.

In the mean time a number of new epidemiological questions had appeared following the successful clinical testing of the microfilaricide, ivermectin, and its registration in 1987 for the treatment of human onchocerciasis. This development had been of great interest to the OCP, which had partly funded the clinical trials. However, before decisions could be made on the use of ivermectin in onchocerciasis control, there remained several questions to be answered. These concerned the safety of the drug in its use for mass-treatment, its effect on transmission and its potential for the prevention of ocular disease. A unique effort of eight community trials was therefore undertaken in which more than 50,000 people were treated and monitored for possible adverse reactions within a period of less than a year.

A treatment coverage of some 60% of the census population, and more than 75% of the infected population, was achieved. The main reasons for non-treatment were the existing exclusion criteria without a change of which it will be impossible to achieve much higher coverage. Mild to moderate adverse reactions were common and occurred mainly during the first day following treatment. Severe reactions were seen in 1 out of every 500 persons treated. All these reactions could be managed successfully, usually with reassurance only or very simple symptomatic treatment. Three cases of severe dyspnoea, which were life-threatening events, were also encountered but their relation with ivermectin treatment was uncertain. The adverse reactions were directly related to the intensity of infection and the incidence was therefore highest in the most endemic areas, i.e. in the areas where ivermectin treatment is most indicated. It is concluded that ivermectin is sufficiently safe for large scale treatment of onchocerciasis provided that monitoring for adverse reactions is maintained by resident nurses for 36 hours after treatment. This is currently the WHO recommendation for mass-treatment of onchocerciasis with ivermectin.

Ivermectin treatment resulted in a major reduction in skin microfilarial loads. In the most endemic trial area there was a 96% reduction in skin microfilarial loads in treated patients, and a reduction of 70%-75% in the total reservoir of microfilariae. This resulted in a reduction in onchocerciasis transmission of a similar magnitude. The study has demonstrated for the first time that mass-chemotherapy can result in a significant reduction in onchocerciasis transmission. However, the remaining level of transmission in this highly endemic focus was still unacceptably high. Furthermore, four months after treatment there appeared to be a faster microfilarial repopulation of the skin than had been observed in the clinical trials. In spite of the promising results, therefore, it is still too early to draw definite conclusions on the potential of ivermectin for transmission control and to predict the long term effect of repeated mass-treatment on the parasite reservoir. The major question is whether ivermectin has a long lasting effect on the reproductive potential of the adult *O. volvulus*, as has been claimed in some clinical trials. So far this hypothesis has not been confirmed by the community trials.

The main promise of ivermectin lies in the field of morbidity control and very important observations were made on the effect of mass-treatment on ocular onchocerciasis in several holo-endemic villages. This study included patients with much higher ocular microfilarial loads than had been seen in the clinical trials. Four months after treatment there was a major reduction in ocular loads but no adverse effect on the eye. On the contrary, a new finding was a significant regression of early lesions of the anterior segment of the eye. After 12 months there was again an increase in ocular loads in this holo-endemic focus, which raises the question whether a six-monthly treatment schedule, rather than an annual, is not indicated in such highly endemic foci. Though more long term studies are needed to estimate the full effect of ivermectin treatment in preventing ocular disease, the current results suggest that its use is certainly indicated for morbidity control in the most endemic areas where there is a high risk of developing ocular disease and blindness.

Until proven otherwise, the planning of ivermectin treatment programmes will have to be based on the assumption that ivermectin is only a microfilaricide which has no permanent, cumulative effect on the adult worm. This implies that annual mass-treatment will have to be given for an unforeseeable period of time. Mass-treatment with 36 hours monitoring by a resident nurse is an onerous and expensive effort in endemic onchocerciasis areas, which are typically very isolated, inaccessible and have little or no health care facilities. Therefore, it is necessary to identify the areas and villages where the risk of onchocercal ocular disease is sufficiently high to warrant such an effort. Applying the findings on the epidemiological pattern of ocular onchocerciasis in the savanna, high risk villages have been defined as those where the CMFL is greater than 10 mf/s. Large scale epidemiological mapping, based on skin snip surveys, is currently going on in the extension areas of the OCP in order to identify the villages which will be included in the ivermectin treatment campaign. This campaign will continue until vector control has sufficiently reduced the parasite reservoir to eliminate the public health problem after some 8 years of effective vector control.

During the next few years the OCP has to take several major operational decisions. These include the decisions on when to stop larviciding in different parts of the Central OCP Area and on what mechanisms to put into place in order to ensure that there will be no recrudescence of the disease after the cessation of vector control. The geographical limits of the 'blinding' form of onchocerciasis need to be determined in the extension areas in order to decide on the boundaries of the operational area. Finally, it has to be decided on how to make optimal and most cost-effective use of vector control, large scale ivermectin treatment and combinations of the two methods in the different epidemiological situations prevailing in the OCP. Much of the basic information needed for these decisions is included in the present thesis. In addition, the host-parasite model has recently been extended into a full transmission model for onchocerciasis and its control. A first version of this transmission model has been completed and has already been used successfully for a comparative evaluation of the predicted long term impact of the currently available, alternative strategies for the control of onchocerciasis in West Africa.

Chapter 7

SUMMARY

SAMENVATTING

SUMMARY.

Onchocerciasis is a major public health problem in West Africa, and in particular in the West African savanna belt where it is responsible for a high incidence of blindness in populations living in river valleys near the breeding sites of the vector. Onchocerciasis is often also a socio-economic problem as it may prevent the repopulation of relatively fertile river valleys. A large scale control programme, the Onchocerciasis Control Programme in West Africa (OCP), was started in 1975 and has been based exclusively on vector control. However, a chemotherapeutic agent, ivermectin, has recently shown promise as an additional tool for onchocerciasis control.

The present thesis deals with research which has been undertaken since 1983 in the context of the OCP with the aim of finding answers to three main questions concerning the epidemiology and control of onchocerciasis in West Africa, i.e.

1.-What are the epidemiological patterns of ocular onchocerciasis in West Africa and what is the geographical boundary of the blinding, savanna, form of onchocerciasis

2.-What has been the epidemiological impact of vector control in the OCP and what are the predicted epidemiological trends for the remainder of the vector control period.

3.-What is the potential of ivermectin as a tool for onchocerciasis control.

Chapter 2 gives a review of onchocerciasis in West-Africa with emphasis on the demographic aspects of its epidemiology and control. The disease is caused by infection with the filarial nematode *Onchocerca volvulus*. The adult worm produces millions of microfilariae which migrate to the skin and which are the main cause of the clinical manifestations of the disease. The most severe complication of onchocerciasis is blindness which may affect as much as 10% of the population of the most endemic communities in the savanna. The parasite is transmitted by a blackfly, *Simulium damnosum* s.l., which consists in West Africa of at least nine subspecies. The disease is most severe in the river valleys near the breeding sites of the vector in fast flowing water, thus earning onchocerciasis the infamous name of river blindness. The intensity of transmission and of infection varies considerably between areas as a result of intrinsic differences between vector subspecies and because of variations in man-vector contact. The latter depends on host-seeking behaviour of the vector, the density of the human population, their location with respect to the breeding sites, and on individual behavioural differences which are related to age, sex and occupation. Before 1975 many of the river valleys in the savanna were severely underpopulated and strewn with the remains of abandoned villages. Onchocerciasis is usually quoted as the main cause for this, even though other factors such as wars and trypanosomiasis epidemics have also contributed. However, onchocerciasis is the single most important obstacle to repopulation of the valleys.

When the OCP was launched it covered the savanna areas of seven countries where 1 to 1.5 million people were infected, 35,000 were blind and another 35,000 severely vision impaired as a result of onchocerciasis. The strategy of OCP is to interrupt transmission by vector control for a sufficiently long period to allow the parasite to die out naturally, and OCP was initially planned to last for 20 years. Vector control involved the aerial application of larvicides to the vector breeding sites in the rivers. Since 1987 control operations have been extended to the west and to the south-east, and the Programme covers presently eleven West African countries. Vector control has been very successful in the original Programme area. In addition to the epidemiological impact which is described in chapter 4, it has resulted in important repopulation of the abandoned river valleys, notably of the White and Red Volta river valleys in Burkina Faso where there has been an annual increase of 9% in both utilized and cultivated land.

Chapter 3 deals with the research on epidemiological patterns of ocular onchocerciasis in different bioclimatic zones in West Africa. In chapter 3.1 a new method is introduced for the analysis of community patterns of ocular onchocerciasis in relation to the intensity of infection as measured by the Community Microfilarial Load (CMFL). Specific features of this method are the clear definition of ocular lesions and their separation into early and advanced stages, and the estimation of the prevalence of onchocercal blindness after exclusion of other causes of blindness. The method is applied to the ophthalmological and parasitological data from 33 villages from the West African savanna in order to obtain a reference pattern for subsequent analyses of ocular onchocerciasis patterns from other bioclimatic zones.

In the savanna, there exists a clear linear relationship between most indices of ocular onchocerciasis and the CMFL. Mean ocular microfilarial loads, prevalences of the advanced lesions of the anterior and posterior segment of the eye and prevalences of different classifications of blindness show a high degree of correlation with the CMFL, as does also early sclerosing keratitis. The correlation is poor for the other early ocular lesions. All relationships are similar for the two sexes with the exception of posterior segment lesions which remain more common in males after correction for intensity of infection. The CMFL is superior to the prevalence of microfilariae in the skin as an index of endemicity. It allows a good prediction of the severity of onchocercal ocular disease in savanna communities using parasitological information only.

In chapter 3.2 this method of analysis is used to describe community patterns of ocular onchocerciasis in relation to the intensity of infection in West African forest villages where *S.yahense* is the sole vector. The pattern is completely different from that found in the savanna, even after correction for the intensity of infection as measured by the CMFL. Lesions of the anterior segment of the eye as well as onchocercal blindness either do not occur or occur only sporadically with increasing CMFL in the Yahense forest whilst a steep linear relation exists between the prevalence of these lesions and the CMFL in the savanna. Lesions of the posterior segment of the eye are also less common in the Yahense forest.

For a given skin microfilarial load, the ocular microfilarial load is lower in the Yahense forest. For a given ocular microfilarial load, a lower prevalence of eye lesion is found in the Yahense forest compared to the savanna. It is concluded that microfilariae of *O.volvulus* in the Yahense forest are less eye invasive than microfilariae from the savanna. Furthermore, they appear to be also less pathogenic to the eye. These findings explain why ocular onchocerciasis is relatively mild in the Yahense forest, in spite of the high intensities of *O.volvulus* infection in the community. Reference is also made to the application of the methodology in other bioclimatic zones and in epidemiological mapping of onchocerciasis in the extension areas of the OCP.

Chapter 4 deals with the evaluation of the epidemiological impact of vector control and the prediction of epidemiological trends using epidemiological modelling. A new analytical methodology is introduced which takes the dynamics of the parasite and of the human population into account. The basis of this work is described in Chapter 4.1. A simple force-of-infection model for onchocerciasis was designed and used for a study of the age-specific epidemiological trends during a period of vector control in the OCP. The most important factors included in the model are the longevity of an infection, the aspect of super-infection, age-specific exposure, and the intensity of transmission during the pre-control period. The aim of the study was to determine the most appropriate statistics for the epidemiological evaluation in the OCP. There was generally good agreement between the epidemiological trends, predicted by the model, and the observed trends in the prevalence and mean load of microfilariae in skin snips taken from a cohort population from 23 villages in an area with 8 years of successful vector control in the OCP. It is concluded that the epidemiological trends during the control period are not uniform but depend on the initial age and the initial endemicity level of the population. The epidemiological indices for cohorts of children, born before the start of control, will not show a decrease during the first 8 years of interruption of transmission. The prevalence is too insensitive to be useful for the evaluation in hyperendemic villages during most of the control period. The most sensitive and meaningful statistic for a comparative analysis and for the assessment of epidemiological changes is the geometric mean microfilarial load in a cohort of adults. This index, which is called the Community Microfilarial Load (CMFL), is now routinely used in the OCP. The new analytical methodology has enabled a much better appreciation of the significant epidemiological impact of 8 years of vector control in the OCP. Several related aspects of the pre- and post-control dynamics of onchocerciasis infection are also discussed and priorities are formulated for further work on applied modelling of onchocerciasis.

Chapter 4.2 describes the effect of 7-8 years of vector control on the evolution of ocular onchocerciasis. A cohort of 1170 people over 5 years of age were examined before the start of and after 7-8 years of effective vector control in 12 originally hyperendemic villages in the central part of the OCP area. The proportion of the cohort which at the outset of vector control was free of ocular onchocerciasis or had an early or recent infection in the form of punctate keratitis only, remained largely free of or lost their signs of ocular infection respectively and only a very insignificant proportion acquired microfilariae in the eyes or developed a severe onchocercal eye lesion at the initial stage. The proportion of the cohort with a heavy ocular microfilarial load had a reduced risk of developing severe eye lesions and no risk of going blind. The proportion of the cohort with already existing severe eye lesions at the advanced stage remained largely unchanged and some lesions at the initial stage disappeared. Blindness occurred only in those who had severe eye lesions at the outset and was comparatively less than in areas of on-going transmission.

Chapter 4.3 deals with the changing population dynamics of *O. volvulus* during a period of vector control. Nodulectomies were undertaken in 256 patients from ten villages in the Onchocerciasis Control Programme (OCP) and in 74 patients from two villages in an area with ongoing transmission. A total of 1198 nodules were excised and 4350 adult worms were isolated and examined for viability and productivity. In the OCP villages, the worm population is ageing and dying without replacement by new generations of parasites and various findings signal a breakdown of worm population after about 12 years interruption of transmission. The sexual activity of the worms was significantly reduced. A Productivity Index was developed to measure the microfilariae production at the nodule level. The reduction in this index for the OCP villages correlates closely with the decline over the control period in the community microfilarial loads in the skin. The results show that it is not only the longevity of the parasite which will determine the duration of vector control, but that the reduced productivity of the ageing parasite population is of equal importance.

Chapter 4.4 gives a summary of all entomological and epidemiological evaluation results of 11 years of vector control. From an entomological point of view the original OCP area can be divided into four major zones, i.e. the central OCP area (covering some 85% of OCP) where vector control has been very effective and transmission has been virtually interrupted, the western and the south-eastern border areas which have been subject to reinvasion by infective flies originating from sources outside the OCP, and Phase IVb in the south of Ivory Coast where control started only in 1979.

The results of the epidemiological evaluation are consistent with the entomological findings. Out of a total of 6,700 examined children from the central OCP area, who were born since the start of the control, only one was found to be infected compared to an expected number of 400 infected children if there had been no vector control. The CMFL showed in most of the central area the predicted, nearly linear, decline and in villages with 10 years of control it had already fallen by more than 90%. In these villages the prevalence of mf in the skin has started the predicted accelerated decline. Microfilariae were hardly found in the eye after 8-10 years of control and the incidence and progression of eye lesions seemed to have been arrested. It is concluded that after 11 years of control onchocerciasis is no longer a public health problem in the central OCP area.

In the reinvasion areas the picture was distinctly different: 37 children were found to be infected against an expected number of 225, the decline in the CMFL was far less than in the central area and the decline in ocular mf loads was also unsatisfactory. Local vector control has significantly reduced transmission in these areas but the reinvading flies still maintain a level of transmission which remains intolerably high and control of the disease will have to await the extension of vector control operations to the west and to the south-east.

Chapter 4.5 provides the latest results on the predicted and observed decline in onchocerciasis infection in the well-protected central OCP area. In 55 villages skin snip surveys have been done at regular intervals since the start of control and a last round of surveys was undertaken after 12-14 years of successful vector control. The observed trends in the prevalence and intensity of onchocerciasis infection in cohorts of adults are compared with the trends which had been predicted by a host-parasite model. A description of this model is provided. After 12-14 years of control the Community Microfilarial Load was close to zero in all villages. During the last years of control the prevalence of infection showed the accelerated decline which had been predicted by the model. There was generally good agreement between observed and predicted trends. The predictions were based on an estimated average duration of infection of 10.4 years, which corresponds to a mean reproductive lifespan of *O.volvulus* of 9-9.5 years, and an upper limit of 15 years for 95% of infections. Differences included the trend in CMFL between the first and second survey which did not show the predicted decline in 18 villages. Furthermore, the final decline in prevalence was faster than predicted in the north-eastern part of the central OCP area. After 14 years of vector control the level of onchocerciasis infection has fallen so low that cessation of larviciding is being considered.

Chapter 5 gives the results of community trials of ivermectin which have been undertaken in the OCP. Chapter 5.1 describes the largest community trial which was undertaken in the isolated focus of hyperendemic savanna onchocerciasis at Asubende in Ghana. One of the objectives was to determine the effect of mass treatment on the microfilarial reservoir and on the transmission of *Onchocerca volvulus*. Since 1978 the focus has been under entomological surveillance. This was intensified from 1 September 1987 till 11 February 1988 with daily vector collection and dissection of over 30,000 flies. A total of 14,991 people were treated with ivermectin between 7 and 10 October 1987. Skin snip surveys were done pre-treatment, and at two and four months after treatment. The mean skin microfilarial load in treated persons had fallen by more than 96% two months after treatment. During the next two months there was an increase in mf loads which appeared to be faster than reported in the clinical trials. The total reservoir of skin microfilariae available for transmission had been reduced by an estimated 68%-78% two months after treatment. This was consistent with the entomological results which indicated a reduction in transmission of 65%-85% during the first three post-treatment months. The study has shown for the first time that mass chemotherapy can significantly reduce onchocerciasis transmission. However, the remaining level of transmission was still unacceptably high and further studies are required to predict the long term impact of repeated mass treatment.

Chapter 5.2 gives the combined results on adverse reactions following ivermectin treatment in all eight community trials undertaken in the OCP. The trial areas, which are located in eight West African countries, represent different epidemiological situations of operational importance for the OCP and vary greatly in their endemicity levels. A total of 50,929 persons were treated with ivermectin and monitored for 72 hours for the occurrence of adverse reactions according to a standardized protocol. The overall treatment coverage was 60% of the census population. The main reasons for non-treatment were the exclusion criteria and absence from the village at the time of treatment. Of the treated persons 9% reported with adverse reactions, 2.4% with moderate reactions and 0.24% with severe reactions. The type of reactions were generally similar to those encountered in the clinical trials and included pain conditions, fever, itching, rash, lymph node enlargement and oedema. Not reported previously were inguinal gland pain and brawny oedema of the limbs which could be a significant cause of morbidity.

The incidence of adverse reactions was directly related to the skin microfilarial load suggesting that they were due to the microfilaricidal effect of the drug and not a result of intrinsic toxicity. The relation with microfilarial loads explains why the incidence of reactions was much higher in the most endemic foci. After correction for intensity of infection there was no difference between the trials. The most frequent severe reaction was Severe Symptomatic Postural Hypotension (SSPH) which was diagnosed in 49 cases. SSPH was also related to mf load. In nine SSPH cases treatment in the form of intravenous injection of hydrocortisone was judged necessary and all improved promptly, usually within a few hours. The most serious were three cases of severe dyspnoea which were life threatening events. However, their relationship with ivermectin treatment is uncertain.

Chapter 5.3 describes the impact of ivermectin mass treatment on ocular onchocerciasis in holo-endemic villages located in the core of the Asubende trial area in Ghana. A cohort of 417 persons, 369 of whom were treated, was followed up at 4 and 12 month post treatment. The mean ocular microfilarial load in the anterior chamber of the eye and in the cornea of treated persons reduced to less than 20% and 10% of the pre-treatment level respectively at 4 month follow-up but had increased significantly by 12 months. Lesions of the eye at the advanced stage of development remained stable. An important new finding was a significant regression of early lesions of the anterior segment of the eye, particularly iridocyclitis, after ivermectin treatment. In view of the substantial increase of ocular microfilarial loads after 12 months, 6 monthly treatment may be indicated in such highly endemic foci. However, a long term observation is needed to give a correct estimate of the full benefit to be derived from mass treatment with ivermectin.

Chapter 6 gives the general conclusions of the study. The central role of the concept of endemicity in the epidemiology of onchocerciasis is highlighted and the importance of the CMFL as a quantitative measure of endemicity is stressed. Special attention is given to the practical implications of the different findings for the planning and evaluation of onchocerciasis control in West Africa and elsewhere.

SAMENVATTING.

Onchocerciasis is een belangrijk maatschappelijk gezondheids probleem in West Afrika, en met name in de West Afrikaanse savanna zone waar het verantwoordelijk is voor een hoge incidentie van blindheid onder de bevolking van de rivier valleien die dicht bij de broedplaatsen van de vector leeft. Onchocerciasis is vaak ook een socio-economisch probleem omdat het de herbevolking kan tegenhouden van de relatief vruchtbare rivier valleien. Een grootschalig bestrijdingsprogramma, het "Onchocerciasis Control Programme in West Africa" (OCP), ging in 1975 van start en is uitsluitend gebaseerd geweest op bestrijding van de vector. Onlangs zijn er echter veelbelovende resultaten bereikt met een nieuw geneesmiddel, ivermectine, dat een aanvullend middel voor de bestrijding van onchocerciasis zou kunnen worden.

In dit proefschrift wordt onderzoek behandeld dat sinds 1983 binnen het OCP is ondernomen met als doel drie belangrijke vragen te beantwoorden betreffende de epidemiologie en bestrijding van onchocerciasis in West Afrika. Die vragen zijn:

1.-Wat zijn de verschillende epidemiologische patronen van oculaire onchocerciasis in West Afrika en wat is de geographische afbakening van de blindheidveroorzakende "savanna-vorm" van onchocerciasis?

2.-Wat is het epidemiologische effect geweest van de vectorbestrijding in de OCP en wat zijn de voorspellingen voor de epidemiologische veranderingen gedurende de rest van de vector-bestrijdingsperiode?

3.-Wat zijn de mogelijkheden van ivermectine als een middel voor onchocerciasis bestrijding?

Hoofdstuk 2 geeft een literatuur overzicht van onchocerciasis in West Afrika waarin speciale aandacht wordt besteed aan de demographische aspecten van de epidemiologie en ziektebestrijding. De ziekte wordt veroorzaakt door infectie met de parasitaire nematode *Onchocerca volvulus*. De volwassen worm produceert millioenen microfilariae die naar de huid van de menselijke gastheer migreren en de voornaamste oorzaak zijn van de klinische manifestaties van de ziekte. De ernstigste complicatie van onchocerciasis is blindheid en in de meest endemische savannadorpen kan meer dan 10% van de bevolking blind zijn als een gevolg van onchocerciasis. De parasiet wordt overgebracht door een zwart vliegje, *Simulium damnosum* s.l., waarvan er in West Afrika meer dan negen subspecies bestaan. De broedplaatsen van de vector bevinden zich in snel stromend water en de ziekte is daarom met name ernstig in de riviervalleien wat onchocerciasis de beruchte naam van rivierblindheid heeft bezorgd. De intensiteit van transmissie en van infectie varieert sterk tussen verschillende gebieden vanwege intrinsieke verschillen tussen vector-subspecies en variaties in mens-vector kontakt. Dit laatste hangt samen met het zoekgedrag van de vector naar een gastheer, de plaatselijke dichtheid van de menselijke bevolking, de lokatie van de bevolking met betrekking tot de broedplaatsen, en met individuele gedragsverschillen die samenhangen met leeftijd, geslacht en beroep. Veel riviervalleien in de savanna waren voor 1975 zwaar onderbevolkt en bezaaid met de resten van verlaten dorpen. Onchocerciasis wordt meestal genoemd als de belangrijkste oorzaak hiervan, hoewel andere faktoren, zoals oorlogen en trypanosomiasis-epidemieen, hier ook aan hebben bijgedragen. Onchocerciasis is zonder meer het belangrijkste obstakel voor herbevolking van de riviervalleien.

In het begin bestreek OCP de savannazones van zeven West-Afrikaanse landen waar 1 tot 1.5 millioen mensen geinfecteerd waren, 35.000 blind waren en nogmaals 35.000 mensen zwaar visueel gehandicapt waren ten gevolge van onchocerciasis. De strategie van OCP is het onderbreken van de transmissiecyclus door middel van de bestrijding van de vector, gedurende een periode die lang genoeg is om het reservoir van de parasiet in de menselijke bevolking te laten uitsterven. Volgens het oorspronkelijke plan zou OCP 20 jaar hebben moeten duren. De vectorbestrijding is gebaseerd op het besproeien vanuit de lucht van de broedplaatsen in de rivieren met larviciden. De bestrijdingsoperaties zijn sinds 1987 uitgebreid naar het westen en het zuid-oosten, en het programma bestrijkt tegenwoordig elf West-Afrikaanse landen. De bestrijding van de vector is erg succesvol geweest in het oorspronkelijke OCP gebied. Naast de epidemiologische resultaten, die beschreven worden in hoofdstuk 4, heeft de vectorbestrijding ook geleid tot een belangrijke herbevolking van ontvolkte riviervalleien, met name in de valleien van de Volta Rouge en Volta Blanche in Burkina Faso waar zowel de oppervlakte van gebruikt land als van gecultiveerd land is toegenomen met 9% per jaar.

Hoofdstuk 3 beschrijft het onderzoek naar de epidemiologische patronen van oculaire onchocerciasis in verschillende bioclimatische zones in West Afrika. In hoofdstuk 3.1 wordt een nieuwe methode beschreven voor de analyse van oculaire onchocerciasis in de dorpsbevolking in verhouding tot de intensiteit van infectie zoals gemeten door de 'Community Microfilarial Load' (CMFL). Specifieke eigenschappen van deze methode zijn de duidelijke definitie van de verschillende oculaire laesies, de onderscheiding van een beginstadium en een voortgeschreden stadium van ontwikkeling van de laesies, en de schatting van de prevalentie van blindheid als gevolg van onchocerciasis na uitsluiting van andere oorzaken van blindheid. De methode is gebruikt in de analyse van de ophthalmologische en parasitologische gegevens die verzameld zijn in 33 dorpen in de West Afrikaanse savanna met als doel een referentie patroon te verkrijgen voor toekomstige analyses van epidemiologische patronen van oculaire onchocerciasis in andere bioclimatische zones.

In de savanna bestaat er een duidelijk lineaire relatie tussen de meeste indices van oculaire onchocerciasis en de CMFL. Het gemiddelde aantal microfilariae in het oog, de prevalentie van de voortgeschreden laesies van het voor- en achtersegment van het oog en de prevalentie van de verschillende klasssifikaties van blindheid vertonen een hoge graad van correlatie met de CMFL. Dit was ook het geval voor de prevalentie van het beginstadium van scleroserende keratitis maar er was geen goede correlatie voor de beginstadia van de andere oculaire laesies. De relaties waren hetzelfde voor de twee geslachten met uitzondering van de laesies van het achtersegment van het oog die vaker voorkwamen onder mannen, zelfs na correctie voor intensiteit van infectie. De CMFL is een betere maat van endemiciteit dan de prevalentie van microfilariae in de huid, en maakt het mogelijk om met behulp van alleen parasitologische informatie een goede schatting te geven van de ernst van oculaire onchocerciasis in een West-Afrikaans savannadorp.

De nieuwe analytische methode is in hoodstuk 3.2 gebruikt om een beschrijving te geven van het patroon van oculaire onchocerciasis in verhouding tot de intensiteit van infectie in dorpen die gelegen zijn in dat deel van het West Afrikaanse regenwoud waar *Simulium yahense* de enige vector is. Het epidemiologische patroon is volslagen verschillend van dat wat in de savanna gevonden wordt, zelfs na correctie voor intensiteit van infectie als gemeten door de CMFL. De laesies van het voorsegment van het oog en blindheid als gevolg van onchocerciasis komen in de Yahense bosgebieden of niet voor, of vinden alleen sporadisch plaats, terwijl er in de savanna een steile lineaire relatie bestaat tussen de prevalentie van deze laesies en de CMFL. De laesies van het achtersegment van het oog komen ook minder vaak voor in de Yahense bosgebieden.

Voor een gegeven gemiddeld aantal microfilariae in de huid is het gemiddeld aantal microfilariae in het oog lager in de Yahense bosgebieden dan in de savanna. Voor een gegeven gemiddeld aantal microfilariae in het oog is de prevalentie van oculaire laesies lager in de Yahense bosgebieden. De conclusie wordt daarom getrokken dat de microfilariae van *O.volvulus* van de Yahense bosgebieden minder invasief voor het oog zijn dan de microfilariae van de savanna. Tevens lijken zij minder pathogeen voor het oog te zijn. Deze bevindingen verklaren waarom oculaire onchocerciasis relatief mild is in het Yahense bosgebied ondanks de hoge intensiteit van onchocerciasis-infectie in de gemeenschap. Een korte vermelding wordt ook gemaakt van toepassingen van de analytische methodologie in andere bioclimatische zones en bij het in kaart brengen van de endemiciteit van onchocerciasis in de uitbreidingsgebieden van het OCP.

Hoofdstuk 4 beschrijft de evaluatie van het epidemiologische effect van de vectorbestrijding in het OCP en de voorspelling van toekomstige epidemiologische trends met gebruikmaking van epidemiologische modellen. Een nieuwe analytische methodologie wordt geintroduceerd waarbij rekening gehouden wordt met de dynamiek van de parasiet en van de menselijke bevolking. De basis van dit werk wordt beschreven in hoofdstuk 4.1. Een eenvouding "force-of-infection" model voor onchocerciasis werd ontwikkeld en gebruikt voor een studie van de leefstijds-afhankelijke epidemiologische trends gedurende de periode van vectorbestrijding in het OCP. De meest belangrijke factoren in het model zijn de duur van een infectie, het aspect van superinfectie, leefstijds-afhankelijke blootstelling aan de vector, en de intensiteit van transmissie gedurende de jaren voor het begin van de bestrijdingsactiviteiten. Het doel van de studie was de meest geschikte statistieken te bepalen voor de epidemiologische evaluatie in het OCP. Er bestond in het algemeen een goede overeenkomst tusssen de epidemiologische trends die voorspeld waren met het model, en de waargenomen trends in de prevalentie en het gemiddelde aantal microfilariae per huidbiopsie in een cohortpopulatie uit 23 dorpen van een gebied met 8 jaar suksesvolle vectorbestrijding. Hieruit wordt de conclusie getrokken dat de epidemiologische trends gedurende de bestrijdingsperiode niet uniform zijn, maar afhangen van de oorspronkelijke leeftijd en het endemiciteits niveau van de bevolking voor het begin van de bestrijdingsaktiviteiten. De epidemiologische indices voor kinderen die geboren zijn voor het begin van de vectorbestrijding, zullen geen daling vertonen gedurende de eerste 8 jaar van onderbreking van de transmissie-cyclus. De prevalentie is te ongevoelig om van enig belang te zijn voor de evaluatie in de hyper-endemische dorpen gedurende het grootste deel van de bestrijdingsperiode. De meest sensitieve en betekeningsvolle index voor een vergelijkende analyse en voor de beoordeling van de epidemiologische veranderingen is het geometrisch gemiddelde aantal microfilariae per huidbiopsie in een cohort van volwassenen. Deze index, de CMFL, wordt nu in alle routine-analyses in het OCP gebruikt. De nieuwe analytische methodologie heeft een veel betere waardering van de belangrijke epidemiologische resultaten van de eerst 8 jaar van vectorbestrijding in het OCP mogelijk gemaakt. Andere aspecten van de dynamiek van onchocerciasis-infectie gedurende de periodes voor en tijdens vector bestrijding worden ook besproken in het hoofdstuk, en prioriteiten voor verdere modellering van onchocerciasis worden geformuleerd.

Hoofstuk 4.2 beschrijft het effekt van 7-8 jaar vectorbestrijding op de evolutie van oculaire onchocerciasis. Een cohort van 1170 dorpsbewoners van boven de vijf jaar uit 12 hyperendemische dorpen van het centrale OCP gebied werden onderzocht voor het begin, en na 7-8 jaar van vectorbestrijding. Het gedeelte van het cohort dat oorspronkelijk geen oculaire onchocerciasis, of alleen de symptomen van het allereerste beginstadium had, was 7-8 jaar later in het algemeen volledig vrij van oculaire symptomen, en slechts een heel kleine groep had microfilariae in het oog of een oculaire laesie in het beginstadium. In de groep met oorspronkelijk een groot aantal microfilariae in het oog was er een verminderd risiko om oculaire laesies te ontwikkelen en niemand in deze groep werd blind. Het gedeelte van het cohort dat reeds voortgeschreden laesies van het oog had toonde in het algemeen geen verandering, terwijl van de laesies in het beginstadium een aantal waren verdwenen. Nieuwe gevallen van blindheid kwamen alleen voor in die groep die al ernstige oculaire laesies had voor het begin van vectorbestrijding en de incidentie van blindheid was laag in vergelijking met gebieden met ononderbroken transmissie.

Hoofdstuk 4.3 behandelt de veranderende populatiedynamiek van *O. volvulus* gedurende de vector-bestrijdingsperiode. Nodulectomieen werden gedaan bij 256 patienten uit 10 dorpen in het OCP en bij 74 patienten uit twee dorpen in een gebied met ononderbroken transmissie. Een totaal van 1198 noduli werden verwijderd en 4350 volwassen wormen werden geisoleerd en onderzocht op levensvatbaardheid en reproductiviteit. In de OCP dorpen is de worm populatie verouderd en aan het uitsterven zonder vervanging door nieuwe generaties van parasieten en verschillende resultaten signaleren een ineenstorting van de wormpopulatie na ongeveer 12 jaar van onderbreking van transmissie. De sexuele activiteit van de wormpopulatie was belangrijk verminderd. Een productiviteitsindex werd ontwikkeld om het produktieniveau van microfilariae per nodule te meten. De reduktie in deze index in de OCP dorpen vertoonde een goede correlatie met de vermindering in de CMFL gedurende de vector-bestrijdingsperiode. De gegevens tonen aan dat het niet alleen de levensduur van de parasiet is die de vereiste duur van de vectorbestrijding bepaalt, maar dat de verminderde productiviteit van de verouderende parasietenpopulatie eveneens van groot belang is.

Hoofdstuk 4.4 geeft een samenvatting van alle entomologische en epidemiologische evaluatie resultaten van 11 jaar vectorbestrijding. Entomologisch gezien kan het originele OCP gebied in vier hoofdgebieden worden onderverdeeld: het centrale OCP gebied (85% van het totale gebied) waar vectorbestrijding heel erg effectief is geweest en waar transmissie praktisch volledig is onderbroken, de westelijke en zuid-oostelijke grensgebieden die onderhevig zijn geweest aan reinvasie door infectieve vliegen vanuit gebieden buiten de OCP, en fase IVb in het zuiden van Ivoorkust waar de vectorbestrijding pas begon in 1979.

De resultaten van de epidemiologische evaluatie komen goed overeen met de entomologische bevindingen. Van een totaal van 6700 onderzochte kinderen, die geboren zijn na het begin van de bestrijdingsactiviteiten, was er slechts één geinfecteerd in plaats van een verwacht aantal van 400 geinfecteerde kinderen als er geen vectorbestrijding had plaats gevonden. In het merendeel van de dorpen in het centrale OCP gebied vertoonde de CMFL de voorspelde, bijna lineaire, daling en in dorpen met 10 jaar bestrijding was de CMFL al met meer dan 90% verminderd. In deze dorpen was de voorspelde versnelde daling in de prevalentie van microfilariae in de huid begonnen. Microfilariae werden bijna niet meer gezien in het oog na 8-10 jaar bestrijding en de incidentie en verdere ontwikkeling van oculaire laesies leek stopgezet te zijn. Geconcludeerd wordt dat na 11 jaar van vectorbestrijding onchocerciasis niet langer een maatschappelijk gezondheidsprobleem is in het centrale OCP gebied. In de reinvasie gebieden is de situatie volslagen anders: hier werden 37 geinfecteerde kinderen gevonden tegen een verwacht aantal van 225, er was veel minder daling in de CMFL dan in het centrale gebied en de daling in het gemiddeld aantal microfilariae in het oog was ook onbevredigend. De lokale vectorbestrijding heeft een belangrijke vermindering in de transmissie teweeg gebracht maar de reinvasie van infectieve vliegen houdt een niveau van transmissie in stand dat onacceptabel hoog blijft. De volledige bestrijding van de ziekte zal daarom moeten wachten op de uitbreiding van de vectorbestrijdings activiteiten naar het westen en het zuid-oosten.

Hoofdstuk 4.5 geeft de meest recente resultaten voor de voorspelde en waargenomen afname in onchocerciasis-infectie in het centrale OCP gebied. In 55 dorpen zijn sinds het begin van de vectorbestrijding regelmatig bevolkingsonderzoeken gedaan waarin huidbiopsieen genomen werden. De laatste ronde van bevolkingsonderzoeken werd gedaan na 12-14 jaar met suksesvolle vectorbestrijding. De waargenomen trends in de prevalentie en intensiteit van onchocerciasis-infectie in cohorten van volwassenen worden vergeleken met de trends die voorspeld waren met een 'host-parasite' model. Een beschrijving van het model is aan het hoofdstuk toegevoegd. Na 12-14 jaar van bestrijding was de CMFL bijna gelijk aan nul in alle dorpen. Gedurende de laatste jaren van vectorbestrijding heeft de prevalentie van infectie de versnelde daling vertoond die voorspeld was met het model. Er was in het algemeen een goede overeenkomst tussen de waargenomen en voorspelde trends. De voorspellingen waren gebaseerd op een geschatte gemiddelde duur van infectie van 10.4 jaar, wat overeenkomt met een gemiddelde reproductieve levensduur van *O.volvulus* van 9-9.5 jaar, en een bovengrens van 15 jaar voor 95% van de infecties. Een verschil tussen voorspellingen en waarnemingen betrof de trend in de CMFL die in 18 dorpen niet de voorspelde daling vertoonde tussen het eerste en tweede bevolkingsonderzoek. In het noord-oostelijke deel van het centrale OCP gebied was de uiteindelijke daling in de prevalentie sneller dan was voorspeld. Na 14 jaar van vectorbestrijding is het niveau van onchocerciasis-infectie zo ver gedaald dat beeindiging van de vectorbestrijding serieus wordt overwogen.

Hoofdstuk 5 geeft de resultaten van bevolkingsexperimenten die zijn ondernomen in de OCP met het microfilaricide ivermectine. Hoofdstuk 5.1 beschrijft het grootste experiment dat gedaan werd in een geisoleerd gebied met hyperendemische savanna-onchocerciasis bij Asubende in Ghana. Een van de doelstellingen van het experiment was het effect te bepalen van grootschalige bevolkingsbehandeling met ivermectine op het reservoir van microfilariae en op de transmissie van *O.volvulus*. Het gebied is sinds 1978 onder entomologische surveillance. Van 1 september 1987 tot 11 february 1988 werd dit geintensiveerd met dagelijkse vector-collectie en dissectie van meer dan 30.000 vliegen. Tussen 7 en 10 october 1987 werd een totaal van 14.991 personen behandeld met ivermectine. Gedurende bevolkingsonderzoeken werden huidbiopsieen genomen voor de behandeling, en twee en vier maanden na de behandeling. In behandelde personen was het gemiddelde aantal microfilariae per biopsie na twee maanden verminderd met 96%. Gedurende de volgende twee maanden nam het aantal microfilariae weer toe en de toename leek sneller te zijn dan was waargenomen in klinische experimenten met ivermectine. Het totale reservoir van microfilariae, dat twee maanden na de behandeling van de bevolking voorradig was voor transmissie, was verminderd met een geschatte 68%-78%. Deze schatting kwam goed overeen met de entomologische resultaten die aangaven dat de transmissie gedurende de eerste drie maanden na ivermectine-behandeling was verminderd met 65%-85%. De studie heeft voor de eerste keer aangetoond dat grootschalige chemotherapie een belangrijke reductie in de transmissie van onchocerciasis teweeg kan brengen. Het resterende transmissieniveau was echter nog steeds onaanvaardbaar hoog en verdere studies zijn nodig om te kunnen voorspellen wat het lange-termijn-effect zal zijn van regelmatige behandeling van de bevolking met ivermectine.

Hoofdstuk 5.2 geeft voor alle acht bevolkingsexperimenten die ondernomen zijn in het OCP de gecombineerde resultaten betreffende ongunstige bijwerkingen na behandeling met ivermectine. De acht experimentele gebieden liggen in acht verschillende West-Afrikaanse landen. Zij vertegenwoordigen verschillende epidemiologische situaties van operationeel belang voor de OCP en verschillen met name in hun endemiciteitsniveau. Een totaal van 50.929 personen werden behandeld met ivermectine en gedurende 72 uur onder controle gehouden voor eventuele ongunstige bijwerkingen. Voor deze controle werd een standaardprotocol gebruikt. In totaal werd 60% van de censuspopulatie behandeld. De voornaamste redenen voor niet-behandeling waren de uitsluitingscriteria en afwezigheid van het dorp ten tijde van de behandeling. Van de behandelde personen rapporteerde 9% ongunstige bijwerkingen, 2,4% bijwerkingen van middelmatige ernst en 0.24% ernstige bijwerkingen. Het soort van bijwerkingen was in het algemeen vergelijkbaar met de bijwerkingen die waargenomen waren gedurende de klinische experimenten en bestonden uit pijn, koorts, jeuk, uitslag, zwelling van lymphklieren en oedeem. Niet eerder gerapporteerd waren pijn in de liesklieren en hard-aanvoelend oedeem van de ledematen, welke soms belangrijke oorzaken van morbiditeit waren.

De incidentie van ongunstige bijwerkingen hing direct samen met het aantal microfilariae in de huid en dit sugggereert dat de bijwerkingen het resultaat waren van het microfilaricidale effect van het geneesmiddel, en niet een gevolg van intrinsieke toxiciteit. De relatie met het aantal microfilariae verklaart ook waarom de incidentie van bijwerkingen veel hoger was in de meest endemische gebieden. Na correctie voor de intensiteit van infectie was er geen verschil meer tussen de experimenten. De meest voorkomende ernstige bijwerking was ernstige symptomatische orthostatische hypotensie wat werd gediagnostiseerd in 49 gevallen. Dit syndroom was ook gerelateerd aan de intensiteit van infectie. In negen gevallen van ernstige hypotensie werd het nodig gevonden om een intraveneuze injectie met hydrocortison te geven.

Alle gevallen herstelden snel, meestal binnen een paar uur. De meest ernstige bijwerkingen waren drie gevallen van ernstige dyspnoe waarbij er sprake was van levensgevaar. Het is echter onduidelijk of deze drie gevallen met de ivermectine-behandeling samenhingen.

Hoofdstuk 5.3 beschrijft het effect van bevolkingsbehandeling met ivermectine op oculaire onchocerciasis in de holo-endemische dorpen die in het centrum van het experimentele gebied van Asubende in Ghana liggen. Een cohort van 417 personen, waarvan er 369 waren behandeld, werd gevolgd 4 and 12 maanden na de behandeling. Het gemiddelde aantal microfilariae in de voorste kamer van het oog en in de cornea verminderde in behandelde personen na 4 maanden tot minder dan 20% en 10% van het oorspronkelijke gemiddelde. Na 12 maanden werd er echter weer een significante toename in het gemiddeld aantal microfilariae in het oog waargenomen. De oculaire laesies in het voortgeschreden stadium van ontwikkeling bleven stabiel gedurende deze periode. Een belangrijke nieuwe bevinding was een significante regressie na ivermectine-behandeling van oculaire laesies van het voorsegment van het oog die nog in het beginstadium waren. Dit werd met name geobserveerd voor iridocyclitis. Gegeven de substantiele toename van het aantal microfilariae in het oog 12 maanden na de behandeling kan het in bijzonder endemische gebieden nodig zijn de behandeling niet jaarlijks maar elke 6 maanden te geven. Waarnemingen over een lange termijn blijven nodig voordat een goede schatting gegeven kan worden van het positieve resultaat dat bereikt kan worden met de grootschalige behandeling van een bevolking met ivermectine.

Hoofdstuk 6 geeft de algemene conclusies van de studie. De nadruk wordt gelegd op de centrale rol die het begrip endemiciteit in de epidemiologie van onchocerciasis speelt en van het belang van de CMFL als een kwantitatieve maat van endemiciteit. Speciale aandacht wordt geschonken aan de praktische waarde van de verschillende bevindingen voor de planning en evaluatie van onchocerciasis-bestrijding in West Afrika en elders.

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This Thesis is based on the following publications which have been reproduced with the kind permission of the respective co-authors and publishers:

Chapter

2.1. Remme,J., J.B.Zongo. Demographic aspects of the epidemiology and control of onchocerciasis in West Africa. In: Service, M., ed. *Demography and vector-borne diseases*. Boca Raton Fl, CRC Press (1989) Ch.24.

3.1. Remme,J., K.Y.Dadzie, A.Rolland, B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. I. West African savanna. *Tropical Medicine and Parasitology*, 40 (1989) 340-347.

3.2. Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. Ocular Onchocerciasis and intensity of infection in the community. II. West African rainforest foci of *Simulium yahense*. *Tropical Medicine and Parasitology*, 40 (1989) 348-354.

4.1. Remme,J., O.Ba, K.Y.Dadzie, M.Karam. A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River Basin area. *Bulletin of the World Health Organization*, 64 (1986) 667-681.

4.2. Dadzie,K.Y., J.Remme, A.Rolland, B.Thylefors. The effect of 7-8 years of vector control on the evolution of ocular onchocerciasis in West African savanna. *Tropical Medicine and Parasitology*, 37 (1986) 263-270.

4.3. Karam,M., H.Schultz-Key, J.Remme. The population dynamics of *Onchocerca volvulus* after 8 years of vector control in West Africa. *Acta Tropica*, 44 (1987) 445-457.

4.4. Remme,J., K.Y.Dadzie, M.Karam, B.Philippon, G.Zerbo. The effects of 11 years of *Simulium* control in the OCP on ABRs, ATPs, prevalence and intensity of *O.volvulus* infection and on the incidence and prevalence of eye lesions. Working paper for the third WHO Expert Committee on Onchocerciasis. Geneva, WHO/ONCHO/EC/WP/86.4 (1986).

4.5. Remme,J., G.De Sole, G.J.van Oortmarssen. The predicted and observed decline in onchocerciasis infection during 14 years of successful vector control with reference to the reproductive lifespan of *Onchocerca volvulus*. Submitted for publication.

5.1. Remme,J., R.H.A.Baker, G.De Sole, K.Y.Dadzie, J.F.Walsh, M.A.Adams, E.S.Alley, H.S.K.Avissey. A community trial of ivermectin in the onchocerciasis focus of Asubende, Ghana. I. Effect on the microfilarial reservoir and the transmission of *Onchocerca volvulus*. *Tropical Medicine and Parasitology*, 40 (1989) 367-374.

5.2. De Sole,G., J.Remme, K.Awadzi, S.Accorsi, E.S.Alley, O.Ba, K.Y.Dadzie, J.Giese, M.Karam, F.M.Keita. Adverse reactions after mass treatment of onchocerciasis with ivermectin: Combined results from eight community trials. *Bulletin of the World Health Organization*, 67, No.6 (1989)

5.3. Dadzie,K.Y., J.Remme, E.S.Alley, G.De Sole. Changes in ocular onchocerciasis four and twelve months after community-based treatment with ivermectin in an holo-endemic onchocerciasis focus. *Transactions of the Royal Society for Tropical Medicine and Hygiene* (in press).

CURRICULUM VITAE

J.H.F.Remme was born on 20 July 1948 in Gouda where he concluded his secondary school education at the Christelijk Lyceum with the HBS-B exam in 1967. After one and a half year interruption because of military service, he continued to study at the University of Delft where he obtained in 1976 his Master of Science degree in mathematics, with as specialization statistics, stochastics and operational research. He was subsequently appointed research assistant at the Department of Medical Statistics of the Faculty of Medicine of the University of Leiden. In April 1978 he became lecturer, and later senior lecturer, in epidemiology and biostatistics at the Division of Community Medicine of the Faculty of Medicine of the University of Dar es Salaam in Tanzania. In July 1983 he joined the World Health Organization as biostatistician for the Onchocerciasis Control Programme in West Africa. He is presently chief of the Biostatistics and Information Systems Unit of this Programme and stationed in Ouagadougou, Burkina Faso. He is a member of the WHO Subcommittee for monitoring of ivermectin trials in onchocerciasis and of the Steering Committee of the Scientific Working Group on Filariasis of the UNDP/Worldbank/WHO Special Programme for Research and Training in Tropical Diseases.