MODELLING ONCHOCERCIASIS TRANSMISSION AND CONTROL

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Cover: Blind onchocerciasis patient guided by a boy; handmade bronze sculpture from Ouagadougou, Burkina Faso. Cover design: Mario van Voorst.

MODELLING ONCHOCERCIASIS TRANSMISSION AND CONTROL

Het modelleren van de verspreiding en bestrijding van rivierblindheid

Proefschrift

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L'Éternel ouvre les yeux des aveugles;
L'Éternel redresse ceux qui sont courbés;
L'Éternel aime les justes.

(Psaume 146:8)

les aveugles voient, les boiteux marchent,
les lépreux sont purifiés, les sourds entendent,
les morts ressuscitent,
et la bonne nouvelle est annoncée aux pauvres.

(Matthieu 11:5)

Voor mijn ouders
Voor Joke

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Chapter I

Introduction

'River blindness - soon an image of the past'

In 1990 the World Health Organization (WHO) coordinated Onchocerciasis Control Programme in West Africa (OCP) used this slogan for evaluating fifteen years of control of the parasitic disease onchocerciasis and for expressing its optimism about the future. Based on the obvious success of OCP and on the availability of a safe and effective drug (ivermectin), the UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR) has announced onchocerciasis to be one of the tropical diseases with good prospects for worldwide elimination, at least as a public health problem (the others being Chagas disease, Lymphatic filariasis, and Leprosy[1]).

To judge slogans and statements like these, and in particular to determine under which circumstances and with what strategies they could become a realistic perspective, one should perform an integrated and detailed study of the dynamics of the disease and the impact of control. Such a study should preferably be embedded in a comprehensive quantitative approach. In the light of this, the objectives of the work reported in this thesis were (1) to develop, quantify, and validate a model for the transmission and control of onchocerciasis in West African savanna and (2) to use this model for aiding decision making in the OCP. Through achieving these objectives we have tried to contribute to a better understanding of the dynamics of the parasite that causes the illness and the impact of intervention measures, and to the as yet successful combat against the disease.

In this general introduction an outline will be given of the epidemiology and control of onchocerciasis. Secondly, an overview of the achievements of the OCP in controlling the disease in West Africa will be provided. Finally, a short history will be presented of the role of quantitative modelling within OCP prior to the work reported in this thesis.

[1] See 'TDR-News' No. 49 (March 1996).

I.1 Onchocerciasis: the disease, its transmission

Geographical distribution and magnitude of the problem

Onchocerciasis is especially endemic in Western and Central Africa and in Central and Southern America (see Fig. 1). Current estimates suggest that about 17,7 million of persons are infected, of whom some 270,000 are blind and a further 500,000 severely visually disabled. Lacking accurate data from a number of countries, these figures will certainly be an underestimate (WHO, 1995). Most of the blinding form of onchocerciasis is found in sub-saharan Africa (outside the areas covered by the OCP, see below). Although onchocerciasis is not a lethal disease as such, there is clear evidence that blindness may cause early death. It has been estimated that the average lifespan at the onset of blindness is only 7 to 9 years (Prost, 1986) and that blindness related excess-mortality varies between 3.3 (in trachoma endemic areas; see Taylor *et al.*, 1991) and 4 times (Prost and Vaugelade, 1981) the mortality of non-blind persons. While blindness is still the most important public health problem, severe skin lesions and troublesome itching are also widely prevalent in large parts of Africa (Remme, 1995; Remme, in press) and constitute a major health problem too.

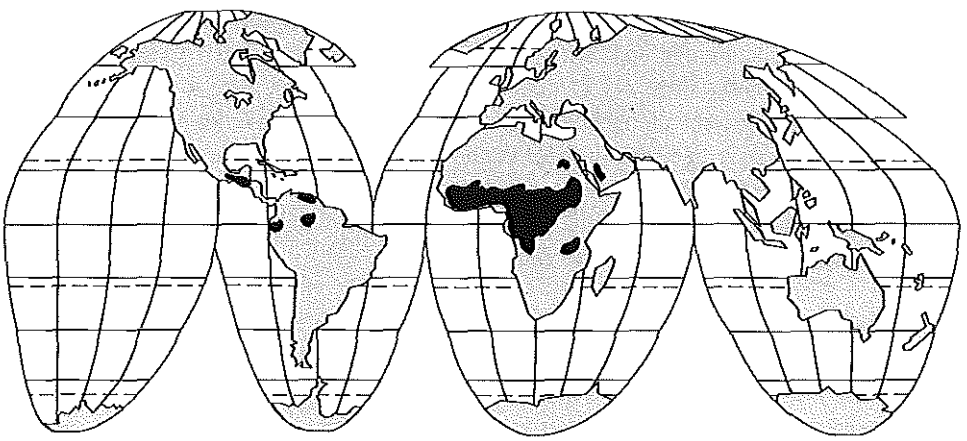

Figure 1 Geographical distribution of onchocerciasis (based on WHO, 1995).

Not only is onchocerciasis infection and morbidity a serious health problem in endemic areas, it has also important social and economic implications. In severely afflicted communities blindness, prevalences of up to 15% in the total population and 40% among the adult males may exist (Duke, 1990; Remme and Zongo, 1989; Prost and Vaugelade, 1981). It has been estimated that, in the absence of control, in

hyperendemic villages in Burkina Faso 45% of males and 35% of females aged 15 are likely to become blind before they die (Prost, 1986). These unbearable conditions gave rise to depopulation of the river basins, leading to a poor utilization of the fertile river basins. In 1972 only about 7% of the valleys of the White and Red Volta river basins were used for agricultural cultivation (Remme and Zongo, 1989).

Biology of parasite and vector

Onchocerciasis is a parasitic infectious disease. The parasite *Onchocerca volvulus* is a filarial nematode which lives in subcutaneous nodules, from where it expels millions and millions of living embryos or microfilariae (Mf) (Duke, 1990; Schulz-Key, 1990). The lifespan of the adult parasite is estimated at 10-11 years on average (Plaisier *et al.*, 1991). The sessile female parasite can reach a length of 20-50 cm (Duke, 1990). The mobile male worm is much shorter (5 cm). Microfilariae (220-300 μm) invade the skin and can be engorged by a blood-sucking fly of the genus *Simulium*. Some of the engorged Mf succeed in developing to infective (L3) larvae which can be transmitted to man during one of the subsequent blood-meals of the fly. The life cycle (see Fig. 2) is closed when invading L3-larvae grow in the human host to the stage of adult male or female worm.

For its reproduction, *Simulium damnosum* s.l. ('blackfly') depends on fast flowing streams and rivers. About 3 days after bloodsucking, female flies shed their eggs in the rivers (Thompson, 1976). Together, the egg, pupa, and larva stage takes 12 - 14 days (Greene, 1990). In the absence of control, in the most notorious onchocerciasis foci of Western Africa - the area considered in this thesis - annual man biting rates (ABR) close to breeding sites are in the range of 50,000 to 250,000 and even higher (Philippon *et al.*, 1990).

Morbidity and diagnosis

The most severe complications of onchocerciasis, or 'river blindness', are irreversible ocular lesions resulting in impaired vision and finally total blindness (Prost, 1986). Ocular pathology is mainly related to inflammatory reactions to dead microfilariae which invaded the eye-tissue. For the progress of lesions of the posterior segment of the eye also immune-complexes and auto-immune mechanisms are thought to be responsible (Van der Lelij *et al.*, 1990). Functional blindness can be the result of opacification of the cornea (reduced visual acuity) and a reduced visual field (key-hole vision). Other clinical manifestations of onchocerciasis include dermal, lymphatic and systemic complications. Dermal involvement is often accompanied by troublesome itching.

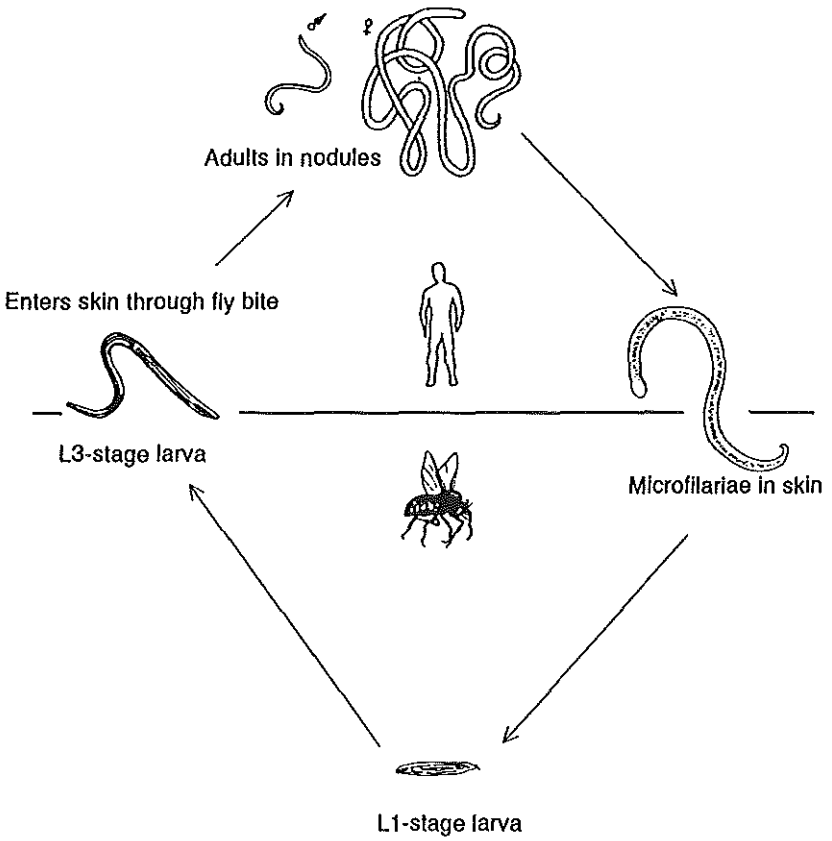

Figure 2 Life cycle of *Onchocerca volvulus*.

Onchocerciasis is usually diagnosed by obtaining a small skin biopsy (skin-snip) in which, after incubation in saline, microfilariae can be observed and counted. Though skin-snipping is the most reliable way of discovering the infection, other less invasive methods are being explored to assess the endemicity in an area. These methods include ocular examination (observing and grading lesions and counting microfilariae), palpation of sub-epidermal nodules with adult worms, observing the presence of dermal lesions, interviewing for complaints like itching, and immuno-diagnosis (though field-applicable specific tests are still not available). Another indication of endemicity can be obtained by catching blackflies and determining the presence of *O. volvulus* larvae.

I.2 Treatment and control

Vector control

By its nature of vector borne disease, onchocerciasis can be controlled by eliminating the vector *S.damnosum* or preventing its contact with man. Control of blackflies can be achieved by killing the adult flies, by killing the larvae or by modifying the environment to prevent breeding of the flies (which could be a consequence of the construction of dams for power-generation). Blackflies bite during daytime and outside the houses. This complicates control of the adult stages by insecticides (adulticiding). The only successful attempts have been helicopter spraying of gallery forests to destroy blackflies which were found to reinvade controlled areas (WHO, 1987a). However, the most effective way of vector control is killing fly-larvae by applying larvicides to rivers and streams. A variety of biodegradable formulations is currently available which are highly effective against the larvae and relatively safe for the rest of the environment. These include chemicals like temephos (the preferred one in view of effectivity and safety), phoxim, pyraclofos, and permithrin and biological compounds like *Bacillus thuringiensis*. Given the development time of eggs to pre-adult stages (1-2 weeks), larvicides should preferably be applied weekly. Furthermore, rotational use of the different formulations is recommended to prevent or control resistance to specific larvicides (Kurtak, 1990). Larvicides are usually applied by helicopter-spraying to achieve an instant killing of larvae in the often very large breeding sites. However, also with limited means remarkable results have been achieved. Especially effective local control by DDT has been reported in the period 1945-1970, i.e. the period between the invention of this chemical as a very successful insecticide and the detection of its persistence and environmental damage (Walsh, 1990).

Chemotherapy

Until the registration of ivermectin in 1987, no effective and safe drug was available for the treatment of human onchocerciasis. The two standard drugs before that time were suramin, which kills the adult worm, and diethylcarbamazine (DEC), which kills microfilariae. Suramin is highly impractical because it has to be given intravenously and, because of its toxicity, under strict medical supervision (Thylefors and Rolland, 1979). DEC, whilst being a safe drug for the treatment of the related disease lymphatic filariasis (Ottesen, 1985), excites severe and dangerous reactions in skin and eyes especially in persons with high skin microfilarial loads (Mazotti-reaction, see WHO, 1987a).

Ivermectin, a broad antiparasitic agent widely used in veterinary medicine, underwent intense clinical testing for its efficacy and safety and has become the drug of choice since 1987 (Goa *et al.*, 1991). Given at a standard dose of 150 μg /

kg body weight, it effectively eliminates microfilariae without the severe inflammatory response induced by DEC. Though also effects on the adult worms are observed (Duke *et al.*, 1992; Chavasse *et al.*, 1992; Plaisier *et al.*, 1995), microfilariae production restarts soon after treatment and, hence, repeated treatment is required to keep Mf levels low enough to prevent progression of ocular lesions (Dadzie *et al.*, 1991).

I.3 The Onchocerciasis Control Programme in West Africa (OCP)

The extremely high levels of endemicity in many foci in the savanna areas of seven of the most afflicted West African countries (1 to 1.5 million people infected), the associated high burden of blindness (35,000 persons blind), and the related socio-economic consequences (underpopulated river valleys) gave birth to the Onchocerciasis Control Programme in West Africa (OCP) in 1974. To pave the way for OCP, in 1970 the WHO - in association with the Food and Agriculture Organization (FAO) and financed by the United Nations Development Programme (UNDP) - instituted the 'preparatory assistance to government' (PAG) mission. The task of this PAG-mission was to perform field investigations, make plans for vector control, and assess the costs of control. The report (PAG, 1973; Hunter, 1981) led to the conclusion that large scale vector control was a feasible option and gave rise to the formal establishment of OCP as a corporate undertaking of seven participating countries, donor communities (countries, foundations, and development banks) and four United Nations agencies (UNDP, FAO, the World Bank, and the WHO). The WHO executive agency and headquarters were located in Ouagadougou, Burkina Faso (Upper Volta). The original programme area comprised most of the savanna area of Burkina Faso, Mali, Ivory Coast, Ghana, Togo, Benin, and Niger covering as much as 764,000 sq. km (WHO, 1987a).

Lacking a safe drug for treatment of onchocerciasis patients, the only control option available to the OCP was aerial larviciding of river stretches where the breeding sites of the vector are found. Armed with helicopters and planes, the objective of OCP is "to eliminate onchocerciasis as a disease of public health and socioeconomic importance throughout the area covered by the Programme and to ensure that there is no recrudescence of the disease in the future, thus allowing the repopulation and development of those valleys previously almost deserted because of onchocerciasis" (WHO, 1987a). Based on limited information on the longevity of onchocerciasis infection in man derived from East African control programmes (Roberts *et al.*, 1967), the Programme was initially planned to last for a period of 20 years.

Evaluations performed 7 to 8 years after the start of the Programme demonstrated that operations have been highly successful. Marked reductions were found in the intensity of infection in most of the communities (as measured by the CMFL, i.e. the geometric mean no. of Mf per skin-snip in adults) (Remme *et al.*, 1986), the viability of the parasite population (Karam *et al.*, 1987), and in the risk of developing ocular disease and blindness (Dadzie *et al.*, 1986). Furthermore, throughout these first 7-8 years the Annual Biting Rate (ABR) and Annual Transmission Potential (ATP; i.e. the product of ABR and the average no. of L3-larvae found per

biting fly) was kept close to zero in most of the Programme area (Philippon *et al.*, 1990).

However, already during the first years of operations the long-distance migratory movements of *S.damnosum* s.l. appeared to be a major threat of the success of control. Especially at the start of the rainy season the southwestern sector of the Programme became re-invaded by the flies leading to unacceptably high man biting rates. In response to this re-invasion phenomenon, the Programme was extended considerably to the West and Southeast. A map of the Central Programme area and the extension areas is provided in Fig. 3. Inclusion of (parts of) Guinea, Guinea-Bissau, Senegal, and Sierra Leone increased the number of participating countries from 7 to 11, the covered area from 764,000 to 1,235,000 km^2, and the protected population from 16,5 to 24,5 million people (WHO, 1987a).

The availability of ivermectin, since 1987, has considerably broadened the possibilities of control and has changed the strategy of OCP. Especially in the extension areas, vector control is supplemented with annual treatment with ivermectin (dose 150 μg/kg body weight) leading to a more rapid improvement in ocular morbidity and a better control of transmission in re-invaded areas (Molyneux, 1995).

Already in the early years of operations it had been recognized that the second part of OCP's objective, the prevention of recrudescence of the disease, can only be achieved if the achievements will be maintained by the participating countries when OCP would cease to exist as a strongly centralized 'vertical' organization. The process of 'devolution' is now one of the major activities of the Programme and comprises the provision of support for country activities to enhance their capacity and ensure that this capacity is sustainable to detect and manage recrudescence of onchocerciasis (Molyneux, 1995).

The conclusion of a recent 'mid term review' is that the Programme has thus far been highly successful and that, to achieve its long term goals, OCP should continue its present strategy of combined larviciding and ivermectin distribution until the year 2002 (WHO, 1994). In a recent analysis it has been argued that OCP has been and will be a highly cost effective programme. It has been estimated that during 1974-1994 a total of 265,000 cases of blindness have been prevented and that this resulted in 1,708,000 additional years of productive labour. Furthermore, for 1994 the total area of new available agricultural land (previously abandoned land, now freed from onchocerciasis) is estimated at almost 10 millions hectares (Kim and Benton, 1995).

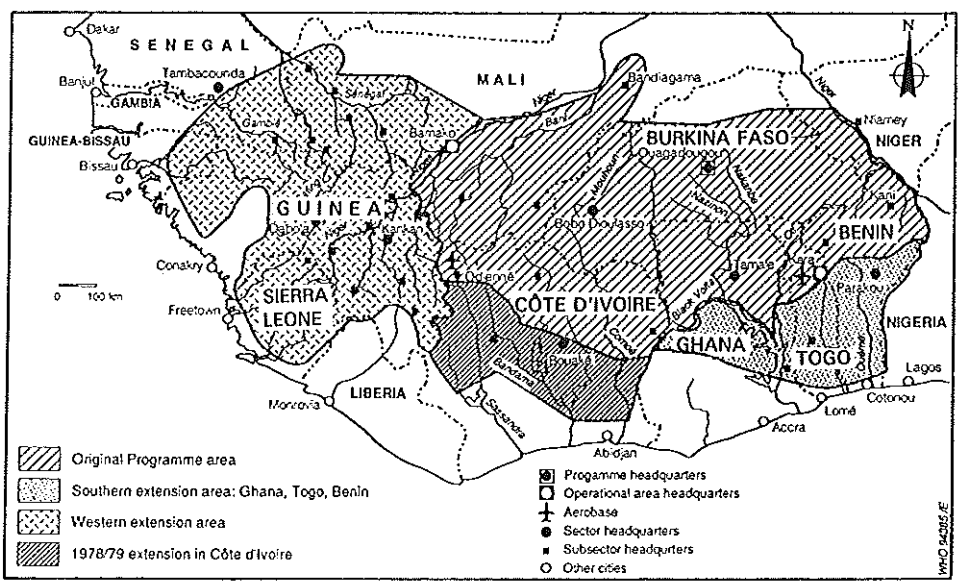

Figure 3 The area covered by OCP operations (detailed map from Samba, 1994).

I.4 A short history of modelling within the OCP[2]

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 entomological evaluations which indicated that transmission had been brought down to insignificant levels. However, epidemiological evaluations had not been able to demonstrate a major epidemiological change during the initial years of control. The routine analysis of skin-snip data had not yet revealed a significant decline in the parasite reservoir. No children below the age of 5 years were found to be infected, but only few infections would have been expected in this age group even if there had been no control. The standardized prevalence of microfilariae (Mf) in the skin-snip, which was the epidemiological index at that time, had shown only a limited decline during the first eight years of control (Kirkwood *et al.*, 1983). 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. 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.

Force-of-infection model

A new analytical methodology was introduced which took the dynamics of the parasite and of the human population into account. The basis of this work was the development of a simple force-of-infection model (or catalytic model; see Muench, 1959) for onchocerciasis, and its application for a study of the age-specific epidemiological trends during a period of vector control (Remme *et al.*, 1986). 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 epidemiological trends calculated by this simple model were tested against the observed trends in the prevalence and mean load of microfilariae in skin-snips taken from a cohort population in 23 villages in an area with 8 years of successful vector control. This resulted in a crude (but first ever) estimate for the duration of the patent period of the infection of 10 years. The model predictions had important implications for the epidemiological evaluation of the impact of vector control. They showed that epidemiological trends during the control period are not uniform but depend on the initial endemicity level of the population and vary between age groups. Moreover, it became clear that the prevalence of infection is too insensitive

[2] Based on Remme *et al.*, 1995.

to be useful for the evaluation in hyperendemic villages during most of the control period. A much more sensitive and meaningful statistic for a comparative analysis and for the assessment of epidemiological changes would be the mean number of infections, or the mean number of productive female worms per person above the age of 20 years. The number of adult worms cannot be measured directly. However, the microfilarial load in the skin provides an indirect measure, assuming that the Mf production per adult female worm and the survival of Mf are not regulated by density dependent mechanisms. This reasoning led to the introduction of an alternative epidemiological index, the Community Microfilarial Load (CMFL) which is the geometric mean microfilarial load per skin-snip among the population above the age of 20 years (Remme *et al.*, 1986). Within and outside the OCP, the CMFL has now become the preferred index of endemicity of onchocerciasis, partly because it could later be demonstrated that the prevalence of onchocercal blindness is linearly related to the CMFL (Remme *et al.*, 1989a). The use of the CMFL in epidemiological evaluation enabled a much better appreciation of the significant epidemiological impact of 8 years of vector control in the OCP, and it could be shown that in 90% of the original Programme area, vector control had already achieved a reduction in the parasite reservoir of more than 70% (WHO, 1987b).

Host-parasite model: prediction of trends during vector control

Once the new analytical methodology had provided the epidemiological evidence of the effectiveness of the first 8 years of vector control, the focus of attention shifted toward the epidemiological trends to be expected in subsequent years. Of particular interest were predictions of the ultimate decline in the prevalence of infection as this would indicate how many years of vector control would be required. The force-of-infection model, with the assumption of a constant longevity of infection, was clearly not appropriate for such predictions and it became necessary to develop a more sophisticated model which would take the variability in the duration of infection into account. Furthermore, for the interpretation of the observed epidemiological trends in different parts of the Programme area it became increasingly important to have predictions of the trends to be expected in the distribution of microfilarial loads in different age groups, and not only in the prevalence and mean Mf load in adults.

In order to respond to these needs, the so-called "Host-Parasite" model was developed (Remme *et al.*, 1990a). This is a stochastic computer simulation model which uses the technique of microsimulation (Habbema *et al.*, in press). It involves the simulation of the life histories of all individual human hosts living in a community, and of the individual life histories of all adult parasites harboured by these human hosts. The life histories are generated from probability distributions for

which the parameters were estimated using demographic information, results from specific parasitological studies (Karam *et al.*, 1987) and by fitting the model to the epidemiological evaluation data for selected reference villages in the OCP. The major parameters of the host-parasite model which govern the epidemiological trends are the pre-control force-of-infection (which determines the endemicity level), exposure heterogeneity between individuals, the longevity of the adult worm and worm-age specific Mf production. Model output shows the predicted trends in the distribution and summary statistics of skin Mf loads by age and sex during the vector control period. The host-parasite model provided much more realistic predictions of the epidemiological trends during the later years of control. The first predictions with this model were made in 1985, after 10 years of control, and indicated that the prevalence of infection would fall to levels close to zero after 14-15 years of interruption of transmission. For several years the host-parasite model became the principal epidemiological tool for the interpretation of the epidemiological evaluation data collected in dozens of indicator villages.

ONCHOSIM: a microsimulation model for onchocerciasis transmission and control
When the duration of vector control approached 12 years, and the prevalence of infection started to show the predicted accelerated decline throughout the central OCP area, it became urgent to answer the next major question: when could the expensive larviciding operations be stopped without running an unacceptable risk of recrudescence of infection and disease. The host-parasite model could not be used for addressing this question since it does not include the transmission by the vector. Hence, it became necessary to develop again another, and this time a much more complicated, model which describes the full transmission cycle. The resulting ONCHOSIM model is a comprehensive transmission model which allows simultaneous simulation of a human population, the population of parasites inside the humans, the dynamics of the vector population and the impact of interventions based on larviciding, chemotherapy, or a combination of these two. The development and application of ONCHOSIM is the subject of this thesis.

The basic structure of the model was finalized during a workshop at OCP headquarters in January 1987, which was attended by scientists from all technical units of the OCP and by several external experts. The meeting identified the most important operational questions for which a model should be developed. It also recommended that, in order to ensure a sufficiently flexible model which could be adapted according to new scientific insights or new operational needs, the same technique of stochastic microsimulation be used as in the host-parasite model.

I.5 Contents of the thesis

The ONCHOSIM model and computer simulation program is presented in Chapter II. Section II.1 describes the model in a semi-formal way and explains how the model has been implemented in a microsimulation computer program. A complete mathematical description, including the most recent estimates of the parameters is given in section II.2. As argued before, one of the most crucial determinants of the required duration of vector control is the reproductive lifespan of *O.volvulus*. A detailed account of the estimation of this parameter is provided in Chapter III. For making valid predictions of the impact of interventions it is not only important to have a valid model for the dynamics of the parasite in the human and vector population, but also to make proper assumptions on the effectiveness of the control measures themselves. The effects of vector control can be simply translated into a reduction in the man-vector contact, and does not require complicated modelling. However, describing the effects of ivermectin treatment, both in terms of the efficacy of the drug in individual patients and in terms of the coverage of the population, is much less straightforward. Chapter IV describes the results of a community trial with annual ivermectin treatment in the OCP area (section IV.1) and how the data from this trial have been utilized to estimate key parameters for the effects of treatment on the parasite. The most important applications of ONCHOSIM in aiding decision making in OCP are presented in Chapter V. Section V.1 reports predictions of the risk and dynamics of recrudescence after stopping vector control. Based on these predictions it is possible to derive a guideline for the required duration of vector control in the original OCP area (i.e. the area where no ivermectin has been used). Assessing the required duration of strategies based on a combination of vector control and ivermectin treatment (the strategy employed in the extension areas of OCP) is more complicated. A search for effective strategies of this type is described in section V.2.

Chapter II

ONCHOSIM

II.1 ONCHOSIM: a model and computer simulation program for the transmission and control of onchocerciasis

A.P. Plaisier, G.J. van Oortmarssen, J.D.F. Habbema, J. Remme, E.S. Alley
Computer Methods and Programs in Biomedicine 1990;31:43-56[3]

Introduction

Onchocerciasis - or river blindness - is a parasitic disease which is endemic in large parts of Western Africa and in some countries of Central and Southern America (WHO, 1987a). Important foci of the disease can be found close to fast-flowing rivers, where transmission is highest. Prolonged and intensive exposure to the parasite can lead to visual decline and even complete blindness, sometimes in more than 10% of the population of a village (Prost and Prescott, 1984). This makes the disease to a major obstacle to socio-economic development of fertile river basin areas, which justifies the broad attention for both the nature of transmission, and the possibilities of control of onchocerciasis (WHO, 1987a).

River blindness is caused by the filarial worm *Onchocerca volvulus*, which is transmitted from man to man by flies of the genus *Simulium* (in Western Africa especially *Simulium damnosum* s.l.). A schematic representation of this transmission and the life cycle of *O. volvulus* is given in Fig. 2.

Adult inseminated female parasites produce millions of microfilariae (Mf, embryos) which migrate to the skin, where they can cause skin lesions, and into the eyes, where they ultimately may provoke blindness. A biting and blood-sucking *Simulium* fly can ingest Mf from the skin. A fraction of these Mf avoids to be digested and becomes an L1-stage larva soon after the blood meal. These L1-stage larvae migrate to the thorax of the fly and develop into the infective stage (L3 larvae) which eventually enter the head capsule.

During a subsequent bloodmeal, infective larvae can be transmitted to man. Only a small fraction of the infective larvae inoculated into a person succeeds in becoming a mature male or female worm. Between inoculation and maturation there is a time lag, which is called the prepatent period. Mature female parasites usually live in nodules where they mate and produce Mf. Male worms are mobile and capable of mating with females in several nodules (Schulz-Key and Karam, 1986). Microfilarial lifespan is estimated between 6 months and 3 years (Duke, 1968). For Mf

[3] Modifications of ONCHOSIM since this publication will be indicated with footnotes.

engorged in a fly it takes about 6-9 days to develop into the infective L3 stage (Philippon, 1977). Following inoculation into man, the parasite is prepatent for about 1-1.5 years (Prost, 1980). The total lifespan of the worm has been estimated to be about 10-12 years on average (Remme *et al.*, 1986; Karam *et al.*, 1987).

Until very recently, the only means of onchocerciasis control was regular spraying of the breeding places of *Simulium* with chemicals which eliminate the fly larvae, and interrupt the transmission cycle of *O. volvulus*. The World Health Organization (WHO)-coordinated Onchocerciasis Control Programme in West Africa (OCP), which started its activities in 1975, has proven that this method can be very successful. After 12 years of larviciding, it had achieved the control of the disease in 90% of the original Programme area (WHO, 1987b). Recently, also chemotherapy has become available. Clinical trials have demonstrated that the drug ivermectin is an effective and safe microfilaricide (i.e. it kills microfilariae) (Awadzi *et al.*, 1986), and community trials have shown that it is sufficiently safe to be used in mass treatment (De Sole *et al.*, 1989a). Until now no significant long-term effect on the viability of the mature parasite has been observed[4]. Regular administration of ivermectin should prevent visual decline and mass treatment has shown to lower the level of transmission (Remme *et al.*, 1989b).

Extensive entomological and epidemiological evaluation data have been collected in the OCP, and it became obvious that a bio-mathematical model was needed to facilitate the integrated analysis of these data and their optimal utilization in the planning of future control. After a start with a simple model for epidemiological trends in controlled areas of the OCP (Remme *et al.*, 1986), modelling has evolved in close association with analysis and applied research, and has culminated in the present, complete model for onchocerciasis transmission and control. Application of the model will involve in the first place the identification of proper assumptions on the various parameters, including a thorough analysis of a range of possible alternatives. Subsequently, the model will be used to analyze the consistency between different evaluation data. The final application of the model will involve the prediction of future epidemiological trends under different assumptions on transmission and interventions in order to provide a framework for the prospective evaluation and monitoring of alternative strategies for the control of onchocerciasis, which is the ultimate aim of the model.

The model can be regarded as a hybrid of two more or less distinct sub-models. One sub-model deals with the human population and calculates the life history of the parasite in the human host. This is a stochastic sub-model. The other part is a deterministic sub-model which calculates the fly dynamics and the fate of the para-

[4] But see Chapter IV, section 2.

site in the fly. In order to carry out simulations with the model, the computer program ONCHOSIM has been developed.

The model

The model describes the transmission and control of onchocerciasis in an endemic focus. In Fig. 4 the structure of the model is presented schematically, with reference to the life cycle of *O. volvulus*. The most important parameters of the model are summarized in Table 1.

The process of infection

During a bloodmeal of a *Simulium* fly a person can become infected with the parasite *Onchocerca volvulus*. This is indicated in Fig. 4 as 'new infections'. Infection is defined as the inoculation in man of an *O. volvulus* larva (L3 larva) that succeeds in developing into an adult male or female worm.

In the human population there is considerable variation in the degree to which individuals are exposed to the bites of the fly, and hence in the risk of becoming infected. Partially, this degree of exposure is related to the sex and age of a person. In general, exposure is higher for males than for females, while for both sexes the highest values are reached at the puberal and adult ages (Remme *et al.*, 1986; Renz *et al.*, 1987).

Beside these systematic differences, there are numerous other factors which determine exposure, such as attractiveness to the flies and behavioral factors that are independent of age and sex (e.g. fishermen will be highly exposed due to their activities near the breeding places of the *Simulium* flies). Therefore, the exposure (*Ex*) is defined as the product of an age- and sex-dependent relative exposure (*Exa*) and an exposure index (*Exi*), which is assumed to be a personal characteristic during lifetime, and which reflects the remaining differences in exposure between individuals. For an individual i with age a_i and sex s_i:

$$Ex_i = Exa(a_i, s_i) \times Exi_i \qquad (1)$$

The random variable *Exi* is governed by a continuous probability distribution (see Table 1).

Microfilarial production

In the model, the duration of the development of the immature parasite, the prepatent period *Tp*, and the total longevity *Tl* of the worm are both random variables governed by a continuous probability distribution. After the prepatent period a

Table 1 Input parameters for the ONCHOSIM model

Parameter	Model specification
Demography	
Initial population size	Number of men and women by age
Human life table	Survival probability as a function of age
Human fertility	Number of offsprings per year as a function of age
Exposure	
Age- and sex-specific relative exposure (*Exa(a,s)*)	Average exposure for an individual of age *a* and sex *s*
Exposure index	P.d.f.[a] of individual exposure (*Exi*)
Life history and productivity of the parasite in the human host	
Worm longevity	P.d.f. of the total lifespan (*Tl*) of the parasite human host
Prepatent period	P.d.f. of the duration of the prepatent period (*Tp*)
Age-dependent potential microfilaria production	Potential relative microfilarial productivity of a parasite by age
Longevity of microfilariae	Lifespan of a microfilaria (*Tm*)
Worm's contribution to the skin load	Factor (*cw*) between skin load (*sl*) and effective load (*el*)
Skin snip variability	P.d.f. of the number of microfilariae per skin snip (mean is *sl*)
Dispersal factor	P.d.f. for a worm's contribution to the skin snip count (*d*)
Mating cycle	Interval (months) between two mating events
Mating factor	Male worm:female worm ratio required to guarantee 100% mating
Parasite and vector	
Fly survival	Fraction of flies surviving during 1 day
Gonotrophic cycle	P.d.f. of the time between two blood meals
Fly fecundity	Number of nulliparous flies resulting from a single brood of a *Simulium* fly

Parameter	Model specification
Fly larval period	Duration of the larval stage of *Simulium* flies
Zoophily	Fraction of bites of *Simulium* flies which are not taken on humans
Maximum biting rate	Monthly biting rate (*mbr*) under undisturbed circumstances (for each calender month)
Fly immigration	Monthly biting rate caused by immigrating flies (for each calender month)
Microfilarial uptake (*lu*)	Average number of L1-larvae per blood meal as a function of the skin load (*sl*) of the human host
Larval development	P.d.f. of the time to reach the L3-stage after engorgement
Larval survival (L1->L3)	Fraction of the L1-larvae that survives to the L3-stage
Larval survival (L3)	Fraction of the L3-larvae that survives one gonotrophic cycle
Larval release	Fraction of the L3-larvae that is released during a human blood meal
Infection as a function of L3 release	Average proportion of released L3-larvae that develop into mature parasites (sr)
Disease	
Blindness threshold	P.d.f. of the critical value for blindness of the accumulated effective load
Excess mortality	P.d.f. of the reduction factor for the residual life expectancy of blind persons
Ivermectin	
Coverage	Average percentage of the census population treated with ivermectin
Age- and sex-specific compliance	Relative probability of compliance with treatment by age and sex
Instantaneous effect	P.d.f. for the reduction in microfilarial load due to treatment
Cumulative effect	Reduction in potential productivity as a function of the number of treatments
Larviciding	
Inter-application period	Number of days between two larvicide applications
Coverage	Percentage of the Simulium larvae killed per treatment

[a] P.d.f. = probability distribution function.

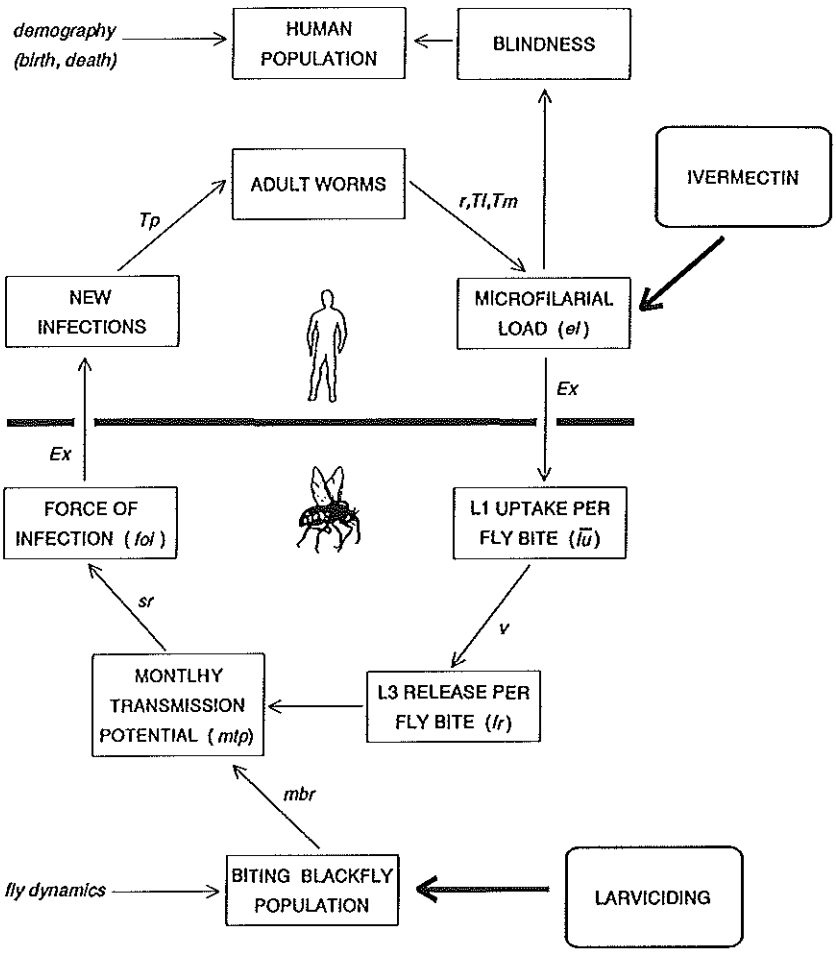

Figure 4 Schematic representation of the structure of the model.

female worm can start producing Mf if there are also mature male worms. Female worms need to mate regularly (Schulz-Key and Karam, 1986). The longevity of the microfilariae *Tm* is given a fixed value, as variability in *Tm* is of minor importance in comparison with variability in *Tl* and *Tp*.

A single female worm can produce millions of Mf during her life. Since the exact number of Mf originating from one female is unknown, we introduce the relative microfilarial offspring *mo*. This *mo* reflects the contribution of a female worm to the

total Mf load in the human body. It is a relative measure with a maximum value of 1.

Following the onset of Mf production, *mo* will build up to an equilibrium value. As Mf longevity is fixed, this build-up phase requires a period equal to *Tm*. The equilibrium level of *mo* depends on the rate at which Mf are produced. This rate is represented by *r*, the relative productivity, which is dependent on the age of the female worm; $r=1$ at maximum productivity.

For a female worm of age *a*, the microfilarial offspring *mo* can be described as follows:

$$mo(a)=\int_0^{Tm}\frac{1}{Tm}r(a-x)dx \qquad (2)$$

It is clear that this relationship is only valid if no microfilaricide is given, as this causes an instantaneous reduction of the Mf load (see paragraph on intervention by mass treatment). Beside the age of the worm, the value of *r* is also dependent on the probability of mating. If mating does not occur *r* reduces to zero. The probability of mating is a function of the parasite sex-ratio weighted by a factor for the mating capability of a male worm.

The microfilarial offspring *mo* of all worms together determines the Mf load of a person. This Mf load is denoted with the effective parasite load *el*, which is calculated as:

$$el_i=\sum_{j=1}^{n_i} mo_j \qquad (3)$$

for all worms $j=1, \ldots, n_i$ in person *i*.

Blindness

Dependent on the Mf load a number of Mf will penetrate the tissues of the skin and the eye. Immunological response to dead Mf in the eye may result in the development of eye lesions and ultimately blindness. This is reflected in the observed incidence of eye lesions and blindness, which is closely related to the Mf load (Dadzie *et al.*, 1986), and in the prevalence of blindness which is highest among old persons. In the model, the risk of going blind is a function of the Mf load (denoted by *el*) accumulated over time.

In agreement with reported excess mortality among persons with eye lesions (Prost and Vaugelade, 1981; Kirkwood *et al.*, 1983), in the model a reduction

factor is applied to the residual life-expectancy of blind individuals.

Skin-load and infection of flies

The density of Mf in the skin is related to the number of Mf in the body, which is quantified by the effective parasite load *el*. The average skin Mf load is defined as the expected number of Mf that can be counted in a skin-biopsy (skin snip, see below) and is denoted as *sl*. It is a linear function of *el*:

$$sl = cw \times el \tag{4}$$

where *cw* is the mean number of Mf contributed by one fully productive female worm (with *r* equal to 1).

Mf in the skin can be engorged by biting and blood sucking *Simulium* flies. Following uptake in the flies, only a fraction of the Mf succeeds in developing to L1-stage larvae. Since this fraction is usually very small, we use a shortcut and consider an L1-'uptake' (*lu*), which is a direct function of the skin Mf load (*sl*). Recent fly feeding and transmission experiments, which were undertaken in the OCP, have enabled the estimation of this function which shows a saturation type of relation between L1-uptake and skin-load (unpublished data[5], see also Philippon, 1977 and Remme *et al.*, 1986).

The probability that a fly will bite a certain individual depends on his exposure (*Ex*, see equation 1) and the following relationship is used to calculate the average L1-uptake of a fly:

$$\overline{lu} = \frac{\sum_{i=1}^{m} Ex_i \times lu_i}{\sum_{i=1}^{m} Ex_i} \tag{5}$$

for all individuals $i = 1, \ldots, m$.

Development in the fly

The vectorial (vector = the intermediate host, the *Simulium* fly) part of the transmission is modelled deterministically, and involves the calculation of the monthly biting rate *mbr* and the probability for an engorged L1-larva to develop into an infective L3-larva and to be released during one of the subsequent bites of a fly. This probability, denoted by *v*, is determined by combining data on the life history

[5] See Appendix of Section V.1.

of the fly (including daily survival and a distribution of the intervals between blood meals), the fraction of bites on non-human objects, the distribution of the duration of development from the L1-stage to the infective L3-stage, and the survival of the larvae during and after development. For a given L1-uptake, averaged over all flies ($\overline{lu}$), this results in an average release of infective larvae per bite (*lr*); so in summary:

$$lr = v \times \overline{lu} \tag{6}$$

In combination with a given monthly biting rate (*mbr*, see paragraph on fly dynamics) the monthly transmission potential (*mtp*) can be calculated as follows:

$$mtp = lr \times mbr \tag{7}$$

Given the average fraction of inoculated L3-larvae that succeeds in developing into a patent infection (*sr*), the ultimate result is a force of infection (*foi*, see Remme *et al.*, 1986) which is here defined as the expected number of new infections per person per month:

$$foi = sr \times mtp \tag{8}$$

For each person *i*, it follows that

$$foi_i = Ex_i \times foi \tag{9}$$

The person *i* is assumed to become infected according to a Poisson process with rate foi_i (Law and Kelton, 1982).

Fly dynamics and intervention by larvicide application

The monthly biting rate (*mbr*) is calculated as the sum of the daily biting rates (*dbr*) per person in a given month. This *dbr* follows from the dynamics and the biting behaviour of the fly population. The level of the *mbr* is dependent on the season (calendar month) and accumulates into the annual biting rate, *ABR* (Walsh *et al.*, 1978).

The size of the fly population can be reduced by spraying larvicides on their breeding sites. Reducing the fly population results in a reduction of *mbr*, and hence larviciding will have a strong limiting effect on the transmission. In order to model the effect of larviciding properly, the fly population is divided into daily age classes. Beside nulliparous and parous flies (flies before and after their first bloodmeal respectively), there are egg, larval and pupal stages. Larvicides will only kill the

larval stage, and hence following the application of larvicides, it will take some days before the size of the fly population decreases. If the larviciding frequency is too low - i.e. with an inter application period longer than the duration of the larval stage - eggs will develop into nulliparous flies, and the population can build up again at a speed which is dependent on the fecundity of the flies.

In the model, a larviciding strategy is governed by three factors:

(1) the duration of the strategy (months)
(2) the period (days) between applications
(3) the fraction of fly larvae killed at each application.[6]

Even following complete eradication, a local fly population can build up again by immigrating flies. Additional assumptions can be made on the infectivity of these immigrant flies.

Intervention by mass treatment with a microfilaricide (ivermectin)

A microfilaricidal drug, such as ivermectin, can be administrated to the population of a village. It will cause a substantial reduction of the effective parasite load *el* by killing a large fraction of the Mf. It does however not kill the mature worms, and therefore *mo* and *el* will increase again after treatment, so that transmission by *Simulium* is still possible. Treatment is especially effective as a means to reduce blindness as the accumulation of Mf load over time will slow down.

In the model, the percentage of the population that will be treated during mass treatment is dependent on both the age and the sex of the individuals. In the case of ivermectin, children below the age of 5 and pregnant and lactating women are excluded from treatment (De Sole *et al.*, 1989a).

Participation in mass treatment is not only dependent on age and sex but also on the compliance of a person. In the model, this is characterized by a personal compliance index, following a uniform distribution on [0,1]. Some chronic diseases (e.g. epilepsy) may also be a reason for non-treatment. For this reason, a fraction of the modelled population is systematically excluded from treatment.

From recent community trials with ivermectin, it became clear that the drug-induced instantaneous reduction in individual Mf load varied from 100% reduction to no reduction at all (Remme *et al.*, 1989b). Therefore, this Mf reduction is treated as a random variable, the value of which is determined for each participating person at each treatment.

In addition, there is a possibility that ivermectin treatment might cause a permanent reduction of a female worm's reproductive capacity. In the model this is incor-

[6] In later versions factors (2) and (3) are directly translated into a reduction of the monthly biting rate (see Section II.2).

porated by the option to specify a percentage reduction of the relative productivity (r) as a function of the number of treatments a worm underwent.[7]

Measuring onchocerciasis

Epidemiological measures. In routine epidemiological surveys, skin snips are taken from each person and the number of viable Mf per snip are counted during microscopic examination of the snip. At least two factors may cause a difference between the average skin Mf load (*sl*) and the number of Mf counted in the skin snip (*ss*):

(1) the worms are dispersed in the body. Thus, *ss* cannot be derived from *sl* directly. Instead, in the model the microfilarial offspring (*mo*) of each individual female worm is weighted with a dispersal factor (*d*) which follows a continuous distribution with mean 1.

(2) the skin snip examination and counting procedure is subject to variation and is considered as a process following a Poisson distribution.

Hence, the skin snip count *ss* of person i, harbouring n_i worms, is a random variable having the following distribution:

$$ss_i \sim \text{Poisson}\left(cw \times \sum_{j=1}^{n_i} mo_j \times d_j\right) \tag{10}$$

An important characteristic of the epidemiology in a population is the distribution of the skin snip count, represented by a geometric series of categories for *ss* (0, 0.5, 1, 2-, 4-, etc.) using the mean of two snips.

For the human population, the skin snip counts of all individuals are usually summarized into the geometric mean skin snip count (*gs*), modified to allow for $ss_i=0$. For a population with m individuals, *gs* is defined as:

$$gs=\left(\sqrt[m]{\prod_{i=1}^{m}(ss_i+1)}\right)-1 \tag{11}$$

The *CMFL* (Community Microfilarial Load, Remme *et al.*, 1986) has the same definition, but is restricted to individuals older than 20 years. Further, the prevalence of persons with a positive skin snip ($ss \geq 1$) is recorded (See Appendix).

An important measure for the burden of onchocercal disease in the population is the prevalence of blindness, which has its model equivalent in the proportion of

[7] Extensions and modifications of the sub-model on ivermectin treatment, based on longer patient follow-up, are presented in Section IV.2.

persons in whom the accumulated effective parasite load exceeds a given threshold level (see paragraph on blindness).

Infectivity of the vector. The common index for the intensity of transmission is the estimated annual transmission potential (*ATP*), which is the product of the estimated annual biting rate (*ABR*) and the average number of L3-larvae found in the head capsule of dissected flies. Furthermore, the number of inhabitant larvae of all developmental stages (L1, L2 and L3) is counted and recorded for each fly. From these detailed counts, the infection and infectivity of the vector, as well as the distribution of the number of larvae, can be derived.

In the model, the most important indices of transmission are the monthly transmission potential (*mtp*) and the average number of L1-larvae and L3-larvae in biting flies.

The program

The computer program ONCHOSIM, which is used to perform simulations with the model described in the previous section, can be considered as a hybrid of two different simulation techniques:

(1) vectorial part: the development of the parasites in the flies and the dynamics of the biting fly population, including the effect of larviciding, is calculated in a deterministic sub-program.

(2) epidemiological part: the largest portion of the program comprises the stochastic microsimulation of the life histories of the human individuals, their inhabitant male and female parasites, and the effect of chemotherapy.

Vectorial part

The vectorial sub-program consists of an initialisation part in which v (the transmission probability of an L1-larva, see paragraph on development of larvae in the fly) is calculated. The value of v is used throughout the simulation. The dynamics of the fly population is calculated by applying appropriate transition probabilities to a state variable that is represented by an array. The elements of this array are the daily fly stages (see paragraph on fly dynamics). Each day, dependent on the biting history, a number of flies (equal to *dbr*) will have a blood-meal. The *dbr* values are accumulated into *mbr*. The growth of the fly population is limited to the maximum *mbr* specified in the input.

The variables *mbr*, v and $\overline{lu}$ are the entry points to the epidemiological part of the program (next paragraph).

Epidemiological part

Data-structure: The backbone of the epidemiological part is a branched linked list of structures. These structures represent individuals of the human population. The branches, that are attached to these human structures, are linked lists themselves, and represent the inhabitant male and female parasites. Of course these branch lists may be empty in the case of uninfected individuals. In addition, especially in lowly infected people, it is possible that only one of the sexes is present (e.g. only female worms).

Each human and worm structure consists of a number of characteristics, that fully describe the state of the human-parasite complex. A human structure is characterized by:

(1) c the time of birth;
(2) c/v the age of death;
(3) c the sex;
(4) c the exposure index (*Exi*);
(5) c the compliance with drug treatment (compliance index);
(6) v the accumulated effective parasite load (see paragraph on blindness);
(7) v the time since the last ivermectin treatment;
(8) v the instantaneous reduction in Mf load at the last ivermectin treatment;[8]
(9) v the number of inhabitant female worms;
(10) v the number of inhabitant male worms.

In this list 'c' means that the characteristic is constant for the entire life, while 'v' denotes a characteristic that will change during program execution. The age of death will only change when the person goes blind.

The characteristics of a female worm structure are:

(1) c the time of maturation;
(2) c the age of death;[9]
(3) v the time since the last mating;
(4) v the number of ivermectin treatments the worm experienced during her life;[10]

[8] In later versions a variable characteristic of a human is the age-structured microfilarial load. Reductions of this load as a result of treatment are then modelled explicitly and characteristic (8) is no longer needed.

[9] At present, it is possible to simulate the effects of a hypothetical macrofilaricidal drug. Treatment with such a drug will, of course, alter the age of death of a worm.

[10] Replaced by a variable which keeps track of the cumulative effect of the drug on the fecundity of worms; see section IV.2.

For male worms only the first two characteristics are needed.

Simulation procedure

Processing the data structure: The program starts by creating an initial population, i.e. a human list with a specified size and age distribution. As soon as a human is added to the list, the human characteristics are determined by random selection from the appropriate distributions. Initially, the worm lists are empty. If desired, also a worm burden can be initialized by assuming a given force of infection during a fixed period before the actual simulation starts. Generally, to reach an epidemiological equilibrium situation and a stable age structure of the population, a simulation must cover a period of many decades.

Each month t, the infectivity of the population is calculated by examining the characteristics and worm lists of each human structure in the human list. This renders $\overline{lu}$, which in combination with v, *mbr* and *sr* results in *foi* (see paragraph on larval development in the fly).

As a next step in month t, the human list is updated by removing structures of persons that have died and by adding structures for newborns. Each person's worm lists are updated too: as a result of the force of infection *foi*, weighted for the exposure of the person, a number of worms is added, and dead worms are removed.

The time step of 1 month is sufficiently short since the prepatent period (*Tp*) will certainly be longer than 1 month. Thus new infections acquired in month t will not contribute to the force of infection in the same month.

Events: In ONCHOSIM two stochastic events are generated from constant hazard rates: the acquisition of a new infection in a human (where the rate is given by foi_i) and the birth of new humans.

Generally, if we have a hazard rate σ, then the time interval between events (ΔT) is:

$$\Delta T = \frac{-\ln u}{\sigma} \qquad (12)$$

with u being a random number with a uniform distribution on the unit interval, and with the assumption that σ does not change during ΔT. An event (new infection, birth) only occurs if $\Delta T \leq 1$ month. If this is the case, then further events may occur, until the sum of ΔT exceeds 1 month.

If we follow the fate of a single worm in a given human, then the events that will occur after infection are: maturation (after *Tp* years), regular mating (if both sexes are available) and death of the worm *Tl* years after infection.

Events that may occur in the human:

(1) the human may become infected with new parasites;
(2) the human may go blind, which has consequences for the residual life expectancy;
(3) a skin snip can be taken during an epidemiological monitoring;
(4) the human may be treated with a microfilaricide;
(5) the human may die.

An event that may affect the fly population is the application of larvicides, which has consequences for the rate at which new infections are acquired (reduced force of infection).

Program output and program application

The output of the program can be presented with several degrees of detail. In its most detailed form, epidemiological information is tabulated for each sex and age group separately. Vector-related results are tabulated for each month. In the Appendix an example is given of detailed epidemiological output. The format of the tables closely corresponds with the standard tabulation in the OCP, which facilitates direct comparison.

The choice of the degree of detail largely depends on the purpose of the simulation. A lot of detail is required when the model is fitted to field data. In simulations where the effects of control strategies are predicted, it is more useful to produce annual output in the form of aggregated indices such as the community microfilarial load *CMFL*, prevalence of blindness and the *ATP*.

Roughly, in the utilization of the program, three phases can be distinguished: model quantification, integrated data analysis, and prospective evaluation.

The quantification phase comprises a systematic search for sets of parameter values which result in program output corresponding to field observations of several endemic situations. During this phase the distribution of Mf per skin snip is simulated for a number of villages in the OCP area that have been monitored at several moments since the start of larviciding control. In Fig. 5 an example of such a simulation is compared with the situation in Folonzo (Burkina Faso) at the start of control (*a*) and after 10 years of control (*b*).

The second phase involves the routine application of the model in the integrated analysis of the extensive entomological, epidemiological and applied research data of the OCP.

The 'prospective evaluation' is the ultimate goal of the development of the model. It includes all simulations in which the effect of control strategies with larviciding and ivermectin administration is evaluated.

One of the steps in this evaluation phase is the use of ONCHOSIM to predict the

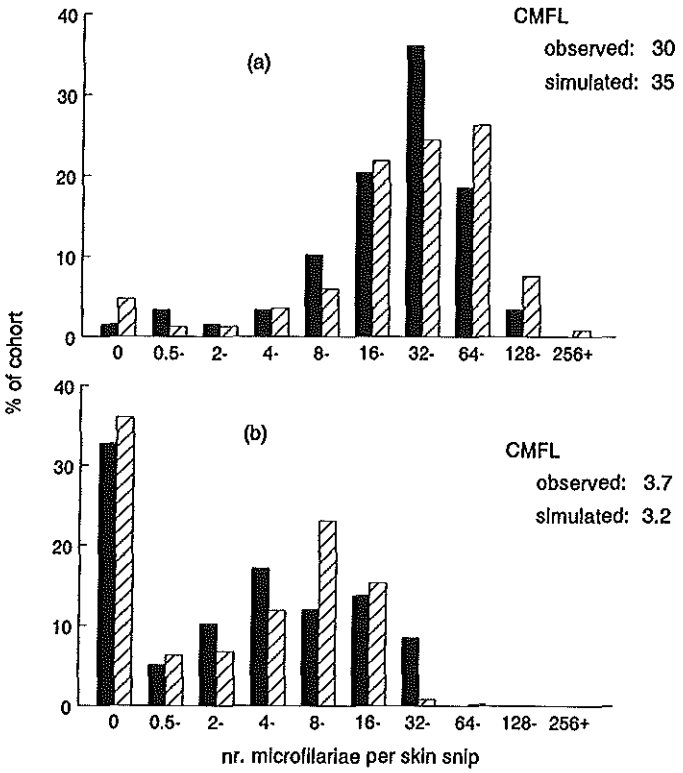

Figure 5 **Example of the simulated distribution of microfilariae per skin snip (black bars) compared with the observed distribution in Folonzo (Burkina Faso; hatched bars) at the start of the control (a) and after 10 years of larviciding control (b). Data apply to a cohort of persons that were older than 20 years at the start of the control.**

risk and dynamics of the recrudescence of infection in villages where, after a period of larviciding control the *Simulium* fly returns and bites at the pre-control intensity. In Fig. 6 an example is given of the trend in the prevalence of positive skin snips, the *CMFL*, and the prevalence of blindness when (100% effective) larviciding control ceases prematurely after 8 years.

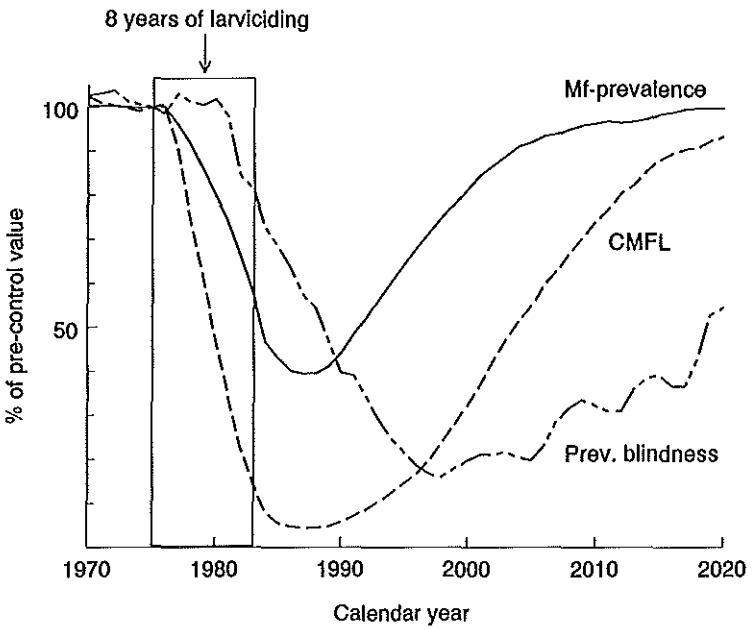

Figure 6 **Example of simulated decline in the prevalence of positive skin snips (solid line), the *CMFL* (dashed line) and the prevalence of blindness (dot-dashed line) during 8 years of larviciding control, and of the recrudescence after stopping control too early.**

Discussion

The development of the ONCHOSIM program is not the first attempt to formalize the processes involved in the dynamics of onchocerciasis. In 1969 Mills reported a quantitative approach to the epidemiology of onchocerciasis in West Africa. Parameters related to the human population, the *Simulium* population and the parasite are integrated into a statement of transmission in different bio-climatic zones. However, it was soon pointed out that this work was based on several incorrect and misleading assumptions (Duke, 1970). Partial models have been developed for certain aspects of the transmission, such as the fly-dynamics (Birley *et al.*, 1983) and the development and migration of parasite larvae in the fly (Jerwood *et al.*, 1984).

A mathematical description of onchocerciasis transmission has been provided by Dietz (1982) (see also the discussion in Anderson and May, 1985). Dietz developed

relationships for the dynamics of the number of parasites in both the human population and the fly-population, using several assumptions on the mechanisms of density dependent regulation, which are required to arrive at an equilibrium situation. Based on these relationships and few field observations, Dietz estimates the basic reproductive rate of the parasite and provides dynamic projections of the effects of vector control. Subsequent evaluations in the OCP have shown that these projections were not correct, mainly because of the assumption of an age-independent survival distribution of the parasite, an assumption which also Dietz had recognised to be a major limitation of the model.

On the basis of a force-of-infection model for onchocerciasis, Remme *et al.* (1986) made predictions of age-specific epidemiological trends and compared these predictions with the results of 8 years of larviciding control in the OCP. This model, which includes a realistic modelling of the life-history of the parasite in the human host, appeared to give reasonable predictions of both the average intensity and the prevalence of infection. However, it was still only a partial deterministic model which did not address the dynamics of transmission.

ONCHOSIM is, to our knowledge, the only existing stochastic model for the transmission and control of onchocerciasis[11]. A distinguishing feature is its close connection with the actual control of the disease (in the OCP) and its development in close collaboration with scientists from all disciplines involved. The model is highly flexible and new research findings can be easily incorporated. Control strategies can be specified in a detailed and realistic way, while almost no restriction needs to be made on the life-history of the parasite (e.g. the longevity of the parasite in the human can take any distribution). Its flexible design and its availability on micro-computer configurations should make ONCHOSIM a valuable tool for research workers and decision makers in the field of onchocerciasis control.

[11] Later, Davies (1993) developed a stochastic model for the forest form of onchocerciasis.

Appendix

Example of detailed epidemiological program output

An example of the epidemiological part of the detailed form of output of the ONCHOSIM program is given below. It concerns output of a simulation of the core villages in the hyperendemic focus of Asubende in Ghana (Remme *et al.*, 1989). In these tables 'MFS' means microfilariae in skin snips.

-- THE ONCHOSIM PROGRAM --

January 1975, OCP_reference_village

	NUMBER EXAMINED			GEOMETRIC MEAN MFS			PREVALENCE OF MFS		
AGE	MALE	FEM.	TOTAL	MALE	FEM.	TOTAL	MALE	FEM.	TOTAL
0- 4	53	59	112	0.03	0.05	0.05	1.9	3.4	2.7
5- 9	45	47	92	3.01	1.20	1.95	62.2	46.8	54.3
10-14	45	32	77	21.53	10.82	16.23	97.8	90.6	94.8
15-19	27	35	62	51.95	16.86	27.67	100.0	94.3	96.8
20-29	47	42	89	80.70	28.94	49.87	100.0	95.2	97.8
30-49	71	67	138	80.52	66.87	73.58	98.6	100.0	99.3
50+	20	22	42	60.48	61.68	61.11	100.0	100.0	100.0
TOTAL	308	304	612	18.39	10.29	13.82	76.9	70.7	73.9
		CMFL ==>		77.31	50.51	62.86			

	PREVALENCE OF BLINDNESS			MAT. FEM. WORMS PER PERS.			PREV. OF MAT. FEM. WORMS		
AGE	MALE	FEM.	TOTAL	MALE	FEM.	TOTAL	MALE	FEM.	TOTAL
0- 4	0.0	0.0	0.0	0.2	0.1	0.2	15.1	11.9	13.4
5- 9	0.0	0.0	0.0	3.4	1.5	2.5	80.0	72.3	76.1
10-14	0.0	0.0	0.0	9.1	4.9	7.4	97.8	93.8	96.1
15-19	0.0	0.0	0.0	17.0	7.5	11.6	100.0	94.3	96.8
20-29	8.5	2.4	5.6	19.1	11.0	15.3	100.0	97.6	98.9
30-49	21.1	7.5	14.5	21.8	17.8	19.9	100.0	100.0	100.0
50+	40.0	18.2	28.6	18.2	16.1	17.1	100.0	100.0	100.0
TOTAL	8.8	3.3	6.0	12.5	8.2	10.4	82.1	77.0	79.6

•MALES• Number of microfilariae per skin snip

AGE	0	0.5-	2-	4-	8-	16-	32-	64-	128-	256+	TOTAL
0- 4	52	0	1	0	0	0	0	0	0	0	53
5- 9	17	4	3	5	7	6	3	0	0	0	45
10-14	1	0	2	5	6	15	12	4	0	0	45
15-19	0	0	0	2	1	3	7	11	3	0	27
20-29	0	0	0	0	2	1	14	17	13	0	47
30-49	1	0	0	0	3	6	10	22	29	0	71
50+	0	0	1	1	0	2	2	12	2	0	20
TOTAL	71	4	7	13	19	33	48	66	47	0	308

•FEMALES•

0	0.5-	2-	4-	8-	16-	32-	64-	128-	256+	TOTAL
57	1	0	0	0	0	0	0	0	0	59
25	7	4	3	5	2	1	0	0	0	47
3	2	1	4	7	9	4	2	0	0	32
2	1	1	6	2	11	7	5	0	0	35
2	1	2	1	1	10	15	8	2	0	42
0	0	0	1	4	6	18	24	13	1	67
0	0	0	0	1	3	5	11	2	0	22
89	12	8	15	20	42	50	50	17	1	304

•TOTAL• Number of microfilariae per skin snip

AGE	0	0.5-	2-	4-	8-	16-	32-	64-	128-	256+	TOTAL
0- 4	109	1	1	0	0	1	0	0	0	0	112
5- 9	42	11	7	8	12	8	4	0	0	0	92
10-14	4	2	3	9	13	24	16	6	0	0	77
15-19	2	1	1	8	3	14	14	16	3	0	62
20-29	2	1	2	1	3	11	29	25	15	0	89
30-49	1	0	0	1	7	12	28	46	42	1	138
50+	0	0	1	1	1	5	7	23	4	0	42
TOTAL	160	16	15	28	39	75	98	116	64	1	612

II.2 Formal description

Annex[12] from:
Habbema JDF, Van Oortmarssen GJ, Plaisier AP. The ONCHOSIM model and its use in decision support for river blindness control
In: Isham V, Medley G [Eds.]. Models for Infectious Human Diseases - Their structure and relation to data. Cambridge, UK: Cambridge University Press 1996: pp. 369-380.

This section gives a complete description of the ONCHOSIM *model* structure and parameter quantification. Except for the quantification of the effect of ivermectin treatment, the version of the model presented is the same as used in Habbema *et al.* (1992). In other applications of the model, other quantifications may be used for situation specific parameter groups like demography, exposure, coverage of drug-treatment, etc. Since the model structure and quantification is regularly updated, in future use of ONCHOSIM assumptions may differ from this description. Note that the ONCHOSIM *computer program* offers the opportunity to change parameter values, to choose other options regarding the type of probability distributions used, and to make structural changes in parts of the model.

Demography

The human population dynamics is governed by birth and death processes. We define $F(a)$ as the probability to survive to age a (apart from excess mortality due to onchocerciasis related blindness). The values used are as follows:

age (a)	0	5	10	15	20	30	50	90
$F(a)$	1.000	0.804	0.772	0.760	0.740	0.686	0.509	0.000

Survival at intermediate ages is obtained by interpolation.

The expected no. of births (per year) at a given moment t is given by:

$$R_b(t) = \sum_{k=1}^{n_a} N_f(k,t) \times r_b(k) \qquad (1)$$

$N_f(k,t)$ no. of women in age group k at time t.
$r_b(k)$ annual birth-giving rate of women in age-group k: 0.109 babies per year

[12] Written by A.P. Plaisier, G.J. Van Oortmarssen, and J.D.F. Habbema.

for women between 15 and 20 years; 0.300 between 20 and 30 years; 0.119 between 30 and 50 years; 0.0 for all other ages.

n_a no. of age-groups considered.

Each month $R_b(t)$ is adapted according to the number of women and their age-distribution.

Exposure to blackflies

The number of bites $mbr_i(m)$ a person i gets in month m is given by:

$$mbr_i(m)=Mbr(m)\times Ex_i \qquad (2)$$

$Mbr(m)$ no. bites in month m (m=Jan., Feb., ..) for a person with relative exposure 1.

The relative exposure Ex_i is calculated as:

$$Ex_i=Exa(a_i,s_i)\times Exi_i \qquad (3)$$

$Exa(a,s)$ relative exposure of person with age a and sex s: Zero at birth, linear increase between age of 0 and 20 years to 1.0 for men and 0.7 for women, and constant from 20 years onwards.

$Exi_i \sim Weibull(1.0,\alpha_{Exi})$
[13]exposure index of person i. The exposure index of a person remains constant throughout lifetime. For selected OCP villages, estimated α_{Exi} values vary between 1.3 (nearly exponential) and 4.5

$Mbr(m)$ values are obtained from six representative years of fly collections near the village of Asubende (Ghana). There, monthly biting rates of on average 2570 bites per person, varying from 1500 in March to 3750 in November have been found. For the actual biting rates ($Mbr(m)$) inside of this village we multiplied these figures with a factor (called the *relative biting rate*) of 0.95 (note: since we have no measurements of biting rates actually experienced by villagers, we have - arbitrarily - defined a *relative biting rate* of 1.0 - i.e., mean Mbr=2570 - as the biting rate resulting in a geometric mean no. of Mf per skin-snip of 100 in hypothetical village with all persons being permanently characterized with a relative exposure of 1.0).

[13] i.e., Exi_i is a random variate described by a Weibull-distribution with mean = 1.0 and shape-parameter $\alpha = \alpha_{Exi}$

Assuming the same seasonal pattern, for other villages relative biting rates have been estimated to vary from 0.4 to 0.9.

Acquisition, development, longevity and productivity of parasites in the human host

If during a bloodmeal of a fly in month m on average lr infective larvae are released, the force-of-infection $foi_i(m)$ - defined as the expected number of new adult parasites per year - acting upon person i in month m is calculated as:

$$foi_i(m) = 12 \times mbr_i(m) \times lr(m) \times sr \qquad (4)$$

sr success ratio: fraction of injected L3-larvae succeeding in growing to adult male or female worms: $sr=0.0031$. An average male:female sex ratio of 1:1 is assumed.

The reproductive lifespan of male and female parasites is a random variable: $Tl \sim Weibull(\overline{Tl}, \alpha_{Tl})$, with $\overline{Tl}=10$ years and $\alpha_{Tl}=3.8$. The Mf productivity $r(a,t)$ of a female worm of age a at time t is calculated as follows:

$$r(a,t) = R(a) \times m(t) \qquad (5)$$

$R(a)$ potential Mf productivity of a female worm of age a (in years): $R(a) = 0$ for $0 \le a < 1$ (i.e., the immature period of the worm is estimated at 1 year); $R(a) = 1$ for $1 \le a < 6$; $R(a) = 1-((a-6)/15)$ for $6 \le a < 21$; $R(a) = 0$ for $a > 21$.

$m(t)$ mating factor at time t

To continue Mf production, a female worm must be inseminated each rc months (rc=reproductive cycle=3). If insemination took place less than rc months ago, then $m(t)=1$. Otherwise, the probability of (re-)insemination $P_{ins}(t)$ in month t is given by:

$$\begin{aligned} P_{ins}(t) &= W_m(t) / W_f(t) && \text{if } W_m < W_f \\ &= 1 && \text{otherwise} \end{aligned} \qquad (6)$$

$W(t)$ no. of male (W_m) or female (W_f) parasites in the human at time t

If no insemination takes place then $m(t)=0$ and the female worm has a new opportunity in month t+1. If insemination occurs in month t_i then $m(t)=1$ during

$t_i \leq t < t_i + rc$.

The skin Mf density at time t ($sl(t)$) is calculated by accumulating the Mf production of all female parasites over the past Tm months:

$$sl(t) = cw \times el(t) \tag{7}$$

$$el(t) = \frac{1}{Tm} \sum_{j=1}^{n_i} \sum_{x=1}^{Tm} r_j(a_j - x, t - x) \tag{8}$$

$el(t)$ the *effective parasite load* at time t. This intermediate variable describes the female parasite load obtained by weighting each worm according to the Mf productivity during the past Tm months.

cw average contribution of an inseminated worm at peak fecundity ($R=1$) to the skin Mf density: $cw=7.6$ Mf/worm.

Tm (fixed) microfilarial lifespan: $Tm=0.75$ years.

n_i number of parasites alive during at least one of the months $t\text{-}1,\ldots,t\text{-}Tm$.

Skin-snip count

The expected no. of Mf in a skin-snip is given by:

$$\hat{ss}(t) = \frac{cw}{Tm} \sum_{j=1}^{n_i} d_j \sum_{x=1}^{Tm} r_j(a_j - x, t - x) \tag{9}$$

d_j *dispersal factor* of female parasite j. This is a random variable accounting for differences in the contribution of female worms to the Mf density at the site of the body where snips are taken. We assume an exponential distribution for describing these differences: $d_j \sim Expo(1.0)$.

The actual number of Mf per skin-snip follows a Poisson distribution: $ss(t) \sim Poisson(\hat{ss}(t))$. At each epidemiological survey 2 snips per person are taken.

Uptake, development and release of larvae in the vector

On the basis of fly-feeding experiments in OCP the following expression for the relation between L1-uptake (lu) and skin-microfilarial density (sl) has been derived

(note: since most of the Mf engorged during a bloodmeal are trapped in the fly, we consider L1-'uptake' rather than Mf uptake):

$$lu=a(1-e^{-b.sl})(1+e^{-c.sl}) \tag{10}$$

with a=1.2, b=0.0213, and c=0.0861 (the initial slope of this relationship equals $2ab$). The mean L1-uptake in the fly population in month m is now calculated as:

$$\overline{lu}(m)=\sum_{i=1}^{N(m)}(Ex_i \times lu_i)/\sum_{i=1}^{N(m)}Ex_i \tag{11}$$

$N(m)$ No. of persons in month m.

It is assumed that a fixed proportion of the L1-larvae develops to the L3-stage and will be released at one of the subsequent bites:

$$lr(m)=v\times\overline{lu}(m) \tag{12}$$

$lr(m)$ mean L3-release per bite in month m.

v transmission probability: average probability that an L1-larva is released as an infective L3-larva.

The calculation of the transmission probability v is complicated. In calculating v we take into account the life-history of the fly starting from her first bloodmeal. We assume that bloodmeals are taken at fixed hours during daytime, so that we can use 1 day timesteps. Though we take into account differences in the length of the gonotrophic cycle between flies, in the model we assume that a particular fly has always the same cycle length (which equals the time between two successive bloodmeals). We further explicitly account for variation in the duration of development from L1 to L3. The basic assumption underlying the use of a fixed proportion v is that at any moment the fly-population has a stable age-distribution and that the no. of bites per person is large enough to reflect this stable age distribution.

Calculation of the transmission probability v

Assume that a fly engorges 1 (one) L1-larva at her m^{th} bloodmeal, then the probability to release an L3-larva n bloodmeals later is given by:

$$P_{rel}(n|i,j,m)=P_{L1\to L3}\times(1-P_{L3\to})^{i}\times P_{L3\to L3}{}^{i}\times P_{L3\to}\times S(m,n\times j) \quad (13)$$

$P_{rel}(n \mid i,j,m)$
The probability to release one L3 larva at the $(m+n)^{th}$ bloodmeal if one L1 larva has been engorged at the m^{th} bloodmeal, given that:
- a gonotrophic cycle takes j days
- between bloodmeal m and $m+n$ there have been i potentially infective bloodmeals (i.e., bloodmeals at which the L1-larva had already developed to the L3-stage)

$P_{L1\to L3}$ The probability that an L1-larva develops to the L3-stage, given survival of the fly: $P_{L1\to L3}=0.85$.

$P_{L3\to L3}$ The probability that an L3-larva which is not released at a given bloodmeal survives to a next bloodmeal, given survival of the fly: $P_{L3\to L3}=0.90$.

$P_{L3\to}$ The probability that an L3-larva is released at a bloodmeal: $P_{L3\to}=0.65$.

$S(m,t)$ The probability that a fly survives for t days since bloodmeal m.

In order to arrive at a general solution for all possible values of i, we use the probability distribution of the number of potentially infective bloodmeals since the intake-meal and before the release meal:

$$P_{rel}(n|j,m)=\sum_{i=0}^{n-1}[P_{rel}(n|i,j,m)\times P_{ib}(i|n,j)] \quad (14)$$

$$P_{ib}(i|n,j)=F_{dL1\to L3}(j(n-i))-F_{dL1\to L3}(j(n-i-1)) \quad (15)$$

$P_{ib}(i \mid n,j)$
The probability that before the n^{th} bloodmeal since intake, i bloodmeals have been potentially infective (L1 has become L3), given a cycle length of j days.

$F_{dL1\to L3}(t)$ Probability that the duration of development of L1 to L3 is equal to or less than t days ($F_{dL1\to L3}(t)=0.0$ for $t\leq 5$; 0.07 for $t=6$; 0.86 for $t=7$; 1.0 for $t\geq 8$ days).

A general solution for all possible values of m can be obtained by incorporating the probability that a fly takes her m^{th} bloodmeal:

$$P_{rel}(n|j)=\sum_{m=1}^{m_{max}}[P_{rel}(n|j,m)\times P_b(m|j)] \tag{16}$$

$$P_b(m|j)=L(j(m-1))/\sum_{m=1}^{m_{max}}L(j(m-1)) \tag{17}$$

$P_b(m \mid j)$ Probability that a feeding fly takes her m^{th} bloodmeal at a cycle length of j days.

$L(t)$ Probability that a fly lives for at least t days. At present we assume an age-independent daily survival of 0.78.

Generalizing for j can be achieved by summation, weighted for the probability distribution for the duration of the gonotrophic cycle:

$$P_{rel}(n)=\sum_{j=j_{min}}^{j_{max}}[P_{rel}(n|j)\times P_{gc}(j)] \tag{18}$$

$P_{gc}(j)$ Probability that a gonotrophic cycle takes j days (i.e., j days between successive bloodmeals; $P_{gc}(j)=0.0$ for $j\leq 2$; 0.2 for $j=3$; 0.6 for $j=4$; 0.2 for $j=5$; 0.0 for $j\geq 6$ days).

Using the following equality

$$S(m,n\times j)=L(j(m+n-1))/L(j(m-1)) \tag{19}$$

the average probability that an L1-larva taken from a human will develop to the L3-stage and released to another human is given by:

$$\begin{aligned}P_{rel}=&P_{L1\to L3}\times P_{L3\to}\\&\times\sum_{j=j_{min}}^{j_{max}}\left\{P_{gc}(j)\times\sum_{m=1}^{m_{max}}\left[\frac{1}{\sum_{m=1}^{m_{max}}L(j(m-1))}\right]\times\sum_{n=1}^{n_{max}}\left\{L(j(m+n-1))\right.\right.\\&\left.\left.\times\sum_{i=0}^{n-1}[(1-P_{L3\to})\times P_{L3\to L3}]^i\times[F_{dL1\to L3}(j(n-i))-F_{dL1\to L3}(j(n-i-1))]\right\}\right\}\end{aligned} \tag{20}$$

In equation (16), (17) and (18):

$$m_{\max}=\left\lfloor\left(\frac{a_{\max}}{j}+1\right)\right\rfloor \qquad n_{\max}=\left\lfloor\left(\frac{a_{\max}-(m\times j)}{j}\right)\right\rfloor \tag{21}$$

a_{max} Maximum attainable age of the fly (i.e., age at which $L(t)$ approaches zero). ($\lfloor\ldots\rfloor$ denotes truncation to integer).

The transmission probability v is now given by:

$$v=P_{rel}\times(1-z) \tag{22}$$

z Fraction of fly-bites on non-human objects (zoophily; $z=0.04$).

Using the indicated quantifications, we have calculated a v of 0.073 released larvae per L1-larva resulting from a given Mf uptake. Note that formula (20) reduces to a much more simple form if we assume that each day a fraction S of the flies survive, that the gonotrophic cycle has a fixed duration of dgc days, and that the number of bloodmeals needed to complete the development of L1 to L3 is fixed to $n1\rightarrow 3$:

$$P_{rel}=P_{L1\rightarrow L3}\times P_{L3\rightarrow}\times\frac{S^{n1\rightarrow 3\times dgc}}{1-S^{dgc}\times(1-P_{L3\rightarrow})\times P_{L3\rightarrow L3}} \tag{23}$$

Blindness and excess mortality

The probability of a person going blind at age a (months) depends on the *accumulated parasite load (elc)* of a person:

$$elc(a)=\sum_{x=0}^{a} el(x) \tag{24}$$

Each person has a threshold level of *elc* (denoted as *Elc*) at which a person goes blind. *Elc* follows a probability distribution: $Elc\sim Weibull(\overline{Elc},\alpha_{Elc})$, with $\overline{Elc}=10{,}000$ and $\alpha_{Elc}=2.0$. Person i goes blind at age a when:

$$elc_i(a)\geq Elc_i>elc_i(a-1) \tag{25}$$

At that moment the remaining lifespan at age a is reduced by a factor rl which follows a uniform distribution on [0,1] (hence on average $rl=0.5$).

Ivermectin: mass treatment coverage and compliance

The primary characteristic of a certain ivermectin mass treatment w is the coverage C_w (fraction of the population treated; typically 0.65). However, a difficulty in calculating individual chances of participation is that there are sveral exclusion criteria for the drug. Moreover, compliance to treatment differs from person to person. Exclusion criteria can be either permanent (chronic illness) or transient (children below 5 and pregnant or breast-feeding women). We define the eligible population as the total population *minus* a fraction fc (=0.05) which is permanently excluded from treatment (in the model from birth to death). The coverage among the eligible population is now given by:

$$C_w' = C_w / (1 - fc) \tag{26}$$

The transient contra-indications and other age- and sex-related factors are taken into account in the age- and sex-specific relative compliance $c_r(k,s)$ for each age-group k and sex s. Based on OCP data we use:

age-group (k)	0-4	5-9	10-14	15-19	20-29	30-49	50+
$c_r(k,♂)$	0.00	0.75	0.80	0.80	0.70	0.75	0.80
$c_r(k,♀)$	0.00	0.75	0.70	0.74	0.65	0.70	0.75

Note that in $c_r(k,s)$ only the *ratio* between the values for the different groups is relevant. The coverage $c(k,s,w)$ in each of the age- and sex-groups at treatment round w is calculated as:

$$c(k,s,w) = \frac{c_r(k,s) \times N(w)}{\sum_{s=1}^{2} \sum_{k=1}^{n_a} c_r(k,s) \times N(k,s,w)} \times C_w' \tag{27}$$

$N(k,s,w)$ Number of individuals eligible to treatment in age-group k and sex s at treatment round w.

$N(w)$ Total number of eligible individuals at treatment round w.

Finally, the probability to participate in treatment round w for an eligible person i of age-group k and sex s is given by:

$$Ptr_{i,w} = co_i^{\frac{1-c(k,s,w)}{c(k,s,w)}} \tag{28}$$

co_i Personal compliance index. This is considered as a lifelong property and is generated from a uniform distribution on [0,1].

Note that for all k and s the average value of $Ptr_{i,w}$ equals $c(k,s,w)$.

Ivermectin: the parasitological effect of treatment

In the model we assume that an effective treatment with the drug causes elimination of 100% of the microfilariae from the skin-tissues. The impact of the drug on the subsequent productivity r of a female parasite j in person i is given by:

$$\begin{aligned} r_{j,i}(t) &= r^0_{j,i}(t) \times (1 - v_i d) \times \left(\frac{t}{v_i Tr} \right)^s \quad \text{if } u_j > v_i m \ ; \ v_i d < 1 \ \text{ and } \ t \le Tr \\ &= 0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{otherwise} \end{aligned} \tag{29}$$

t Time (months) since treatment.

$r_{j,i}(t)$ Mf productivity of female worm j at t months after treatment with ivermectin of person i (see eqn. (5))

$r^0_{j,i}(t)$ The Mf productivity of this worm j had person i not been treated at the last round.

v_i Relative effectivity of treatment in person i.

d Average permanent (unrecoverable) reduction in Mf productivity resulting from treatment (d=0.35).

Tr Average duration of the period of recovery, i.e., the period during which the Mf productivity of the female worm increases from 0 to the new equilibrium (Tr=11 months).

s Shape parameter of the recovery function (s=1.5).

u_j Random number on [0,1] generated for each female worm j.

m Average fraction of female worms killed as a result of treatment (at present: m=0).

The relative effectivity v_i is a random variable generated a probability distribution: $v_i \sim Weibull(1.0, \alpha_v)$, with α_v=2.0. In the model we explicitly consider persons (5% of the treated population) which do not at all react on the drug at a certain round (malabsorption, e.g., due to vomiting).

Vector control

Vector control is modelled as the fraction reduction of the monthly biting rates during a given period of time (*eff*). A period of vector control is specified as the year + month + day of the beginning of the strategy and the year + month + day of the end of a strategy. If in a certain month during a period of d days larvicides have been applied, then the reduction in *Mbr(m)* in that month equals ($d \times eff/30$) x 100 %.

Chapter III

The lifespan of *Onchocerca volvulus*

The reproductive lifespan of *Onchocerca volvulus* in West African savanna

A.P. Plaisier, G.J. van Oortmarssen, J. Remme, J.D.F. Habbema
Acta Tropica 1991;48:271-284.

Introduction

The productive lifespan of *Onchocerca volvulus* is the major determinant of the required duration of onchocerciasis control operations which aim at interruption of transmission and the subsequent elimination of the local parasite reservoir (Roberts *et al.*, 1967; Remme *et al.*, 1986; Karam *et al.*, 1987). Thus far, estimates for the average lifespan of the parasite and the variability around this average have been based on experimental infections in monkeys (Duke, 1980) and on cross-sectional nodulectomy surveys and skin-snip surveys in areas with different periods of vector control (Roberts *et al.*,1967; Karam *et al.*, 1987). Based on extensive longitudinal skin-snip data, Remme *et al.* (1990a) provide a model based estimate of the average longevity of onchocerciasis infection and its variability by fitting observed trends in prevalence and intensity of infection during vector control. However, these authors note that their estimate represents only one possible quantification and that a detailed sensitivity analysis is required to determine the complete range of parameter values which are consistent with observations.

The present paper provides such a detailed analysis. The comprehensive stochastic model for onchocerciasis transmission and control, ONCHOSIM (Plaisier *et al.*, 1990), is used to systematically test different parameter quantifications of the worm lifespan distribution, using longitudinal skin-snip data collected in selected reference villages during 13-14 years of vector control operations in the area of the Onchocerciasis Control Programme in West Africa (OCP). The changes in microfilarial load are not only determined by the parasite lifespan. Therefore, other aspects are explicitly taken into account, including the pre-control endemicity level and infection heterogeneity among the inhabitants of the reference villages.

The aim of the analysis reported here is to arrive at a plausible range of values for the average reproductive lifespan of the West African savanna strain of the *O. volvulus* parasite, and for the age at which the large majority of the worms have reached the end of their reproductive period. Especially the latter, which we will characterize by the age at which 95% of the adult worms have ceased reproduction, is an important determinant of the period during which vector control must be continued to minimize the risk of recrudescence of onchocerciasis.

Materials and Methods

Epidemiological surveys and reference villages

Epidemiological surveys have been undertaken at regular intervals of 3-4 years in a large number of villages in the OCP in order to monitor the epidemiological impact of vector control (WHO, 1987a). In all surveys two skin-snips were taken from each person. These snips were incubated in distilled water for 30 minutes, examined by microscope for the presence and density of *O. volvulus* microfilariae (Mf), and the number of Mf per snip was recorded for each individual at each survey (Prost and Prod'hon, 1978). From this extensive epidemiological data-set, four villages have been selected as reference for the analysis. Table 2 lists some demographic and epidemiological characteristics of these villages, which are all located in Burkina Faso in the core area of the OCP and which have been under vector control for at least 13 years. The selection of the villages was such that they fitted into the general pattern for the epidemiological trends observed during the vector control period (see Remme *et al.*, 1990a). All 4 villages were hyperendemic (prevalence of Mf >60%, Prost *et al.*, 1979) but they were chosen to cover a fairly wide range for the intensity of infection as measured by the Community Microfilarial Load (CMFL), i.e., the geometric mean Mf/snip for all individuals older than 20 years (Remme *et al.*, 1986). At least four surveys were done in each of the villages.

The model

Simulations have been carried out with the stochastic computer simulation model ONCHOSIM (Plaisier *et al.*, 1990). An important characteristic of ONCHOSIM is the use of the technique of microsimulation. The life-histories of individual persons and their individual inhabitant male and female worms are simulated. Together, the persons constitute a simulated village population. In the model, the reproductive lifespan is defined as the period between inoculation of the infective larva and the end of the fecundity period of the adult worm. This includes the pre-mature period in which the worm cannot yet reproduce. The end of fecundity may be due to factors such as disease or death of the worm. The requirement of regular mating is explicitly considered in the model and a temporarily cessation of Mf production when no mating takes place is not considered as the end of fecundity. The average reproductive lifespan is taken equal for male and female worms. In the remainder of the analysis, all causes leading to the end of the fecund period are simply referred to as 'death', while 'reproductive lifespan' is abbreviated to 'lifespan'. The variability in the lifespan is considered to be solely the result of the worm's genetic variability and does not depend on intrinsic host factors. The lifespan is described by a probability distribution of the Weibull type. Weibull distributions are widely used in

reliability models for lifetime of devices and for survival analyses (see Kalbfleisch and Prentice, 1980). The Weibull distribution is a generalization of the exponential distribution which is often used for describing lifetimes in infectious disease models. However, the exponential distribution has been shown to be inappropriate for describing the lifespan of *O. volvulus* (Remme *et al.*, 1990a). In addition to the mean, a second 'shape' parameter is used in the Weibull to manipulate the variability of the lifespan (independent from the mean). In this paper, the 'shape' parameter is represented by the 95th percentile, i.e., the age at which 95% of the parasites have died (see appendix for further details).

Apart from the lifespan, the model enables a detailed description of a number of other aspects of the worm life-history. Fecundity starts after a pre-mature period of one year on average (Duke, 1980; Prost, 1980). Following this period, Mf production only takes place when worms mate (Schulz-Key and Karam, 1986). In accordance with several observations, the Mf output of fertilized female parasites is modelled to decrease with age after a few years of optimal productivity (Albiez, 1985; Karam *et al.*, 1987). The appendix gives details about modelling worm mating and fecundity. Newly produced Mf are assumed to live for 1.5 years. In the current quantification of the model one fertilized female worm at peak fecundity corresponds with an average of 5 Mf/snip (this value is arrived at in an analysis which will be reported elsewhere).

The model takes account of the fact that the exposure to (new) infections in the pre-control situation is unequally distributed in the human population. This exposure heterogeneity, which acts as a major determinant of differences in skin-snip counts between persons, results from differences between sexes (females are on average 20% less exposed than males), differences between ages (beyond the age of 20 years the maximum exposure is reached), and individual variation which is a.o. related to attractiveness to the flies and behavioral factors. Systematic simulations using various model assumptions pointed out that a considerable degree of age- and sex-independent variation between individuals must be stipulated in order to obtain a good fit with skin-snip distributions. This variation can take different values for different village populations.

A detailed description of the model and of the parameter quantifications is provided in section II.2.

Estimation procedure

The validity of different quantifications of the model parameters are tested by determining the goodness-of-fit of simulated skin-snip data to the observed skin-snip results. For this purpose, both the observed and simulated skin-snip counts are summarized in a frequency distribution with geometric class boundaries: 0, 0.5, 1,

2, ... , 256 Mf/snip. The analysis is restricted to cohorts of persons who have been snipped at each survey and who were older than 20 years at the first survey. The restriction to adults follows previous arguments that it is only for this age group that one may expect a stable age-structure of the initial parasite population and, therefore, regular epidemiological trends during the control period (Remme *et al.*, 1986). Furthermore, only the first survey and the surveys after 10 years of control are used for the sensitivity analysis because in particular the differences between early and late surveys are sensitive to variations in the quantification of the parasite lifespan parameters.

The goodness-of-fit is characterized by the P value of a χ^2 test. Each comparison of a simulated and observed skin-snip distribution renders one P value. Since we are interested in the goodness-of-fit with all relevant surveys, the results for separate surveys for a given reference village can be combined into one overall P value. Finally, P values for different villages can be combined into an overall measure for the goodness-of-fit. The procedure for combining P values is described in the appendix.

Because of the difficulties involved in assessing the correct number of degrees of freedom in a model in which a number of parameters are estimated simultaneously from data from different sources, the P value resulting from the χ^2 test should not be used as a formal criterion for accepting or rejecting assumptions on the lifespan. Instead, it will be used to identify regions with good and poor fitting parameter values. Therefore, we will use the term 'score' instead of P value in the remainder. Goodness-of-fit scores have been determined for many combinations of values for the mean lifespan (between 7 and 12 years, with steps of 1 year) and for the 95^{th} percentile (between 9 and 20 years).

Table 2 strongly suggests that the pre-control endemicity of the villages (as measured by the CMFL of the first survey) is different and, hence, that the average vector biting density before the start of control must have been different. However, average biting rates are unknown. Therefore, each quantification of the lifespan parameters is tested for a range of values for the pre-control biting rate such that the observed endemicity levels fall within the range of simulated endemicity levels. As mentioned before, the reference villages also differ in their degree of exposure heterogeneity. Testing of lifespan quantifications for a village is therefore always done for the village specific best fitting values of the biting rate and exposure heterogeneity.

Results

Lifespan parameters

Fig. 7 shows for each of the villages the goodness-of-fit score as a function of the two lifespan parameters. The 95th percentile is plotted on the horizontal axis and the values for the mean lifespan are represented by different lines. The scores are plotted on the vertical axis using a reversed log-scale, which implies that values in the upper part of the graph represent poor fitting model quantifications, whereas values close to the horizontal axis represent good fitting, plausible quantifications. For each village, the four values for the mean lifespan are shown which give the best fit.

A straightforward conclusion from Fig. 7 is that only a limited range for the mean lifespan and the 95th percentile gives a good fit with the trends observed in the villages. At both sides of an optimal range for the two lifespan parameters, the goodness-of-fit gets worse. The only exception is the mean lifespan of 12 years fitted to data of Sarba-Baforo, which shows a good score even when there is very little variation (95th percentile of 12.3). Both the width and the position of the optimal range is not identical for the four villages, as should be the case, if only because of random sampling fluctuations. The data for Folonzo and Sarba-Baforo allow for a fairly wide range for the 95th percentile while a more limited range is obtained from Tiercoura and Loaba. Except for Loaba, at least three values for the mean lifespan give rise to very high scores (close to the horizontal axis). In Loaba, only one value for the mean lifespan (8 years) gives a reasonable fit with the data. In this village there is also a preference for low values of the 95th percentile. In contrast, Folonzo shows a preference for higher values of the 95th percentile.

A more regular picture, with a more restricted range for the 95th percentile is obtained when the results of the villages are combined. This is shown in Fig. 8. Loaba is not included in this combination. It is so different from the other villages, that no acceptable over-all fit could be obtained for all 4 villages combined.

A summary of the results in Table 3, together with Figs. 7 and 8, shows that the best fit is obtained for a mean lifespan of 9 to 11 years and a 95th percentile of 13 to 15 years.

Example of simulated Mf distributions

In addition to the goodness-of-fit test, it is important to have a visual check of the appropriateness of the estimates for the description of a given data set. As an example, in Fig. 9 for Folonzo the observed Mf distributions from three surveys are shown together with simulated distributions. In this simulation, the mean lifespan is 10 years and the 95th percentile 13.7 years (which is a plausible quantification given

Table 2 **Characteristics of the four villages that are used for testing the assumptions on the parasite lifespan.**

Village	River basin	Initial census population	Size of study cohort	CMFL at first survey (Mf/snip)	Timing of surveys (yrs. since start of control)
Tiercoura	Leraba	160	31	53	0.8, 5.0, 7.0, 10.0, 12.0, 14.0
Folonzo	Comoé	285	48	30	0.8, 4.9, 7.0, 10.0, 12.0, 14.0
Sarba-Baforo	Bougouriba	600	76	17	1.4, 8.9, 11.0, 13.3
Loaba	White Volta	270	19	41	1.8, 5.1, 10.1, 13.1

Table 3 **Ranges for the mean lifespan and the 95th percentile with a goodness-of-fit score > .1 for the reference villages and for the combination of Folonzo, Sarba-Baforo, and Tiercoura.**

Village	Mean lifespan	95th percentile
Tiercoura	8-11	11-14.5
Folonzo	7-11	12.5-16
Sarba-Baforo	8-12	12.5-16
Loaba	8	11-13
Combination (excl. Loaba)	9-11	12.5-15

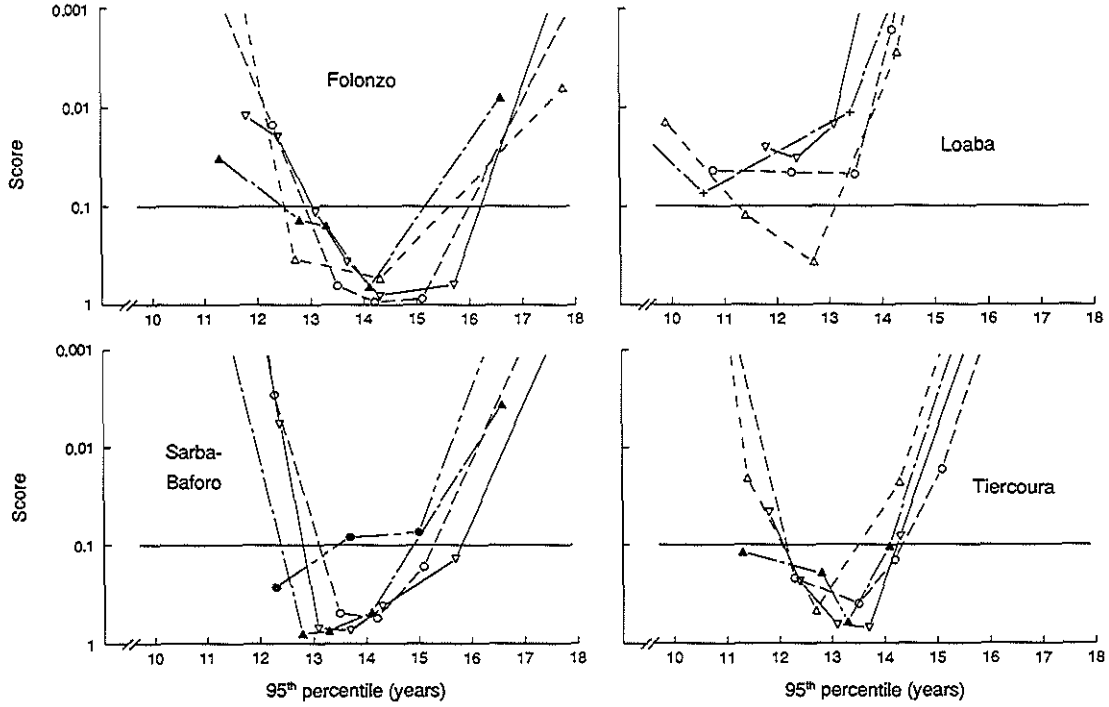

Figure 7 Goodness-of-fit scores between simulation results and observed skin-snip count distributions in the 4 reference villages for different values of the mean lifespan (years) and the age at which 95% of all parasites have died (95th percentile, years). Results are plotted on a reversed log-scale, i.e. lower values indicate a better fit. For each village, only the four best fitting values of the mean lifespan are plotted. As a result, a mean lifespan of 12 years is only included for Sarba-Baforo, and 7 years only for Loaba. Symbols: Mean lifespan (years) + = 7; △ = 8; ○ = 9; ▽ = 10; ▲ = 11; ● = 12.

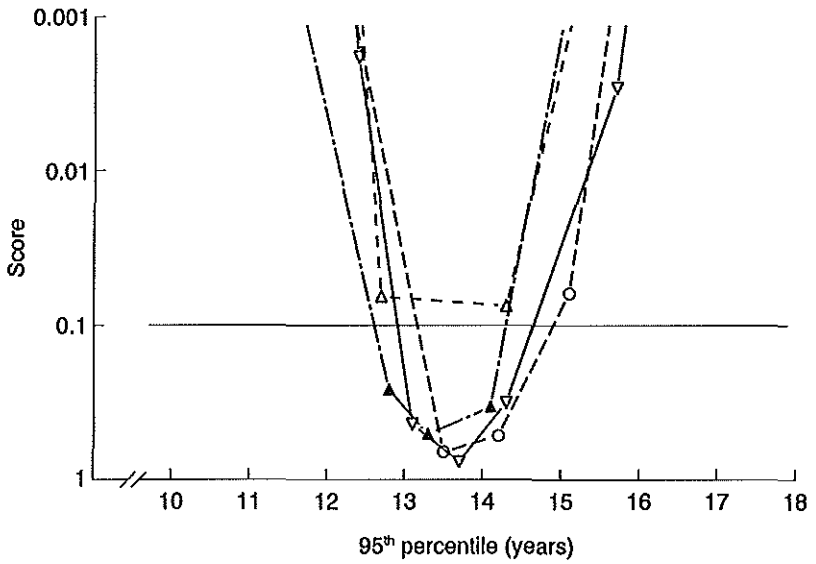

Figure 8 **Goodness-of-fit score as a function of the mean lifespan and the 95th percentile for the combined test results of Folonzo, Sarba-Baforo, and Tiercoura. See also Fig. 7 (For explanation of symbols see Fig. 7).**

the results of Figs. 7 and 8). Fig. 9 shows that the change in the Mf distribution is simulated quite well.

Simulated trends in prevalence of Mf and in CMFL

Skin-snip distributions are usually summarized to Mf-prevalence and CMFL, the level of onchocerciasis infection. Parameter quantifications with a good fit appear to provide also a close agreement between observed and simulated trends in these indices, see Fig. 10. The exception is again the Loaba data, which can only be fitted with a lower value for both the mean lifespan and the 95th percentile. This is clear from the overestimation of the infection prevalence.

Discussion

Reliable estimates of the parasite reproductive lifespan are not only important for the quantitative understanding of endemic onchocerciasis, but also for the prediction of the epidemiological impact of vector control and the determination of the

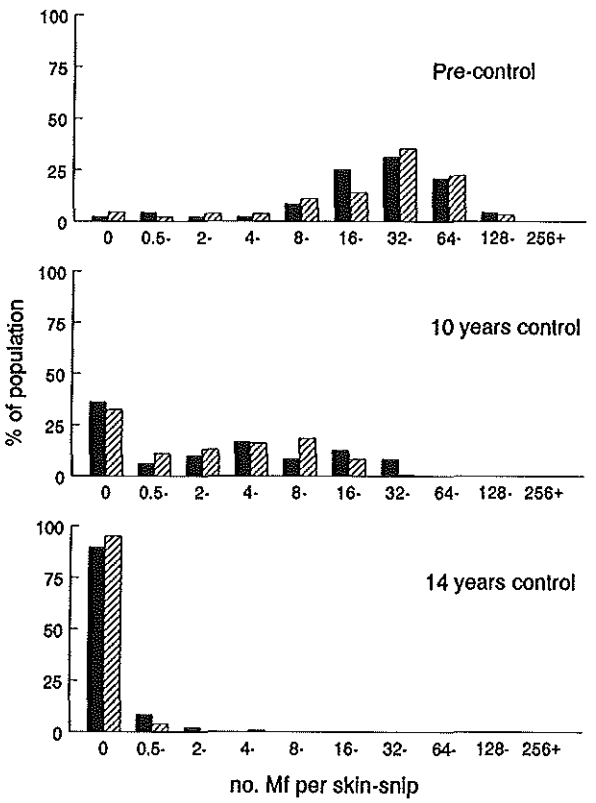

Figure 9 **Folonzo: Simulated (hatched bars) and observed (black bars) trend in skin-snip count distribution. In the simulation the mean lifespan is 10 years and the 95th percentile is 13.7 years.**

required duration of vector control (see a.o. Remme *et al.*, 1986, 1990a; Habbema *et al.*, 1990). Several previous attempts at estimation of the lifespan have been made, though often on the basis of limited data.

Roberts *et al.* (1967) reported on onchocerciasis infection levels after elimination of the vector from several isolated foci in Kenya. Cross-sectional surveys showed still life adult worms present in nodules and alive Mf in the skin 11 years after interruption of transmission, but no more Mf in the skin 18 years after vector elimination. These authors postulated, therefore, that *O. volvulus* loses its reproductive potential after a lifespan of 16 years or possibly earlier. Though this study did not explicitly address the question of variability, it is fair to assume that their

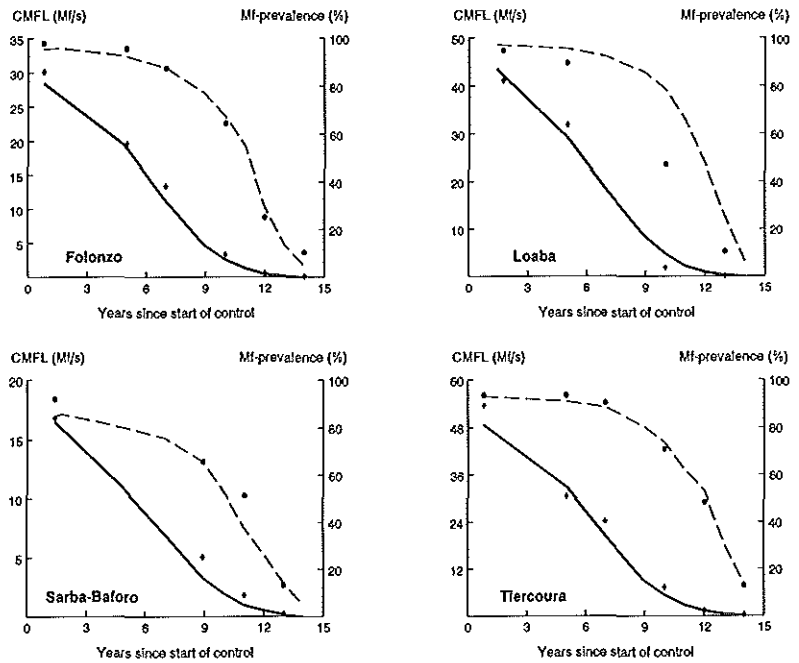

Figure 10 Simulated and observed trends in CMFL and Mf-prevalence in the four reference villages. The simulations use a mean lifespan of 10 years and a 95th percentile of 13.7 years. Symbols: + = CMFL observed; —— = CMFL simulated; ● = Mf-prevalence observed; - - - = Mf-prevalence simulated.

postulate refers to an upper limit for the reproductive lifespan.

A direct estimate of the duration of onchocerciasis infection is provided by Duke (1980) who recorded the intervals between inoculation of infective larvae in chimpanzees, the appearance of Mf in the skin, and the final disappearance of skin Mf. Based on an experiment in a single chimpanzee, he found for the savanna strain of *O. volvulus* an interval of less than 6 years between the last inoculation and the complete disappearance of Mf from the skin. Though it cannot be excluded that the last inoculum was ineffective, this duration (which includes both the adult parasite lifespan and the microfilarial lifespan) is extremely short and does not correspond with other estimates and with the trends observed in the OCP.

Karam *et al.* (1987) present an analysis of epidemiological data obtained during the first 7 to 8 years of the OCP. Based on longitudinal changes in skin Mf loads

and in differences in the adult worm composition as compared to non-controlled areas, they postulate a breakdown of the worm population 11 to 12 years after the beginning of control. Furthermore, they demonstrate that the Mf productivity was significantly reduced in aged worms.

The question of variability in the reproductive lifespan was first addressed in the study by Remme *et al.* (1990a). Following the introduction of a simple force-of-infection model, which led to a preliminary estimate of 11 years for the average duration of infection (Remme *et al.*, 1986), they developed a more sophisticated host-parasite model which actually was a predecessor of ONCHOSIM. The host-parasite model was quantified using longitudinal skin-snip data for the first 8-9 years of vector control in the OCP and this resulted in an estimate for the mean longevity of infection (including Mf-survival) of 10.4 years and a variability which was such that 95% of the longevities were less than 15 years. The model allowed the prediction of trends in the prevalence of skin Mf and in the CMFL for different levels of endemicity and it was shown that the predicted trends gave a good description of those observed in 55 villages during 12-14 years of control. However, no formal estimation procedures were followed in this study and no attempts were made to investigate other quantifications.

The distinguishing feature of the present analysis is the systematic search for plausible quantifications of the major parameters which determine the reproductive life-history of *O. volvulus*. The model used, ONCHOSIM, takes account of all aspects that ultimately determine the mean duration of onchocerciasis infection and its variability. Several model simplifications have been considered in order to arrive at a more simple and tractable estimation procedure. A first simplification would be to assume a (single-parameter) exponential distribution for the lifespan (see, among others, Anderson and May, 1985). However, this assumption is not compatible with the trends and is especially in conflict with the accelerated decline in Mf-prevalence during the late years of control (10 to 14 years, see Fig. 10). Also the restricted range of the 95th percentile of the lifespan distribution, which can be concluded from Figs. 7 and 8, demonstrates the inappropriateness of the exponential distribution which has still a 95th percentile of 21 years at the very low mean of 7 years.

By systematically varying model assumptions it appeared that only with a considerable degree of age- and sex-independent exposure variation between individuals a good fit is obtained between simulated and observed skin-snip distributions. A simple model which disregards this personal variation, could be fitted to trends in aggregated measures like CMFL and Mf prevalence, but is not suitable for describing the more detailed data that we have available.

Two rather detailed assumptions that are not necessary for obtaining a fit of the skin-snip data are the age-dependent fecundity and the requirement of regular mat-

ing for the female worms. The assumption of a constant fecundity level - though conflicting with nodulectomy results (see Karam *et al.*, 1987) - will lower the estimates of the lifespan. When female worms can produce Mf even in the absence of male worms, the residual worm population in the final years of control will be much more productive and this must also be compensated by a shorter lifespan. The inclusion of these refinements which cannot be tested against skin-snip data is justified because of the (biological) face validity of the model. This is important in view of the role of ONCHOSIM in prospective evaluation of control measures.

Other parameters that influence the mean duration of infection include the Mf production per worm and the lifespan of Mf. Variations in these parameters are expected to influence the estimate of the worm lifespan. Alternative quantifications of the Mf production level have been tested by using the same goodness-of-fit procedure as reported in this paper. Lower values for the lifespan (especially the 95^{th} percentile) result when a lower Mf production per worm, and thus a higher worm load, is assumed. The opposite applies to a high per-worm productivity. However, these alternative quantifications for the Mf-production will affect the lifespan estimates with at most 0.5 year.

Another parameter which may still alter our estimates is the microfilarial lifespan, which we have taken equal to 1.5 years. We tested the influence of other values between 0.5 and 2 years, which is the widest range compatible with the observations of Duke (1968). Intuitively, one would expect that a change in the lifespan of the microfilariae will be compensated by exactly the opposite change in the lifespan of the macrofilariae. Thus, a Mf lifespan of 0.5 years instead of 1.5 years would add 1 year to the worm lifespan. However, because of a reduced Mf-production of old worms, this mechanism does not apply exactly. It was found that values of 0.5 or 2 years for the Mf-lifespan will not change our estimates of the worm reproductive lifespan with more than 0.5 year.

Different alternative values for the length of the prepatent period have been tested. This revealed that, in the range of 0.5 to 1.5 years, these alternative values do not influence the estimate of the lifespan.

The goodness-of-fit results suggest some systematic differences between the lifespan estimates which were obtained with the longitudinal data for each of the four villages. Some of these differences may reflect discrepancies between actual transmission patterns and the model assumptions of a stable pre-control transmission level and complete interruption of transmission during the vector control period. Circumstantial evidence suggests that the actual transmission pattern around the start of control may have been different in at least three villages and we will therefore discuss each village in some detail.

The lowest estimate for the lifespan was obtained with the data for the village of

Loaba. This village is located along the White Volta River, much more to the east than the other three villages. It has been noted previously that the decline in infection levels was much faster in the north-east of the original OCP area. This has been attributed to a major reduction or even interruption of transmission during the last years of the pre-control period when there was hardly any local vector breeding because of severe drought and when there was no more vector invasion from the south-west where vector control started one to two years earlier than in the east (Karam *et al.*, 1987; Remme *et al.*, 1990a). If local transmission was indeed absent for one or two years before the start of control, then our mean lifespan estimate of 8 years for Loaba, is an underestimate.

The highest estimates for the mean lifespan were obtained with the data for Sarba-Baforo. This village is located along the River Bougouriba, which was during the first few years of vector control subject to reinvasion by infective flies from outside the Programme area (Garms *et al.*, 1979). This initial reinvasion may have been responsible for a significant incidence of (super)infection and this has been given as the explanation for the different epidemiological trends in the first line villages along this river, where the CMFL started to show the predicted linear decline only after a delay of a few years (WHO, 1987b). Sarba-Baforo is not a first line village and no significant delay in the decline of the CMFL has been observed previously. However, it is possible that the detailed analysis presented here has detected some minor impact of the reinvasion phenomenon.

Extensive entomological evaluation data are available for a fly catching point near the village of Folonzo where vector control resulted in an immediate reduction in fly biting rates. Nevertheless, the Annual Transmission Potential, an entomological index of *O. volvulus* transmission (Walsh *et al.*, 1978), was during the first three years of control equal to 274, 50 and 107 infective larvae per year respectively before falling to levels close to zero during subsequent years. Annual Transmission Potentials in the range of 100 to 200 infective larvae per year are usually taken as evidence of a low level of active transmission (Thylefors *et al.*, 1978), but it should be noted that the fly population during the first three years of control at Folonzo consisted nearly exclusively of reinvading flies which stay close to the riverine vegetation and have less chance of man-fly contact (Garms *et al.*, 1979). One may speculate, therefore, that there have been occasional new infections during the first three years of control which explain the higher estimate for the 95th percentile but which were too few to affect the estimate for the mean lifespan.

At the fourth village of Tiercoura there has never been a catching point, but available evidence from the two nearest catching points at a distance of 8 and 17 kilometres respectively suggest that complete control of the vector population has been achieved since the start of the larviciding operations.

Combining the results of our analysis, the above background information about the four reference villages, and the results of previous studies, we conclude that the mean reproductive lifespan of the savanna strain of *O. volvulus* lies between 9 and 11 years, and that 95% of the parasites reach the end of reproduction before the age of 13 to 14 years.

Appendix

Worm mating and age dependent fecundity in the model

According to Schulz-Key and Karam (1986) and Schulz-Key (1990), a reproductive cycle of a female *O.volvulus* worm takes about 3 months, and hence for ongoing microfilarial production, insemination must take place at 3 monthly intervals. The mating probability is taken to be equal to the ratio of male to female worms, with a value of 1.0 when there are more male than female worms. By means of random number generation, on the basis of this probability, it is determined for each female worm that needs insemination - i.e., for which the last insemination took place at least 3 months ago - whether (re-)insemination takes place indeed. If not, then Mf production ceases immediately. Each month, all uninseminated female worms have a new chance to mate. It is obvious that in the case of low (residual) worm loads, the worm mating probabilities in the human host will be reduced and will vary considerably from host to host.

Apart from mating, the Mf output is also dependent on the age of the worms. We tested several models for the age-specific fecundity. In the simulations of the present analysis, female worms have their maximum fecundity during the first 5 years of patency. So, with an average pre-patent period of 1 year, this maximum level of fecundity ends at the age of 6 years. Thereafter, fecundity reduces linearly, and becomes zero at the (practically unattainable) patent age of 20 years.

Finally, it is assumed that, due to genetic variability and due to the differential distance to the snipping site, inseminated female worms of the same age can make a different contribution to the skin-snip count. The latter variability is described by an exponential distribution function.

Combining test results

Test results for several surveys or for several villages are combined as follows:

1. The P value obtained from a goodness-of-fit test is under the null hypothesis uniformly distributed on [0,1]. Hence, $-\ln(P)$ is exponentially distributed with a mean of 1.
2. In combining the P values of n tests (P_1, P_2, ..., P_n), we use the fact that the

sum of n independent exponentially distributed random variables follows an n-Erlang distribution.

Thus,

$$x=\sum_{i-1}^{n} -\ln(P_i)$$

follows the n-Erlang distribution:

$$F(x)=e^{-x}\sum_{j=0}^{n-1}\frac{x^j}{j!}$$

3. $F(x)$ is the goodness-of-fit score for the combination of n tests.

Lifespan distribution

The lifespan is described by a Weibull distribution, using an offset of 4 years, which implies that no parasite will reach the end of the reproductive period before the age of 4 years.

One of the plausible distributions is characterized by a mean lifespan of 10 years and a 95th percentile of 13.7 years. This distribution can be described as follows (to be read as the probability to be dead before the age of x):

$$F(x)=\begin{cases} 0 & \text{if } 0<x<4 \\ 1-e^{-((x-4)/\beta)\alpha} & \text{if } x\geq 4 \end{cases}$$

Other percentiles of this distribution: 80th=11.9; 90th=12.9; 99th=15.2.

Chapter IV

Parasitological effects of ivermectin

IV.1 The impact of five years of annual ivermectin treatment on skin microfilarial loads in the onchocerciasis focus of Asubende, Ghana

E.S. Alley, A.P. Plaisier, B.A. Boatin, K.Y. Dadzie, J. Remme, G. Zerbo, E.M. Samba
Transactions of the Royal Society of Tropical Medicine and Hygiene 1994;88:581-584.

Introduction

Ivermectin (Mectizan®) is an effective and well tolerated microfilaricidal drug which is suited for large-scale treatment of onchocerciasis (Awadzi *et al.*, 1985; Remme *et al.*, 1989b; Whitworth *et al.*, 1991; Collins *et al*, 1992). The registration of the drug in 1987 was the starting point of a series of community trials conducted by the Onchocerciasis Control Programme in West Africa (OCP) and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The main objectives were to determine the safety of the drug when used on a large scale and to assess its potential for morbidity and transmission control. In the OCP, as many as 8 trials were started, initially covering a total of more than 50,000 persons (De Sole *et al.*, 1989a). The largest trial, which had also the longest series of follow-up surveys, was carried out in the holoendemic focus of Asubende in Ghana. In that trial the impact of treatment on transmission was studied over a period of 3 years. It has been reported by Remme *et al* (1989b) that transmission was reduced with 65 to 85% during the first 3 months after treatment. In the present paper we report the changes in skin-snip microfilarial counts during the first 5 years of annual treatment in this area.

Materials and methods

Study population.
A detailed description of the study area has been provided by Remme *et al* (1989b). The results presented here concern the 3 holoendemic villages located in the core of the focus, close to the breeding sites of *Simulium* in the river Pru (west of Lake Volta). The total census population at the beginning of the trial was 892 persons, 796 of whom were present at the baseline survey in September 1987. Treatments were done in October 1987, October 1988, October 1989, November 1990, and November 1991. Tablets of ivermectin were given as a single oral dose of 150-200

μg/kg body weight. Children below 5 years or with weights of less than 15 kg and breast-feeding and pregnant women were excluded from treatment. The coverage of treatment at each round is summarized in Table 4. Follow-up skin-snip surveys were conducted at 2, 4, and 12 months after the first 3 treatments, 12 months after the 4th treatment, and 6 and 12 months after the 5th treatment. Skin-snips were taken according to the standard OCP method. Two snips were taken from the iliac crest using a Holtz corneo-scleral punch. The snips were incubated in distilled water and microfilariae (Mf) were counted after 30 min (Prost and Prod'hon, 1978). The changes in skin-snip counts 2, 4, and 12 months after the initial treatment and 2 and 4 months after the second round have been extensively reported (Remme *et al.*, 1989b, 1990b). Ophthalmological information was also collected at each of the surveys, except for the follow-up after 2 months. The changes in ocular onchocerciasis for the first 2 rounds of treatments have been documented (Dadzie *et al.*, 1990, 1991). The results for a longer treatment period will be published elsewhere.

Table 4 Coverage of ivermectin treatment for onchocerciasis

Date of treatment	Total population		Population >5 years old	
	No.	No. treated	No.	Percentage treated
October 1987	892	572 (64%)	710	81
October 1988	874	583 (67%)	696	84
October 1989	838	521 (62%)	670	78
November 1990	821	605 (74%)	681	89
November 1991	830	588 (71%)	687	86

Vector control

In the Asubende focus, which is at the northern boundary of the southern extension of the original OCP area, vector control operations were started in January 1986. However, since an important aim of the trial was to assess the impact of large-scale treatment on the transmission of the parasite (Remme *et al.*, 1989b), larviciding was interrupted several times to allow the vector population to establish itself and build up to an equilibrium level before ivermectin delivery.

Results

For the interpretation of the results presented in this paper it is important to notice that treatment took place in a situation of reduced vector biting levels. To provide an idea of the joint effect of ivermectin treatment and vector control on transmission, Fig. 11 shows the trend in the monthly transmission potential (MTP, i.e., the product of the monthly biting frequency and the average number of infective larvae per biting fly) for the period 1979 to 1992. The MTP's are given as 6-monthly averages: January to June and July to December. From 1979 to 1985 the average value was 172.3. From January 1986 to the end of 1991 it was reduced to 56.2.

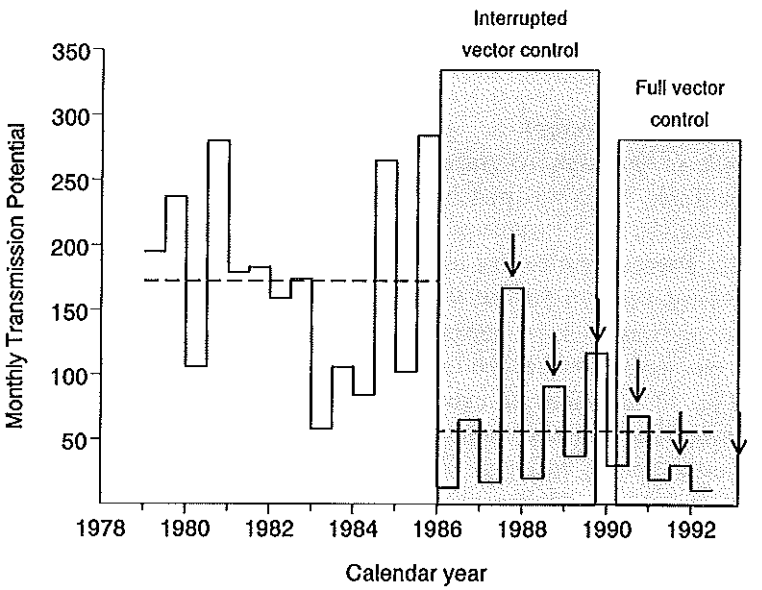

Figure 11 Six-monthly averages of the monthly transmission potential for onchocerciasis, based on blackfly collections during 1979-1992. Vector control operations started in 1986, but were interrupted several times to enable assessment of the impact of treatment on transmission. The horizontal dashed lines show the average values before and during vector control; arrows indicate ivermectin treatment.

Basic results for the study population

The observations made at each of the follow-up surveys are summarized in Table 5. Except for the follow-up 2 months after the first treatment round, a considerable

percentage of the census population could be examined. The second survey was an exception since it was intended to select only those who had been treated in the first round. In the other surveys, 80 to 91% of the census population was monitored. Each treatment caused a marked reduction in microfilarial counts. However, 4 months after treatment the loads had increased considerably, and this increase was maintained until the subsequent round of treatment. Twelve (or 11) months after each treatment the relative reductions in Mf load compared to the observations just before each treatment were 46%, 32%, 12%, 52%, and 39%, respectively. The over-all reduction observed between September 1987 and October 1992 is 90%. During this period the population examined in October 1992 received slightly fewer than 3 treatments on average. The total reduction in the prevalence of infection was much less. Only 25% of the persons who were initially positive had become negative at the end of the total trial period.

Results for treatment cohort

As a result of the high coverage, especially among the eligible population (>5 years; see Table 4), it was possible to select a considerable cohort of 268 persons who had received all 5 treatments. The basic observations on this cohort are shown in Fig. 12. Participation of this treatment cohort in the pre-treatment and follow-up surveys varied between 80 and 96%. Following the 4th treatment the earliest follow-up survey was after 11 months. Connecting the outcome of this survey with the previous one would obscure the (most probable) actual trend. We have used dashed lines in Fig. 12, therefore, to indicate the direction of the expected trends had there been intermediate follow-up surveys comparable to those after the first 3 treatments.

The trends for the treatment cohort generally followed the pattern of the total examined population (Table 5). However, in the treatment cohort, the initial increase after the first 3 treatments is slower. This was most probably due to the fact that this cohort did not include (untreated) young children, who have a relatively young parasite population and whose Mf levels therefore increase. Fig. 12 clearly shows the increase in Mf prevalence between the follow-ups at 2 and 4 months after the first 3 treatments. Apparently, worm loads are so high that, even though the worms might (initially) have produced Mf at a lower rate, treatment did not result in long-standing clearance of all Mf.

A detailed overview of the results with the treatment cohort is provided in Table 6. Only those people who participated both in the first survey (September 1987) and the last (October 1992) have been included. As a result, the cohort size has been reduced to 222 persons. The Table shows the relation between the pre-treatment skin-snip count distribution (using 7 classes) and the distribution 11 months after the last treatment (using 3 classes). In addition, for each of the pre-treatment groups,

Table 5 ***Onchocerca volvulus*** **microfilarial counts and prevalence at each of the follow-up surveys and the average number of ivermectin treatments given to the population examined.**

Survey description	No. of persons	Mean Mf count[a]	Prevalence (%)	Average no. of treatments
September 1987	796	72.1	79.9	-
October 1987: 1st treatment				
December 1987	422[b]	3.73	55.0	0.93
February 1988	679	20.0	69.7	0.66
October 1988	747	39.2	79.3	0.65
October 1988: 2nd treatment				
December 1988	611	6.61	34.2	1.31
February 1989	756	16.2	62.7	1.26
October 1989	762	26.6	74.1	1.24
October 1989: 3rd treatment				
December 1989	894	2.60	24.7	1.70
March 1990	750	12.7	62.4	1.83
October 1990	728	23.5	72.4	1.80
November 1990: 4th treatment				
October 1991	709	11.2	67.1	2.33
November 1991: 5th treatment				
May 1992	661	3.44	50.7	2.98
October 1992	698	6.86	60.6	2.91

[a] Mean no. of microfilariae per skin snip.
[b] At this survey people treated in the first round were actively selected.

the reduction in the mean skin-snip count is given. About one-half of the subjects with pre-treatment counts <32 Mf per skin-snip became totally amicrofilaridermic as a result of treatment. However, in the highest category (≥ 128 Mf/snip), less than 5% became negative, although the percentage reduction in the mean load was highest for this category. A relatively small reduction in Mf count was shown by the lowest Mf density pre-treatment category. Moreover, a number of persons negative before treatment became positive notwithstanding 5 treatments. In part this effect

Table 6 **Distribution and reduction of *Onchocerca volvulus* microfilarial counts 11 months after 5 rounds of ivermectin treatment in relation to the counts before the first round**

Pre-treatment count[a]	No. of patients	Percentage of pre-treatment group having microfilarial counts within the ranges shown 11 months after their last treatment[b]			Arithmetic mean no. of microfilariae/skin-snip		
		0	0.5-7	≥8	Before treatment	After treatment	Reduction (%)
0	14	50.0	42.9	7.1	0	3.9	-
0.5-7	18	44.4	50.0	5.6	4.0	2.7	33.0
8-15	12	50.0	50.0	-	11.6	1.5	87.1
16-31	13	46.2	46.2	7.7	23.8	2.8	88.2
32-63	26	23.1	53.8	23.1	48.0	4.4	90.8
64-127	76	18.4	57.9	23.7	91.1	6.2	93.2
>128	63	4.8	57.1	38.1	182.5	9.9	94.6
Total	222	22.5	54.5	23.0	91.0	6.2	93.2

[a] No. of microfilariae per skin-snip
[b] All values apply to persons who had been treated 5 times

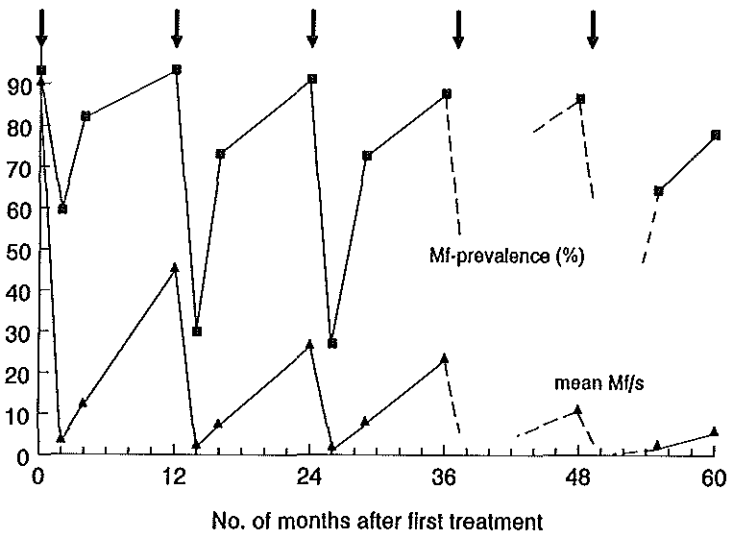

Figure 12 Trends in prevalence of *Onchocerca volvulus* microfilaridermia (Mf prevalence) (■) and arithmetic mean number of microfilariae per skin snip (mean Mf/s) (▲) in persons who were treated in all 5 rounds. Note that these persons did not necessarily participate in all follow-up surveys. After the 4th round of treatment only an 11-month follow-up survey was done, so the expected outcome of an intermediate survey is shown.

can be attributed to 'regression to the mean': due to variations in the skin-snip procedure, persons could have been classified as low-density while their actual density was higher; this would reduce the apparent effectiveness of treatment at subsequent surveys. However, since most of the low-density persons were children (≤5 years), it is also possible that at the pre-treatment survey they had a relatively high number of immature worms, which may have started Mf production during the trial thus giving rise to higher subsequent Mf loads despite the effect of 5 treatments. The average reduction caused by 5 treatments - in combination with vector control - was 93%.

Long-term impact of a single treatment

The available combinations of treatment and surveillance histories enabled us to select individuals with a considerable follow-up period after their first treatment. Most of them received their first treatment during the first round in 1987, but some people entered the trial subsequently. A combined summary of results after a single

(first) treatment is shown in Fig. 13. Because persons could have been examined in several of the indicated follow-up periods, the overall number of observations shown in this Figure is larger than the total patient population. During the first year, Mf counts increased rapidly to about 45% of the pre-treatment count (see also Fig. 12). During the second year, however, a clear levelling-off occurred. Microfilarial counts barely increased after 14-16 months and stabilized around 55% of the pre-treatment counts 2-4 years after treatment.

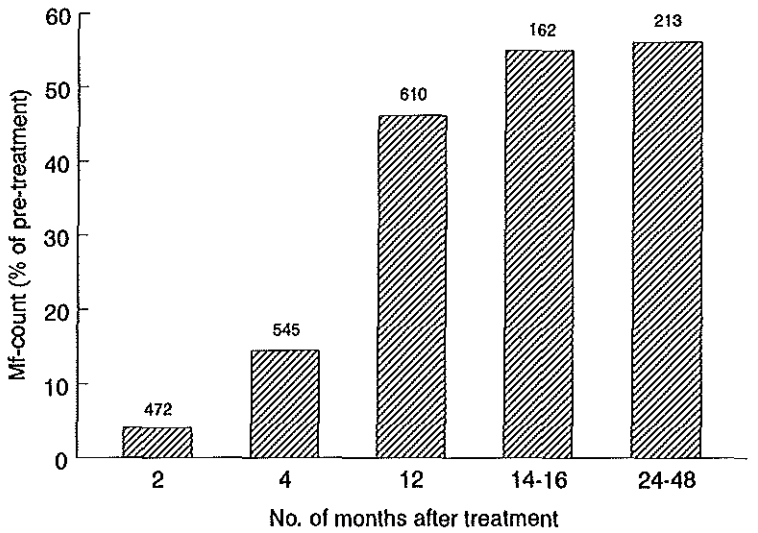

Figure 13 Long-term effect of a single treatment on *Onchocerca volvulus* microfilaridermia. The bars indicate microfilariae (Mf) count per skin snip as a percentage of the pre-treatment value (the pre-treatment value was not necessarily obtained before the first treatment round and some persons are included who received their first treatment later in the trial). The numbers above each bar are the numbers of observations.

Discussion

Pre-treatment surveys during 1987 showed that Asubende is a highly endemic focus of the severe blinding form of onchocerciasis. The high endemicity was reflected in the high skin Mf loads and in the very high loads in the eye (Remme *et al.*, 1989b; Dadzie *et al.*, 1990). Since the risk of developing ocular lesions and blindness is directly related to the intensity of infection in the community (Thylefors and

Brinkmann, 1977; Remme *et al.*, 1989a), the area is particularly suited to study the beneficial effect of ivermectin treatment on both the intensity of infection and ocular lesions. The results presented here show the effect of repeated annual ivermectin treatment over a period of 5 years on the skin Mf load and hence on a major risk factor for blindness.

The general pattern observed after each of the treatments (both in the total population and in the cohort treated 5 times) was a marked reduction shortly after treatment followed by a steady repopulation of the skin by Mf. The same pattern has been observed in most other trials (Larivière *et al.*, 1985; Taylor and Greene, 1989; Greene *et al.*, 1991), although these trials mostly showed a slower and sometimes a very slow repopulation during the first year (Larivière *et al.*, 1985). Although in our study repopulation occurred after each treatment, the highest Mf level reached after one year was consistently reduced during the course of the trial. Among those who received the drug during each of the rounds, the overall reduction of Mf loads one year after the last treatment was 93% compared to the pre-treatment survey in 1987. For comparison, about 12 years of effective vector control alone are required to arrive at a similar reduction (Remme *et al.*, 1990a).

Our study emphasizes that even a single treatment with ivermectin has a significant medium term (2-4 years) impact on Mf loads (see Fig. 13), which suggests that the impact of the drug on Mf production by female parasites is fairly long-lasting. Evidence of a short-term cessation of Mf production by the females has been reported by Schulz-Key and colleagues (1985). In addition to this, Schulz-Key *et al* (1992) and others (Chavasse *et al.*, 1992; Duke *et al.*, 1992) have provided evidence that the impact on adult parasites is more than temporary. The profound and long-lasting effect of treatment observed in our trial cannot be attributed to the effect of the large-scale ivermectin distribution alone. The vector control activities, which started in January 1986, must have had a major impact as well. The mean reduction in MTP for the whole period was 67% (see Fig. 11).

Additional analysis and field work are required to answer the question whether ivermectin has macrofilaricidal effects, and if so what is the nature of these effects (killing or partially disabling worms). An important next step in the analysis of our results will be the utilization of an epidemiological simulation model (Plaisier *et al.*, 1990) to isolate the impact of ivermectin *per se* from the overall result of treatment and vector control, and to estimate basic parameters for the effect of the drug.

IV.2 Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa

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The Journal of Infectious Diseases 1995;172:204-210

Introduction

The registration of the anthelminthic drug ivermectin (Mectizan; Merck, Rahway, NJ) in 1987 was a landmark in the control of human onchocerciasis or river blindness, a parasitic disease caused by the filarial nematode *Onchocerca volvulus*. Oral administration in a standard dose of 150-200 μg/kg body weight is followed by rapid elimination of microfilariae (Mf) from the skin and gradual reduction of ocular Mf levels (Awadzi *et al.*, 1985). Side effects are generally mild. This makes ivermectin a better therapeutic option than diethylcarbamazine, which is often accompanied by severe Mazotti reactions and ocular damage. Ivermectin also produces a longer suppression of Mf repopulation of the skin (Greene *et al.*, 1985; Larivière *et al.*, 1985). To explain this difference, which was obvious in all studies done so far, the effects of ivermectin on adult parasites were studied.

Adult female parasites in treated persons show an interruption of the normal embryogenesis, but after a single treatment, this appears to be reversible for most of the worms (Schulz-Key *et al.*, 1985; Duke *et al.*, 1991a). Excess worm mortality was not observed after a single treatment (Awadzi *et al.*, 1985; Greene *et al.*, 1985), although significant numbers of dead and moribund worms were reported after multiple treatments at intervals between 2 weeks and 6 months (Duke *et al.*, 1990b, 1991b, 1991c, 1992; Chavasse *et al.*, 1992, 1993). Furthermore, after multiple treatments, the reproductive activity of the surviving worms was markedly reduced. The suppression of Mf production persisted 1.5 years after five 6-monthly doses (Kläger *et al.*, 1993), which suggests the existence of irreversible effects of the drug.

An important question in view of the limited resources available to health services in developing countries is whether these findings for shorter treatment intervals are applicable to regimens with intervals of 1 year, the current practice in nearly all control programmes (WHO, 1995). In this study we addressed this question by analyzing data from a large community-based study of annual treatment in a region with hyperendemic onchocerciasis (Asubende, Ghana), organized by the

Onchocerciasis Control Programme in West Africa (OCP) (Remme *et al.*, 1989b; De Sole *et al.*, 1989b; Dadzie *et al.*, 1991; Alley *et al.*, 1994).

The available data consist of Mf counts in skin snips from persons who were repeatedly surveyed over ~5 years during treatment. We investigated whether the observed changes in Mf counts could be explained if ivermectin had only transient effects on adult worms, or whether long-term irreversible effects on the fecundity of adult worms were required to explain the data. In addition to the direct effect in individual patients, community treatment with ivermectin also reduces the level of transmission in the area (indirect effect; see Remme *et al.*, 1989b; Alley *et al.*, 1994). To take both effects into account, we did the investigation with the aid of an epidemiologic model of onchocerciasis transmission.

Material and Methods

Study population

The Asubende region is along the lower reaches of the Pru river, just west of Lake Volta. OCP initiated a programme to control the vector of *O.volvulus*, the blackfly *Simulium damnosum*, in this river basin in January 1986. Flies have been collected since 1979 to assess the vector biting rate and the vector infectivity. A clinical survey was done in September 1987 among 796 persons living in a cluster of three villages in the middle of the area. Both entomological and clinical findings revealed that the savanna form of *O.volvulus* is hyperendemic in this area. Skin Mf densities were among the highest encountered in the OCP area (Remme *et al.*, 1989b). The community trial of annual ivermectin treatment was started in October 1987.

In the present analysis we use data consisting of counts of Mf in skin snips that were collected during the period covered by the first five treatments (1987-1991). The organization of the trial, the trends in the skin Mf densities, and the joint effect of vector control and ivermectin treatment on the transmission potential of the flies have been described elsewhere (Remme *et al.*, 1989b; Alley *et al.*, 1994). Treatment dosage varied between 130 and 200 μg/kg.

From the 796 persons examined at the baseline survey in 1987, we selected 2 cohorts that comprised a total of 114 adults. Cohort 1 is 78 persons who were treated in all five rounds and were examined in all eight follow-up surveys. These surveys were done at 4 and 12 months after the first two treatments, 5 and 12 months after the third, 11 months after the fourth, and 6 months after the fifth treatment. Cohort 2 is 36 persons who were treated in the first but not in the second round and who were examined 24 months after the first treatment. We restricted the study to adults to exclude the confounding effect of ageing; only for older ages do

we expect a constant infection level (Remme *et al.*, 1986).

Model and hypotheses

We tested two hypotheses: The first (H_1) assumes that treatment has only a transient effect on the Mf production of female worms; the second (H_2) assumes that ivermectin's effect is partially irreversible, manifested by a permanently reduced fecundity of the worms in a treated patient. Hypotheses were tested with the stochastic microsimulation model ONCHOSIM. This model simulates the life histories of hypothetical individuals (birth, acquisition of parasites, death) and individual parasites (maturation, mating, production of Mf, death) and can be used to describe and test effects of ivermectin on a patient level. ONCHOSIM further allows for a detailed simulation of control strategies. The model simulates ivermectin treatments and surveys at the same times as in the field. It also mimics the vector control activities in the Asubende area, which strongly affected the transmission potential of the flies both before and during the trial (Alley *et al.*, 1994). The microsimulation method makes it possible to select persons from the simulated population who satisfy the same criteria used for selecting the cohorts and whose Mf counts before the first treatment are the same as those of the cohorts.

A full description of ONCHOSIM and the validation of the model is given elsewhere (Plaisier *et al.*, 1990, 1991; Habbema *et al.*, 1992, 1996). Here we will present only those relationships and parameters that are directly relevant to the effects of ivermectin.

Modelling the effects of ivermectin

An assumption used throughout the analysis is that a treatment with ivermectin instantly eliminates all Mf in a person, except in 3% of treatments which totally fail as a result of malabsorption (e.g., diarrhea, vomiting; see De Sole *et al.*, 1989a). Under the first hypothesis (H_1), each treatment further causes a transient interruption of the normal release of Mf by adult female parasites. During a *recovery period*, the rate of Mf production increases from zero to the pre-treatment level. We explicitly test whether this increase is linear or not.

The same assumption regarding the initial effect of treatment is made under the alternative hypothesis (H_2). However, in this case, we assume that worms do not recover to their full capacity to release Mf, but that this capacity is irreversibly reduced with a fraction called *productivity reduction*. This productivity reduction affects all worms in a patient.

Since the available data do not reveal much about the exact mechanism of a (possible) irreversible effect, we also tested an alternative form of the hypothesis (H'_2), in which a certain fraction of worms loses their fecundity totally, while the

others recover completely. This fraction is called *fecundity loss*.

Between-treatment (and within-patient) variation in recovery period, productivity reduction, and fecundity loss is governed by *effect variability*, defined as the variation coefficient (i.e., the quotient of SD and mean) of treatment effects. The time between treatment and the stabilization of the Mf density in the skin is determined not only by the effect of ivermectin on adult worms but also by the lifespan of Mf. This *Mf lifespan* is estimated when the hypotheses are tested. A mathematical description of the sub-model for the effect of ivermectin treatment is given in the Appendix. A graphic representation of the hypotheses and role of the model parameters are provided in Fig. 14.

Hypothesis testing

To test hypotheses and quantify model parameters, both observed and calculated survey results were represented as frequency distributions of Mf counts, using the classes shown in Fig. 15. The agreement between observations and predictions was determined by calculating a total χ^2 for all follow-up surveys of cohorts 1 and 2. Some adjacent skin snip count classes were combined so that the number of individuals is at least 5 per class. Estimating parameters for a specific hypothesis was achieved by minimizing χ^2 using a downhill-simplex method (Nelder and Mead, 1965). The goodness-of-fit implied by the minimum χ^2 was quantified by the P value of the χ^2-distribution with 16 *df* (only transient effects) or 15 *df* (also irreversible effects). Generally, $P < .05$ indicates a poor fit and suggests rejection of the underlying hypothesis.

After model parameters were estimated a 95% confidence interval (CI) of a particular estimate was determined by searching around the original estimate for values resulting in $\chi^2 = 3.84$ units (0.95 point of χ^2-distribution with 1 *df*) higher than the minimum. For each of the values tried, the other ivermectin-related parameters were reestimated by minimizing χ^2.

Results

For the baseline and follow-up surveys, the number of Mf per skin snip observed in the 2 cohorts are shown in the frequency distributions in Fig. 15. Considering the data from cohort 1, both short-term and longer-lasting effects of treatment were apparent. At 4-6 months after each treatment, the distribution was consistently skewed towards low Mf counts. Although after 11-12 months the distributions again tended to the pre-treatment shape, it is clear that, as the number of treatments increased, the peak of the distributions shifted to lower counts: ~32-64 Mf/snip 1

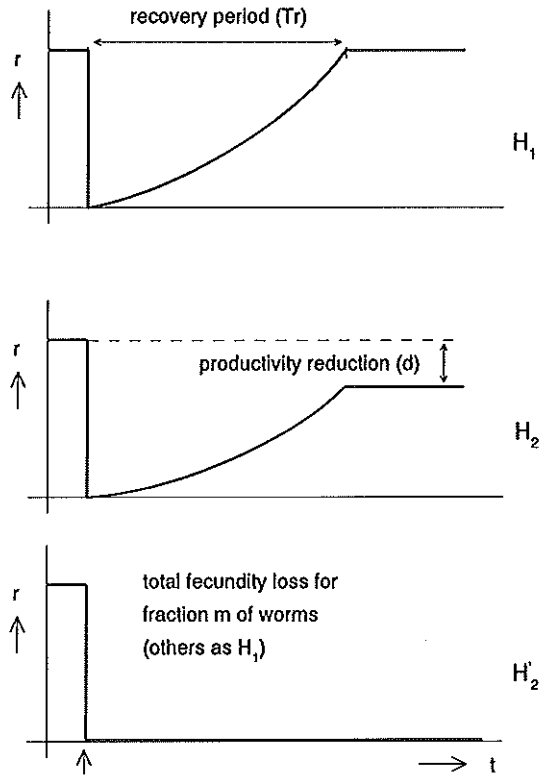

Figure 14 **Schematic representation of hypotheses tested. Each graph shows rate of microfilaria production (*r*) of parasite as function of time (*t*) after single treatment. Moment of treatment is indicated with vertical arrow below *x* axis. In hypothesis H_1, no irreversible effect is assumed; treatment only results in recovery period of length *Tr*. According to hypothesis H_2, the productivity after recovery period is permanently reduced (factor *d*); with H'_2, fraction *m* of worms totally loses fecundity. See Appendix for further explanation of symbols.**

year after the first treatment to 4-16 Mf/snip 1 year after the fourth round. A long-term effect was also observed in the data from cohort 2 (Fig. 15b); before treatment, ~30% of the population had >128 Mf/skin snip. Two years after a single treatment this was only slightly >15%.

We tested two hypotheses for explaining the data (see Fig. 14). The results are shown in Table 7. For each hypothesis, estimates of relevant parameters and goodness-of-fit (*P* values) are given. H_1, which assumed no irreversible effects of iver-

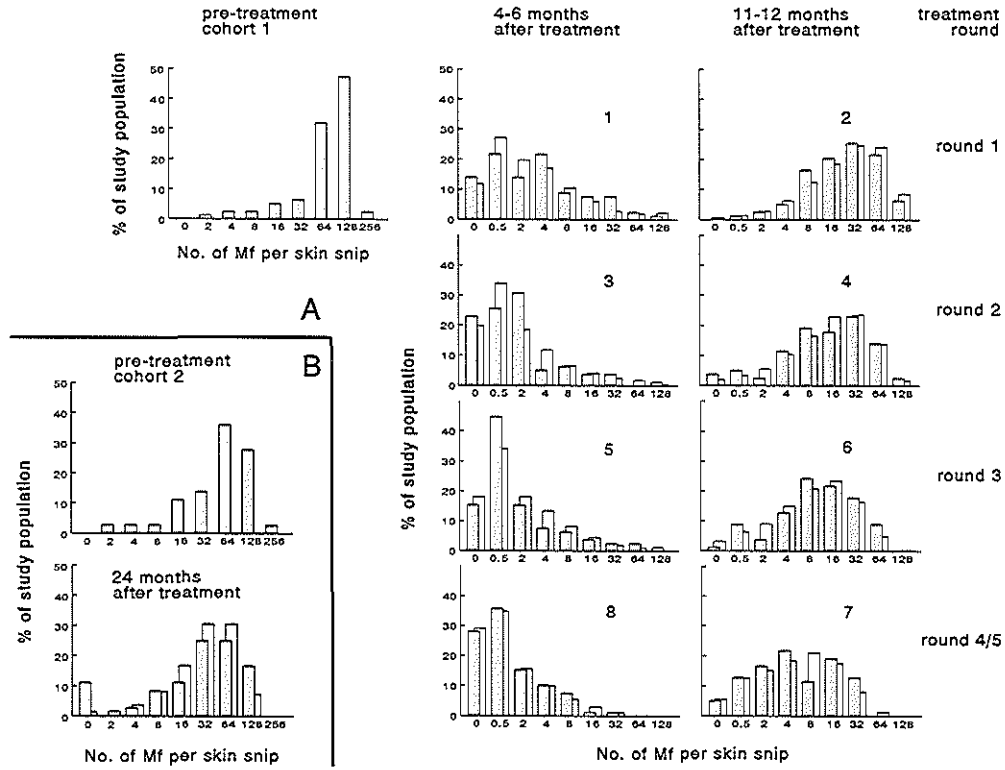

Figure 15 Frequency distributions of microfilarial (Mf) counts for the pre- and post-treatment surveys. (A) Cohort 1, 78 patients treated 5 times and examined 8 times. (B) Cohort 2, 36 patients treated once and examined 24 months later. Shaded bars = observations; open bars = predictions based on hypothesis H_2 (using parameter estimates of Table 7); x axes = lower boundaries of skin snip count classes; nos. in graphs = survey order.

mectin, fits poorly (P = .0013) and must be rejected. By contrast, a good fit was obtained when an irreversible productivity reduction for all worms was considered (H_2:P = .68). This productivity reduction was ~35% per treatment (95% CI, 26%-40%). Assuming another mechanism for the irreversible effect of treatment (H'_2) did not lead to significantly different conclusions. Total fecundity loss was ~28% per treatment, while the other parameter estimates were about the same for H_2 and H'_2. A model that combines both types of irreversible effect (not shown) did not produce a significantly better fit to the data. In such a model, the combined loss of Mf production in a patient was ~32% per treatment (95% CI, 22% - 40%).

Table 7 **Parameter estimates and goodness-of-fit for the different hypotheses about the effect of ivermectin on the microfilaria (Mf) production of adult parasites.**

	Hypothesis[a]		
Parameter	H_1	H_2	H'_2
Productivity reduction	-[b]	35% (26%-40%)[c]	-
Total fecundity loss	-	-	28% (22%-35%)
Recovery period (months)	19.0	10.4 (7-16)	10.7
Effect-variability (coefficient of variation)	0.87	0.54 (0.4-0.7)	0.52
Mf lifespan (months)	14	9 (4-12)	10
Goodness-of-fit ($P[\chi^2]$)	.0013 [39]	.68 [11.9]	.42 [15.5]

[a] See legend of Figure 14 for a description of the hypotheses.
[b] -, this parameter is not considered and thus has the value 0.
[c] Nos. in parentheses are 95% confidence intervals.

The irreversibly reduced level of Mf production was preceded by a recovery period of ~10 months during which the production rate accelerated (see the non-linear trends in Fig. 14; s = 1.5, Appendix). Both the recovery period and the Mf lifespan are inversely related to the speed of the Mf repopulation of the skin after treatment. Therefore, apparently to compensate for the lack of irreversible effect, under the first hypothesis both parameters were estimated at significantly higher values.

The effect of treatment varies considerably between treatments. The value of 0.54 estimated for effect variability (H_2) means that one-fourth of treatments resulted in a

recovery period of <6 months and a productivity reduction of <20%. By contrast, for another one-fourth these numbers were >14 months and >47%, respectively. Half of treatments had an intermediate efficacy.

Model results, assuming irreversible effects, were compared with the observations (Fig. 15, open bars). There were no systematic differences between prediction and observations for cohort 1 (Fig. 15a). The lowest and highest Mf count categories of the follow-up survey of cohort 2 were underestimated (Fig. 15b), suggesting more treatment variability in this cohort. For cohort 1, model predictions under both hypotheses are shown in Fig. 16. Here, predictions and observations are represented as the geometric mean Mf count. Only the pre-treatment and follow-up surveys at 11-12 months are shown (i.e., just before another treatment). Under both hypotheses, the geometric mean Mf counts decline sharply after the first treatment and more gradually thereafter. However, the slope of the line connecting the follow-up surveys is much steeper if irreversible changes are considered (H_2). Under H_1, the Mf counts after repeated treatment decline only because the transmission dynamics of the infection are disturbed by the combination of treatment and vector control. This decline is too slow to fit the observations.

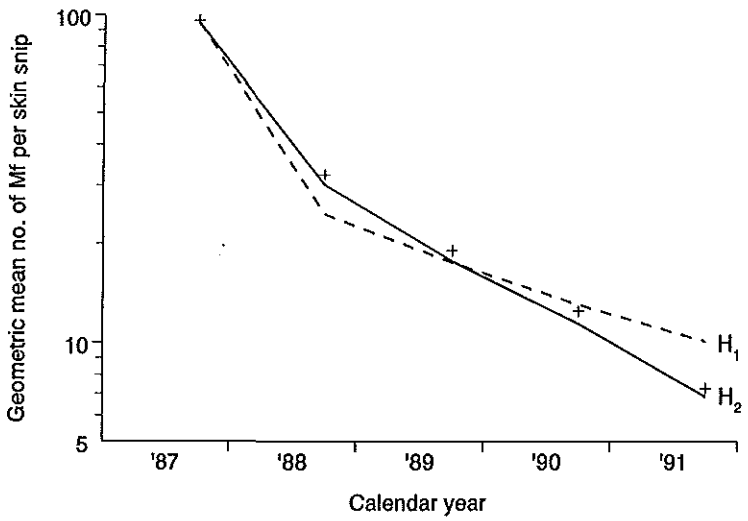

Figure 16 Observed (+) and predicted geometric mean microfilaria (Mf) counts (log scale) for pre-treatment and 11-12 follow-up surveys of cohort 1. Solid line = prediction based on hypothesis H_2 (using parameter estimates of Table 7); dashed line = prediction based on hypothesis H_1.

Discussion

Our analysis of the results of five consecutive annual treatments provides strong evidence that apart from killing Mf, ivermectin reduces the viability of adult female parasites. The trend in Mf counts was explained by the hypothesis that after each treatment, Mf production gradually increases over 10 months (transient effect) and then reaches a plateau that remains 32% lower than before treatment (irreversible effect; combining H_2 and H'_2).

The transient effect agrees with the results from earlier studies, which showed that in most parasites the normal release of Mf was interrupted after treatment, but 10 to 12 months later, Mf production had largely been restored (Schulz-Key *et al.*, 1985; Duke *et al.*, 1991a; Albiez *et al.*, 1988a). Although none of these studies revealed excess mortality of worms from a single treatment, after 1 year a considerable fraction (40%, see Duke *et al.*, 1991a) was not (yet) releasing Mf, which explains the considerable delay in repopulation of the skin by Mf (Awadzi *et al.*, 1985, 1986; Larivière *et al.*, 1985; Taylor *et al.*, 1986; Diallo *et al.*, 1986). In some studies, even 2 years after treatment, Mf density was markedly reduced (Greene *et al.*, 1987; Schulz-Key *et al.*, 1992), although most persons had become Mf-positive again. Indeed, in cohort 2 (treated only once), the mean Mf density after 2 years was still less than half the pre-treatment level, suggesting a lasting effect.

On the other hand, as Fig. 16 makes clear, one must be careful in drawing conclusions from decreasing Mf trends. Also, without irreversible drug effects, the model predicts a decrease (albeit insufficient) in Mf count at the follow-up surveys at 11-12 months. This decrease is exclusively due to the reduced transmission of the parasite as a consequence of ivermectin treatment and (partial) vector control (Alley *et al.*, 1994). This effect on the transmission was taken into account under the assumption that the parasite larvae in flies originate from inhabitants of Asubende and will again be transmitted to them. Such an assumption would not be valid in areas with migration of flies, but Asubende is an isolated focus with a local transmission (Remme *et al.*, 1989b).

So far, irreversible effects of ivermectin have been observed only after multiple treatments at intervals of $\leq$6 months. In patients who received 4-12 doses at intervals of 2 weeks to 6 months, more dead or moribund female parasites are found than in controls who receive no or only 1 treatment (Duke *et al.*, 1990b, 1991a,b, 1992; Chavasse *et al.*, 1992). Excess worm mortality of 25%-33% is observed after 8-11 doses at 3-month intervals (Duke *et al.*, 1992). Though these are significant percentages, they are about equal to the irreversible effect we found for each round of treatment. This suggests that killing of worms is not the most important compo-

nent of the irreversible effect: 25% excess mortality after 8 treatments implies (only) ~3.5% excess mortality per treatment. Furthermore, 6 months after the last dose (the longest follow-up in most studies), most female worms had not yet resumed normal embryogenesis and viability was markedly reduced. Recent investigations suggest that recovery to full productivity after this short follow-up period is unlikely or will at least take >2 years (Kläger *et al.*, 1993).

The available data on Mf counts do not allow us to draw inferences on the biologic mechanisms responsible for the irreversible treatment effect. The data are equally well fit by two quite different mechanisms: an average productivity reduction of 35% for all worms in a patient or the total loss of fecundity by an average of 28% of the worms. The difference between these estimates is caused by the different impact of the two mechanisms on the Mf counts in persons with low worm loads. If each treatment eliminates a certain fraction of productive worms, then in such persons frequently no productive worm is left (especially after repeated treatment) and, as a consequence, the skin snip is negative (no Mf). In the simulated population this leads to more skin snip-negative persons than with an equal percentage of productivity reduction. This explains the (slightly) lower estimate for fecundity loss.

Other mechanisms also could cause both transient and irreversible changes. For example, some studies demonstrate a significant reduction of the number of male worms (Duke *et al.*, 1990b, 1992). Although these lower counts may be the result of the ability of male worms to leave nodules (Schulz-Key and Karam, 1986), it may at least temporarily lead to reduced mating chances and a lower Mf output of female worms. Hence, we cannot exclude that part of the effect estimated for female worms should be attributed to males. It is important to stress that the results of our analysis are based on data collected during annual treatment using a dose of 130-200 μg/kg. Changes in treatment frequency or dose may lead to other effects per treatment.

In all model calculations, we have assumed that variability in treatment effect is exclusively between-treatment variability. Two extensions which have been tested explicitly are effect-variability between the worms in one patient and between-patient variation of treatment effect (some patients systematically respond well, others poorly). Neither extension affects our conclusion or produced a better fit. The absence of between-patient variability justifies the use of the χ^2 statistic for calculating the goodness-of-fit (P) and determining CIs, the χ^2 assuming independence between successive observations on the same persons.

Our conclusions have important implications for the public health impact of strategies based on annual ivermectin treatment, which is the currently recommended regimen. In earlier studies, we emphasized the potential of the drug for reduc-

ing the burden of blindness (Habbema *et al.*, 1992; Remme *et al.*, 1990b). However, lack of sufficient follow-up data at that time meant that an irreversible effect of treatment on adult worms could not be demonstrated. This was the main cause of doubt about the potential of ivermectin for transmission control and thus for our cautiousness in designating it as the successor of vector control.

Now, this point of view merits reconsideration. If each treatment leads to an irreversible reduction of fecundity by ~30%, after five treatments the loss will be >80% (not counting reinfections). These results should stimulate the assessment of the impact of higher doses on the viability of adult parasites. Extrapolating to a longer period of annual treatment is less straightforward; not everybody will be treated (a coverage of 65%-70% would be excellent in routine health care), and transmission will continue (albeit on a lower level), causing new infections. Preliminary computer simulation studies indicate that, although the impact of long-term ivermectin regimens is more pronounced than previously expected, the parasite is unlikely to be eradicated within a period of 15 years of annual treatment in an area where it is endemic.

Appendix

Here we describe the model that combines hypotheses H_2 and H'_2. By making the appropriate simplifications, the models for H_1, H_2 and H'_2 are obtained.

If m denotes the mean fraction total fecundity loss and v_{ij} is the effectiveness of treatment round i ($i = 1,..,5$) in person j, then fraction $v_{ij}m$ of the worms in person j will permanently cease Mf production immediately after treatment i. v_{ij} is a random variable, which for each treatment i and each person j is generated from a gamma probability distribution with mean = 1.0 and a variation coefficient equivalent to the effect variability. For female worms in person j that do not lose fecundity after treatment i (a fraction $1 - v_{ij}m$), the rate of Mf production r_{ijk} of each worm k at time t after treatment is described by the following:

$$r_{ijk}(t) = r^0_{ijk}(t) \times (1 - v_{ij}d) \times \left(\frac{t}{v_{ij}Tr}\right)^s \qquad \text{for } t < v_{ij}Tr.$$

$$= r^0_{ijk}(t) \times (1 - v_{ij}d) \qquad \text{for } t \geq v_{ij}Tr.$$

In this expression, r^0_{ijk} is the rate of Mf production of worm k without treatment. This basic Mf production depends on the age and the mating history of the worm. Parameter d is the mean irreversible productivity reduction, Tr is the mean duration of the recovery period, and s is the shape of the recovery. If $s > 1$, then the

increase in the Mf production is initially slow and accelerates by the end of the recovery period. If $s = 1$, then this increase is linear.

In case the random variable v_{ij} would take such high values that $v_{ij}m$ or $v_{ij}d$ (or both) is >1, the products are truncated to 1. However, given the estimates of the effect variability (~ 0.5; Table 7), these situations are highly unlikely.

In case of repeated treatment ($i > 1$), the model does not allow that an ineffective treatment (which implies a short recovery period) accelerates the recovery of a previous (effective) treatment. In case of total treatment failure (3% of treatments), $v_{ij} = 0$ and no Mf are killed. It is assumed that Mf will in principle be detectable in the skin immediately after their release from the worm. No provision is made for a delay due to dispersal in the body and penetration of skin tissues. Mf are assumed to have a fixed lifespan (Tm). In this simple concept, if the Mf production rate of the worms in a person stabilizes at time t, then the Mf density in the skin stabilizes at time $t + Tm$.

Chapter V

Control of infection and prevention of recrudescence in the OCP

V.1 The risk and dynamics of onchocerciasis recrudescence after cessation of vector control

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Introduction

The objective of the Onchocerciasis Control Programme in West Africa (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 (WHO, 1987a). The strategy has been to interrupt transmission by vector control through larviciding and this has been very successful. After 8-10 years of control operations, onchocerciasis was no longer a public health problem in more than 90% of the original OCP area (WHO, 1987b), and after 12-14 years the prevalence of infection had fallen to very low levels or zero in most of this area (De Sole *et al.*, 1990a; Remme *et al.*, 1990a). Because of the major decline in the parasite reservoir and the high costs of the aerial larviciding, it was important to determine how many years of successful vector control were needed before the operations could be discontinued, and the vector allowed to return, without running an unacceptable risk of onchocerciasis recrudescence thereafter.

The risk of recrudescence depends on the interaction between many factors. This made it necessary to use an epidemiological model to study the required duration of vector control. The computer simulation model ONCHOSIM (Plaisier *et al.*, 1990), which has been developed especially to analyze epidemiological trends and to evaluate prospectively alternative control strategies, simulates the transmission of onchocerciasis and the effects of vector control and chemotherapy (Habbema *et al.*, 1990; Remme *et al.*, 1990b). Using this model, we have investigated the risk and dynamics of recrudescence after different periods of vector control in an onchocerciasis focus. Reported is the impact of the major confounding model parameters on recrudescence and on the recommendations about the required duration of vector control.

Materials and methods

Simulation of recrudescence

The ONCHOSIM model uses the technique of microsimulation; this involves the simultaneous simulation of life-histories of individual persons and of individual

female and male parasites in the human host (Plaisier *et al.*, 1990). Collectively, the simulated persons constitute the population of a hypothetical endemic focus. One of the most important outputs of the simulation is the microfilarial (Mf) load in skin-snips for each member of the population. In order to facilitate detailed comparison with observed data, the results of the simulation are presented in the same statistical format as used in the epidemiological evaluation of vector control in the OCP.

Fig. 17 illustrates the results obtained with ONCHOSIM for the simulation of a period of vector control and recrudescence thereafter. Soon after the start of control, the Community Microfilarial Load (CMFL), i.e., the geometric mean number of Mf per skin-snip (Mf/s) in adults (Remme *et al.*, 1986), starts to decrease, followed by the Mf prevalence. When vector control is interrupted after 11 years, new inoculated worms become productive after a delay of several years, and the trends reverse; the Mf prevalence starts rising first, followed by the CMFL much later.

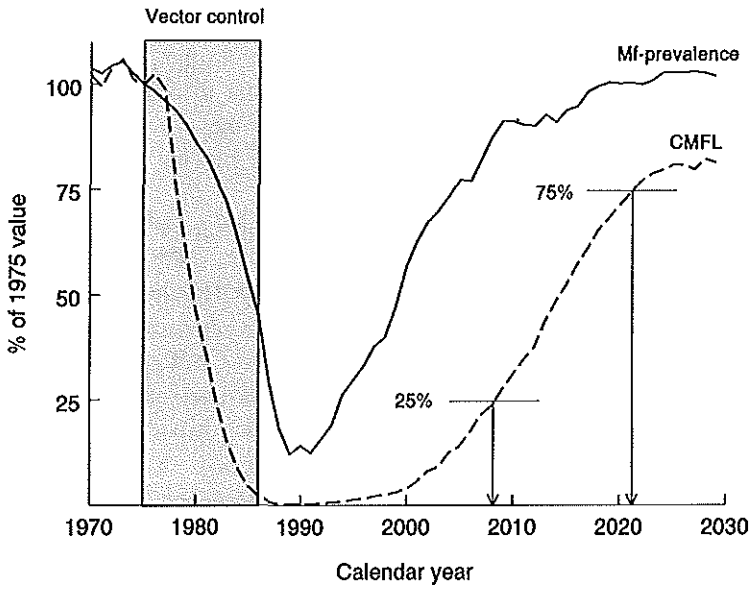

Figure 17 **Simulation of the recrudescence of onchocerciasis after 11 years of full-scale vector control (1975-86). The trends in microfilarial (Mf) prevalence and Community Microfilarial Load (CMFL) are shown as percentages of the values at the start of vector control. Indicated are the years when the CMFL reaches 25% and 75% of the pre-control value.**

Confounding model parameters

The transmission and control of onchocerciasis are governed by many parameters, most of which also influence the risk and dynamics of recrudescence. The following parameters are very important in this respect: the pre- and post-control level of exposure to the bites of *Simulium* spp. and the exposure variation in a community; the lifespan of the *Onchocerca volvulus* worm and possible variations in this; and the infection level of biting flies as a function of the human skin Mf density. Estimates for these important confounding parameters are discussed below. They are based on epidemiological data collected by the OCP, especially the frequency distributions of skin-snip counts obtained at various intervals since the start of control, and on experimental results.

Exposure level (relative biting rate) and exposure heterogeneity

After a given period of vector control, communities with a high pre-control endemicity level, and hence a high biting rate per person, have a higher risk of recrudescence than communities in less endemic areas. Analysis of the risk and dynamics of recrudescence for different endemic situations is, however, difficult because the real average biting rate per person in a village is not known. Reported values of the Annual Biting Rate (ABR) apply to passive collection of flies close to the breeding sites (Walsh *et al.*, 1978). Although the ABRs are valuable for assessing the potential endemicity of an area and for monitoring the effects of vector control, the actual ABR experienced by village members may be quite different. In the OCP area it has therefore not been possible to establish a direct relation between the average skin-snip count of a village and the pre-control ABR.

We have therefore defined a scale parameter (the relative biting rate, *rbr*) to assess the biting rate relative to the skin-snip counts. A value of $rbr=1.0$ corresponds to a biting rate in a village where the individuals are equally exposed and the mean Mf/s is 100.

The risk of recrudescence is also influenced by the heterogeneity of exposure among members of a community. When the heterogeneity is high, infection will be concentrated in a few extremely highly exposed individuals, who will act as frequently bitten, highly infective sources of transmission. Exposure heterogeneity is quantified by the variation coefficient of the biting rate.

Estimates for the *rbr* and exposure variation coefficients for a village are based on goodness-of-fit between observed and simulated skin-snip distributions. The estimates are not unique; using the estimation procedure reported by Plaisier *et al.* (1991a), a good fit (with $\chi^2_{0.05}$ as the critical point) can be obtained for a range of values of *rbr* and the coefficient of variation. Here, we analyze the recrudescence for two different quantifications of *rbr* and the variation coefficient in each of the

villages of Tiercoura and Folonzo, Burkina Faso. The standard quantification for both villages are shown in Table 8 as models 1 and 3, respectively. Models 2 and 4 represent quantifications that are among the most unfavourable from the point of view of recrudescence risk, but are nevertheless still compatible with the observed data for the two villages. Table 9 shows the observed pre-control CMFL and the pre-control Mf/s distribution in the villages. Also, the simulated Mf/s distributions for models 1-4 are shown. It should be noted that, although in Tiercoura the observed CMFL (a geometric mean) is 71 Mf/s, a large number of persons has a skin-snip count of >128 Mf/s; this is reflected in a relative biting rate of 1.10 in the standard quantification for Tiercoura.

Table 8 Model quantifications used for the determination of the risk and dynamics of recrudescence in the villages of Tiercoura and Folonzo, Burkina Faso.

Model number and designation	Relative biting rate	95th percentile lifespan (years)	L1-uptake curve
1 (standard Tiercoura)	1.10 (0.36)[a]	13.7	I
2 (high-risk Tiercoura)	1.16 (0.52)	13.7	I
3 (standard Folonzo)	0.61 (0.52)	13.7	I
4 (high-risk Folonzo)	0.67 (0.68)	13.7	I
5 (low-risk lifespan)	1.10 (0.36)	12.8	I
6 (high-risk lifespan)	1.10 (0.36)	14.8	I
7 (high-risk L1-uptake)	1.10 (0.36)	13.7	II

[a] Figures in parentheses are the coefficients of variation.

Parasite lifespan

The estimation of the parasite's reproductive lifespan has been reported in detail by Plaisier *et al.* (1991a). In the West African savanna, *O.volvulus* is estimated to live 9-11 years on average, while the variability is such that 95% of the parasites die before the age of 13-14 years. Especially the extreme longevity, as measured by the 95th percentile of the lifespan distribution, is important for recrudescence. For a mean lifespan of 10 years, the best fit for the 95th percentile is 13.7 years, and this value is used here as a standard quantification. The 95% confidence interval is estimated to be 12.8-14.8 years, and the risk and dynamics of recrudescence are analyzed for the boundaries of this interval (models 5 and 6, respectively, in Table 8).

Table 9 **Characteristics of the reference villages of Tiercoura and Folonzo (for comparison, the simulated skin-snip count distributions of models 1-4 are shown).**

Village	River basin	1975 census population[a]	Initial CMFL (Mf/s)[b]	% of adults with an initial skin-snip count (Mf/s) of:[b]					
				0	≥0.5	≥2	≥8	≥32	≥128
Tiercoura	Leraba	160 (66)	71	3.0	0	3.0	6.1	57.6	30.3
				Model 1					
				0	0.2	0.9	4.3	59.0	35.6
				Model 2					
				0.7	0.7	1.3	9.1	49.8	38.4
Folonzo	Comoé	285 (123)	30	2.4	2.4	7.3	27.7	56.9	3.3
				Model 3					
				2.5	1.4	5.3	29.3	58.5	3.0
				Model 4					
				3.5	1.8	5.5	27.3	53.6	8.2

[a] The first figure shown is the total population, while the figure in parentheses is the number of adults.
[b] Mf/s = microfilariae per skin-snip.

Skin microfilarial density, microfilarial uptake, and larval load of blackflies

The relationship between skin microfilarial density and the microfilarial uptake by biting flies is an important factor in the transmission of onchocerciasis. A number of studies have reported that the uptake increases with Mf density, but that saturation occurs at high densities (Duke, 1962). Infection levels of blackflies from the West African savanna suggest that, probably also because of the excess mortality of flies with very high larval loads, this saturation level is about 1.2 larvae per biting fly, and 2-3 larvae per infective fly, since, in general, the proportion of flies that engorge microfilariae does not exceed 50% (OCP, 1989), and most first-stage (L1) larvae survive to the infective stage (Philippon, 1977). However, if the parasite reservoir has been reduced by a long period of vector control, then in view of recrudescence, the capability of flies to engorge Mf at low skin densities rather than the saturation level, is important. This capability determines the degree of danger of the residual parasite reservoir for renewed transmission. Recently, in the OCP area, a series of experiments has been conducted to determine the relationship between fly infection and skin Mf density (OCP, 1989). Volunteers with a known skin-snip count were exposed to blackflies, and the Mf load in the flies was then determined. Especially important are Mf that avoid encapsulation by the fly's peritrophic membrane and which can be considered to be the potentially infective larvae.

For the model, the relationship between the Mf density in human skin and the resulting number of L1 larvae in biting flies needs to be quantified (resulting in the L1-uptake curve). Based on the experimental results, and using the procedure outlined in the appendix, a maximum likelihood estimate (MLE) was obtained for this relationship. The MLE determined for the saturation level of the larval load was 1.8 L1 larvae per fly (3.6 per infective fly). However, since the flies were dissected shortly after the bloodmeal, excess mortality as a result of high larval loads could not be taken account of. Therefore, for the standard relationship in the simulations we set the saturation level at 1.2 L1 larvae per fly. Imposition of this restriction upon the relationship gives an MLE shown as curve I in Fig. 18. In the analysis, we tested also the impact of a relationship with the same initial slope as curve I, but with a saturation level of 0.8 L1 larvae per fly (1.6 larvae per infective fly, shown as curve II in Fig. 18; see also Table 8, model 7).

Assessment of the risk and dynamics of recrudescence

The analysis reports the risks and dynamics of recrudescence for the model quantifications shown in Table 8. For each of these models the recrudescence is analyzed for several periods of vector control, ranging from 9 to 15 years. To determine the risk for a given model and a given duration of control, we carried out 50 simulations. Because of the stochastic microsimulation approach, the outcomes for these

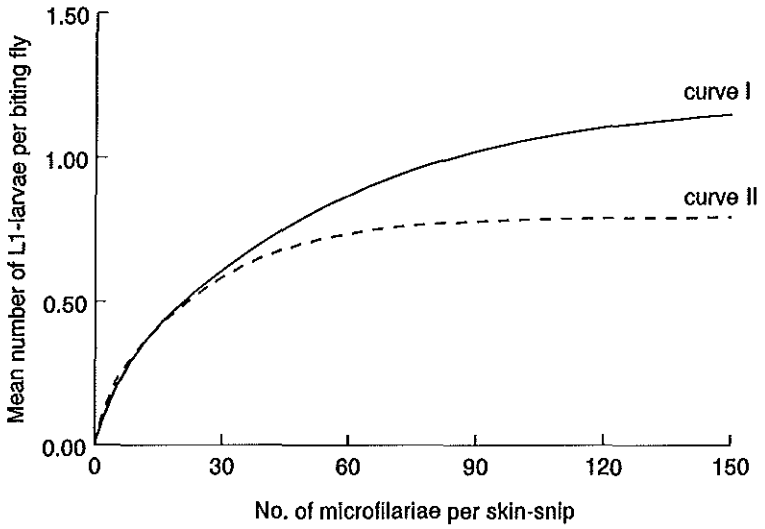

Figure 18 The two curves used in the study for the relationship between skin microfilarial density (skin-snip count) and the resulting number of L1 larvae in biting flies (L1-uptake).

50 simulations are different, reflecting the chance character of the underlying processes. If 50 years after cessation of control the simulated CMFL is still lower than 10 Mf/s, the given simulation is termed a 'non-recrudescence' case. The risk of recrudescence was taken to be the fraction of the 50 simulations that lead to recrudescence. Logistic regression was used to smooth the risk as a function of the duration of control and to estimate the required duration of control needed to arrive at risk values of 50%, 5%, and 1% (see Fig. 19).

The dynamics of recrudescence is characterized by the time to reach a given level of the CMFL after stopping control measures. Especially the time needed to establish a CMFL of 10 Mf/s is considered, since at this load onchocercal blindness starts to become an important public health problem in a stable endemic situation (Remme *et al.*, 1989a). This period of time is denoted the 'recrudescence time'. For comparison, we also examined the times needed to produce CMFLs that correspond to 25% and 75%, respectively, of the pre-control value.

Basic assumptions and starting points

The following underlying assumptions were made for all the simulations:

- the force of infection during the years preceding control is stable;

- the larviciding-based vector control effectively interrupts transmission;
- there is no migration of infected persons into the area; and
- there is no invasion by infected flies and only a slight invasion by uninfected flies.

Because of this invasion, the flies can repopulate the breeding sites, and the pre-control biting rate will be reached in a few months after the end of larviciding (Davies *et al.*, 1981; Remme *et al.*, 1989b). In the simulations, the pre-control village consisted of about 200 individuals and the annual rate of population increase was about 2.5%.

Results

Biting rate and exposure heterogeneity

Fig. 19 shows the probability of recrudescence for different durations of vector control for models 1-4, which differ in the values of biting rate and exposure heterogeneity, and which represent the standard and high risk models for Tiercoura and Folonzo (see Table 8). From Fig. 19 it can be inferred that the specific circumstances in a village markedly influence the recrudescence risk. Although both villages are hyperendemic, the duration of vector control required to reduce the risk to acceptable levels in Folonzo is shorter than that in Tiercoura. If for both villages the model is used that gives the best fit with the observed skin-snip data (standard Tiercoura and standard Folonzo), the risk of recrudescence in Tiercoura is 1% if vector control is continued for about 13.5 years. In Folonzo vector control needs to be carried out 11.5 years (i.e., 2 years less) to achieve the same risk of recrudescence.

In Folonzo, to arrive at a risk of 1%, the high risk model predicts a vector control period of 13 years, i.e., 1.5 years more than the standard model. Similarly, in Tiercoura the high-risk model predicts 14 years, i.e., only 0.5 year longer than the standard model. The most plausible explanation for the different behaviour of the two high-risk models is that in a holoendemic village such as Tiercoura, the risk of recrudescence is mainly determined by the lifespan of *O.volvulus*, so that increasing the fly biting rate only causes a minimal increase in the risk. In Folonzo, however, because of the lower pre- and post-control infection loads of the human hosts, the risk of recrudescence is also determined by the mating chances and subsequent production of Mf by the few remaining parasites. Here, a slight increase in biting rate (which causes the over-all worm load to increase) and exposure heterogeneity (which favours clustering of the worms, and hence increases the mating chances) has more impact on the risk of recrudescence.

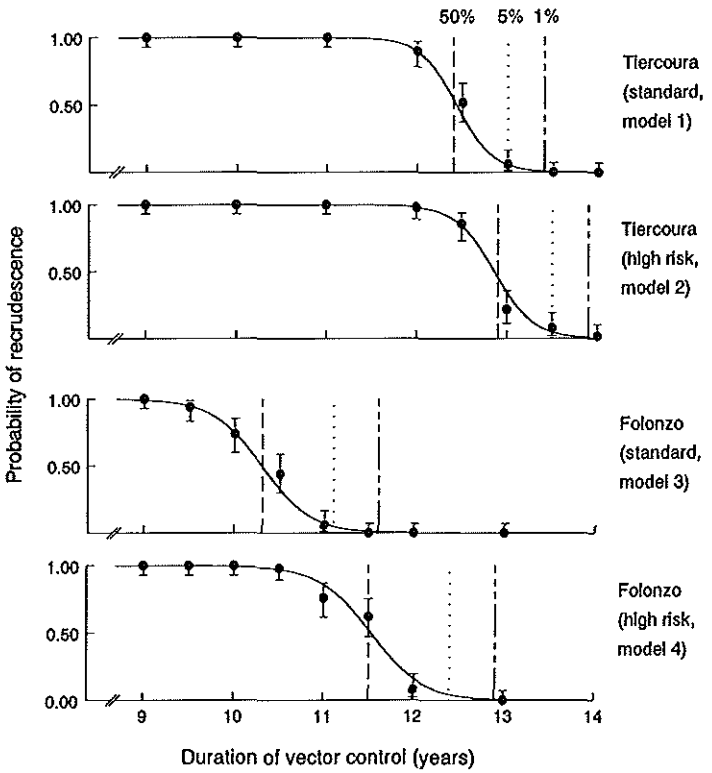

Figure 19 **Probability of recrudescence as a function of the duration of vector control determined using four different model quantifications. Bars show the 95% confidence intervals. The vertical dashed lines indicate the vector control period after which the risk of recrudescence is reduced to 50%, 5%, and 1%.**

Fig. 20 shows the recrudescence time, i.e., the period after cessation of vector control for the CMFL to reach 10 Mf/s. With all four models, the recrudescence time increases with the duration of vector control. Extending the duration of control therefore not only reduces the risk of recrudescence, but also reduces the rate at which the epidemiological indices increase. Furthermore, Fig. 20 indicates that for a given period of control the recrudescence time becomes shorter as the biting rate and exposure heterogeneity increase. Also the difference between the recrudescence times for the standard and high-risk models for Folonzo is greater than that for these models in Tiercoura. In the high-risk Folonzo model the clustering of worms result-

ing in increased chances of mating and production of Mf had a greater impact than in the high-risk Tiercoura model.

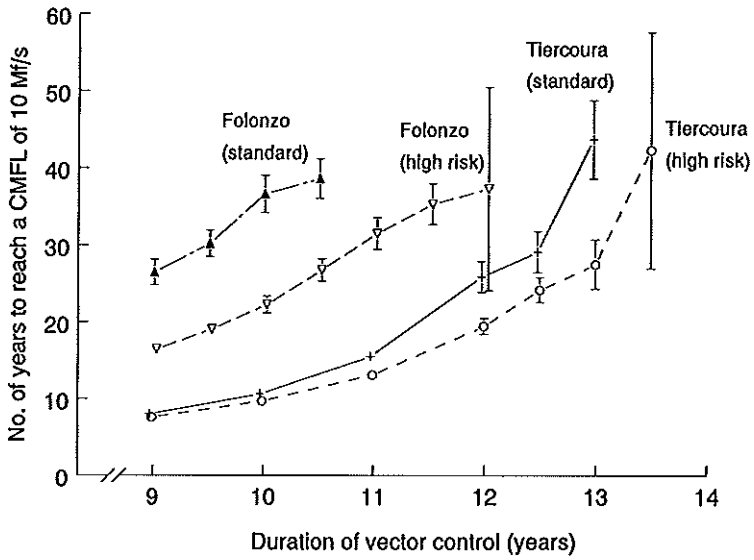

Figure 20 Average period (including 95% confidence intervals) after cessation of vector control before a Community Microfilarial Load (CMFL) of 10 Mf/s is reached, as a function of the duration of vector control in Tiercoura and Folonzo (models 1-4, Table 8). Results are shown only when at least 3 simulations showed recrudescence.

With the standard model for Folonzo (model 3), 9 years of vector control, although not sufficient to prevent recrudescence, guarantee that for more than 25 years after the end of control activities the CMFL will still be below a dangerous level. For Tiercoura this recrudescence time is less than 10 years. For longer periods of control, the differences in recrudescence times between the various models remain virtually unchanged, notwithstanding the decreased recrudescence risks.

The times after control which elapse until 25% and 75% of the pre-control CMFLs are reached are shown in Fig. 21 for the standard models for Tiercoura and Folonzo. The clear differences between the two models demonstrate that not only the absolute recrudescence rate, but also the rate relative to the pre-control situation, is higher for villages with a higher endemicity. Since for both villages the plots for the 25% and 75% levels have the same slope, it can be concluded that if recrudescence exceeds 25% of the pre-control CMFL (which for Folonzo is still less than 10

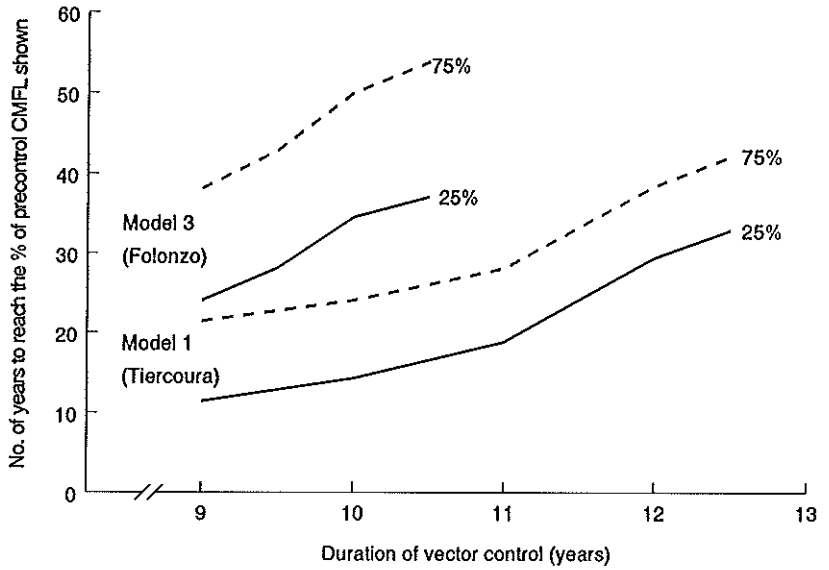

Figure 21 Average period after cessation of vector control before a Community Microfilarial Load (CMFL) of 25% or 75% of the pre-control value is reached, as a function of the duration of vector control for the standard models in Tiercoura and Folonzo (models 1 and 3, respectively, Table 8). Results are shown only when at least 3 simulations showed recrudescence.

Mf/s) the rate of progression no longer depends on the duration of vector control.

O.volvulus *lifespan*

The effect of different values for the lifespan of *O.volvulus* on the results is shown in Table 10. As might be expected, the period of vector control needed to reduce the risk of recrudescence to acceptable levels increases with the value of the 95th percentile of the lifespan probability distribution. Using the most unfavourable assumption for the 95th percentile (5% of the worms reach an age of $\geq$14.8 years), we estimate that in a village such as Tiercoura vector control operations have to be continued for 14 years and 14.5 years, respectively, to reduce the recrudescence risk to 5% and 1%..

Also, the recrudescence time is a function of the *O.volvulus* life expectancy. After 12 years of control, the time to reach a CMFL of 10 Mf/s increases from 16 to 34 years when the 95th percentile of the lifespan decreases from 14.8 years to 12.8 years.

Table 10 Duration of vector control to reduce the risk of recrudescence to 50%, 5%, and 1%, and the recrudescence time after 12 years of vector control, for three different assumptions about the 95th percentile of the lifespan distribution of the adult worm, and two L1-uptake curves.

	Model number	Duration of vector control (years) at a risk of recrudescence of:			Recrudescence time (years)
		50%	5%	1%	
95th percentile lifespan (years)					
12.8	5	12.2	12.5	12.7	34.0 (28.7-39.3)[a]
13.7	1	12.4	13.0	13.4	25.9 (23.8-27.9)
14.8	6	13.3	14.0	14.5	16.2 (15.7-16.8)
L1-uptake curve					
I	1	12.4	13.0	13.4	25.9 (23.8-27.9)
II	7	12.8	13.4	13.8	20.8 (19.4-22.2)

[a] Figures in parentheses are 95% confidence intervals.

L1-uptake

Table 10 also shows the impact of two different assumptions about the L1-uptake of *Simulium* spp. as a function of the skin Mf density. For the curve with a low saturation level at high skin densities (curve II, Fig. 18), the risk of recrudescence is greater than that with the standard curve (curve I): about 6 months of additional vector control are required to produce recrudescence risks comparable with those obtained with the standard Tiercoura model. To reduce the risk to about 1%, approximately 14 years of vector control are required with the L1-uptake curve II. The high-risk characteristic of curve II arises because, to maintain a given pre-control endemicity level, the low saturation level must be balanced by higher values for other transmission parameters (e.g., the probability that infective larvae transmitted by biting flies become a mature parasite). After vector control, before saturation has occurred, these higher values increase the recrudescence risk.

If vector control is stopped after 12 years (risk of recrudescence about 100%), approximately 20 years are required to arrive at a CMFL of 10 Mf/s; this is 5 years less than with the standard uptake curve I.

Discussion

The decision to stop vector control after many years of interruption of onchocerciasis transmission in the well-protected central OCP area is a difficult one to make. Premature interruption of vector control, when the residual parasite reservoir is still too large, may jeopardize all the achievements obtained so far and result in the recrudescence of onchocerciasis as a public health problem. On the other hand, aerial larviciding operations are very costly and any unnecessary continuation of them would prevent the use of funds where they are urgently needed, e.g., in the extension areas of the OCP where vector control has only recently been started.

A further complication is that there are no precedents which can serve as guidelines. The decision-making process, therefore, has to rely exclusively on the optimal use of epidemiological information and on current understanding of the dynamics of onchocerciasis transmission, infection, and about the disease itself. Epidemiological modelling has been helpful in this respect. The ONCHOSIM computer simulation model has been used to carry out an integral assessment of the relevant information and to provide objective predictions of the risk and dynamics of recrudescence after different periods of vector control.

Table 11 summarizes the recrudescence risks for the different models tested. The data indicate that in areas with the highest potential risk (such as Tiercoura) 14 years of vector control are required to reduce the risk of recrudescence to $<1\%$ (estimated using the most plausible quantifications of the confounding parameters). Predictions for other quantifications for the confounding parameters, which are also compatible with the epidemiological data for the OCP, show that in the worst case after 14 years the risk of recrudescence is still greater than 1%, but less than 5%.

The simulations show that the risk of recrudescence is dependent on the local endemicity level and the associated relative vector biting rate. For the holoendemic village of Tiercoura the simulations indicate that the required duration of vector control is 14 years, while for the hyperendemic village of Folonzo they indicate 1.5-2 years less than this. The endemicity level of Folonzo (in terms of CMFL) was only half that in Tiercoura, where the pre-control CMFL of 70 Mf/s made it one of the most endemic onchocerciasis villages of the original OCP area. The dependency of recrudescence on the biting rate also has implications for the epidemiological surveillance system that will be set up during the post-larviciding period to detect as early as possible eventual recrudescence. The biting rate varies greatly between villages and it is essential that the surveillance will be carried out in villages where the vector biting rate per inhabitant is extremely high.

It has long been recognized that the required duration of blackfly control depends largely on the lifespan of *O.volvulus* (Roberts *et al.*, 1967; Remme *et al.*, 1986).

Table 11 Risk of recrudescence for different durations of vector control and for the various model quantifications.

Model number and designation	Risk of recrudescence at a duration of vector control (years) of:[a]					
	10	11	12	13	14	15
1 (standard Tiercoura)	+	+	+	±	-	-
2 (high-risk Tiercoura)	+	+	+	+	-	-
3 (standard Folonzo)	+	+	-	-	-	-
4 (high-risk Folonzo)	+	+	+	-	-	-
5 (low-risk lifespan)	+	+	+	-	-	-
6 (high-risk lifespan)	+	+	+	+	±	-
7 (high-risk L1-uptake)	+	+	+	+	-	-

[a] + = risk > 5%; ± = 1% < risk < 5%; - = risk < 1%.

Our findings confirm this and show that the remaining uncertainty about the upper limits of the lifespan distribution, which was estimated from longitudinal epidemiological skin-snip data from the OCP, has a significant effect on the predicted risk of recrudescence. Using the limits of a confidence interval for the age at which 95% of the worms have died, we calculated that the required duration of vector control was 12.7-14.5 years. In an earlier attempt to project the epidemiological trends after cessation of vector control, Dietz (Dietz, 1982) used a model in which he assumed an exponentially distributed lifespan for the worms with a mean of 8.3 years. From this assumption, which could not be verified against longitudinal data, it follows that 5% of the parasites lived for more than 25 years. Dietz's implausible assumption about the lifespan of *O.volvulus* therefore explains why he predicted recrudescence even after 20 years interruption of transmission.

Different quantifications of the relationship between L1-uptake and the skin Mf load of human hosts also affect the predicted risk and rate of recrudescence, although the effect was less than we expected. The L1-uptake curve with an early saturation point, and hence a high ratio between the initial slope and the saturation level (curve II), resulted in the greatest risk and the shortest recrudescence time. In view of the available experimental data, curves with a lower saturation point and a greater initial slope seem unprobable (see appendix). However, it should be noted that in our simulations the levelling off of the L1-uptake curves at higher Mf loads is the most important density-dependent regulating mechanism in the transmission of

onchocerciasis. Other regulation mechanisms may, however, exist (Dietz, 1988) and could increase the risk of recrudescence. It can, therefore, be argued that the realism of curve II would increase when the L1-uptake curve in the our model took other possible regulating mechanisms into account.

Our study has clarified several aspects of the dynamics of recrudescence. The recrudescence time, i.e., the time after cessation of control for the CMFL to reach 10 Mf/s, depends on the duration of the preceding period of vector control: the longer the period of control, the longer it takes for the prevalence and intensity of infection to climb again to significant levels. This recrudescence time increases exponentially as the period of vector control approaches 14 years, and in this respect the last few years of vector control are the most cost-effective. After 10 years of vector control, recrudescence is relatively slow. Even in instances of recrudescence after 12-13 years of vector control, it would take more than 20 years for the CMFL to reach levels of public health importance.

These predictions for recrudescence apply only to situations where no other intervention is undertaken after cessation of vector control. However, it is important to note that ivermectin, an effective and well-tolerated microfilaricide, has recently become available for the treatment of onchocerciasis, while research is continuing to develop a macrofilaricide (Brown *et al.*, 1990). Although some studies suggest that the potential of ivermectin to control transmission in an endemic area is limited (Remme *et al.*, 1989b, 1990b), it may play an important role in the control of onchocerciasis recrudescence.

Our conclusions depend on some basic assumptions, i.e., the existence of a stable endemic situation during the pre-control period, complete interruption of transmission during the vector control period, no reinvasion by infective flies, and no immigration of infected humans. There are, however, many situations where these assumptions do not hold. Variations in epidemiological trends during blackfly control have been attributed to major variations in transmission during pre-control years (Remme *et al.*, 1990a). Isolated foci have been identified where there has been a relapse in transmission (De Sole *et al.*, 1990a), while the western and eastern flanks of the OCP area were reinvaded by infective flies (Philippon *et al.*, 1990). Immigration of infected individuals has not yet been proven to lead to problems (De Sole, 1990), but more extensive field studies are currently being carried out, and computer simulation studies are planned to investigate the effects of immigration by infected persons and of reinvasion by infective flies.

There will be other situations where not all the assumptions made in the current analysis will hold true. However, these do not invalidate the above analysis, which is intended to provide general guidelines as a reference for operational decision-making on cessation of larviciding. For each situation the decision will have to be

based on a critical analysis of the relevant epidemiological and entomological information using classical statistical methods, epidemiological modelling, and a large amount of common sense.

Appendix

To describe the mean L1-uptake of 50 flies (y) as a function of the skin-snip count (x), we use the following relationship:

$$y=a(1-e^{-bx})(1+e^{-cx})$$

where $a(1-e^{-bx})$ describes a simple saturation curve with saturation level a and initial slope ab, and $(1+e^{-cx})$ permits adjustment of the initial slope. At a given skin load, x_i, the uptake follows a negative binomial distribution with mean, y_i, and parameter of aggregation, k. It is further assumed that k is independent of x.

Using a downhill simplex method (Press *et al.*, 1988), this model is fitted to the experimental data by maximizing the likelihood function (i.e., searching for the maximum likelihood estimate, MLE). The MLE gives values for a, b, c, and k of 1.82, 0.0096, 0.0677, and 8.0, respectively. Restricting the saturation level to 1.2 larvae per fly (2.4 per infective fly) in the above relationship, implies setting a = 1.2. The MLE for this restricted relationship gives values for b, c, and k of 0.0213, 0.0861, and 6.6, respectively.

For curve II the values for a, b, and c were fixed to 0.8, 0.044, and 0.1686, respectively. With this relationship the MLE gives a value for k of 4.4. A likelihood ratio test of curve II to curve I results in a P value of slightly more than 0.05, so that curve II falls within a 95% confidence region of curve I.

V.2 The required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in West Africa

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Bulletin of the World Health Organization 1997;75 (in press)

Introduction

When the Onchocerciasis Control Programme in West Africa (OCP) started its activities in 1975, the only reliable strategy for controlling river blindness was larviciding of the rivers where the vector *Simulium damnosum* breeds. This technique would enable the interruption of transmission of the *Onchocerca volvulus* until the parasite reservoir in the human host was reduced to insignificant levels that will not lead to recrudescence after withdrawal of control and the return of the flies. On the basis of model calculations it was estimated that 14 years of complete vector control would be sufficient to achieve this objective, provided there was no importation of new infections (through humans or flies) (Plaisier *et al.*, 1991b).

The registration of ivermectin for human use in 1987 was a breakthrough in the control of the disease. Treatment causes a drastic decline in microfilaria (Mf) densities and has a significant impact on the development of ocular pathology (Dadzie *et al.*, 1987, 1991; Abiose *et al.*, 1993). Furthermore, ivermectin has little side effects and is proven to be suitable for large scale application (De Sole *et al.*, 1989a, 1990b). The availability of ivermectin implied a reorientation of OCP and a review of its original plans. The anticipated primary role of the drug was the control of morbidity in the extension areas and in those parts of the original area where vector control was unsuccessful or where vector reinvasion was reported (WHO, 1991). It was, however, of operational importance to determine to what extent ivermectin mass treatment, either on its own or in combination with vector control, could contribute to control of transmission. Community trials suggested a noticeable impact of treatment on transmission (Remme *et al.*, 1989b; Cupp *et al.*, 1992; Guillet *et al.*, 1995), but the remaining level of transmission was too high to justify total substitution of vector control by mass chemotherapy. This was confirmed by tentative model predictions, showing that annual ivermectin treatment alone is not expected to eradicate the parasite from an endemic area within a period of 25 years (Remme *et al.*, 1990b; Habbema *et al.*, 1992).

The subject of the present paper is to determine the required duration of a strategy based on the combination of vector control and annual ivermectin treatment.

This strategy is currently applied in the extension areas of OCP. In these areas, vector control was instituted during the years 1988 to 1990, while routine ivermectin treatment started in 1990 (OCP, 1994a; Guillet *et al.*, 1995). An important question is whether and to what extent the addition of ivermectin to larviciding allows a relaxation of the original guideline of 14 years as the minimum duration of vector control for the prevention of recrudescence (Plaisier *et al.*, 1991b; Remme *et al.*, 1990a). A shortening of this duration would imply important savings in efforts and money. In addressing this question, we will utilize recent findings of the effects of ivermectin on the viability of adult worms (Plaisier *et al.*, 1995). Assessment of the potential effects of alternative strategies will be based on model predictions.

Materials and methods

In this study, the effectiveness of a strategy - a certain combination of vector control and annual ivermectin treatment - is summarized into the risk of recrudescence of infection after stopping control. Calculation of these risks is based on simulation of strategies with the stochastic microsimulation model ONCHOSIM and statistical analysis of simulation results. A complete description of the model and its validation has been reported elsewhere (Plaisier *et al.*, 1990, 1991a; Habbema *et al.*, 1996). In this paper, the most important assumptions for the present study will be given and the procedure for performing simulations and calculation of recrudescence risks will be explained.

Basic assumptions

Vector control operations are assumed to be 100% effective, i.e., to reduce the biting rate to zero. In agreement with observations, flies immediately recolonize their former breeding sites after cessation of larviciding (Remme *et al.*, 1989b). It is, therefore, assumed that the post-control biting rate is equal to the pre-control level. Based on the analysis of longitudinal data from a community trial of annual treatment in Asubende (Ghana) (Alley *et al.*, 1994; Plaisier *et al.*, 1995), the following assumptions are used with respect to the effect of an ivermectin treatment (given at a standard dose of approximately 150 μg / kg body weight): (1) all microfilariae are eliminated, (2) after a temporary loss of fecundity, the Mf production of female worms increases during 10 to 11 months and (3) reaches a new stable Mf production level which is 35% lower than before treatment (irreversible effect; confidence interval (CI) 25%-40%). Both the period needed to recover and the irreversible impact of the drug vary between treatments (var. coeff.=0.54). The irreversible effect of the drug has a multiplying outcome, i.e., after n treatments an

average female worm produces at only 100×0.65^n percent of the level before the first treatment (e.g., 12% after five treatments). We will also test the implications of a lower efficacy of the drug by assuming 25% irreversible reduction of fecundity per treatment (the CI lower bound). It is further assumed that 3% of treatments totally fail as a result of malabsorption (diarrhea, vomiting) (De Sole *et al.*, 1989a). The coverage of treatment (% of census population in a village getting the drug) is one of the variables in the present analysis. In the model we take account of age- and sex-differences in the proportion treated (in part due to temporary exclusion criteria, see Alley *et al.*, 1994), individual variation in willingness to participate in a treatment round, and a proportion permanently excluded from treatment due to chronic illness. The explanation of how these individual-based factors and the mean population coverage are interrelated is provided in the appendix.

Based on these assumptions ONCHOSIM has been used to simulate control strategies in human populations of around 300 persons (a representative village-size). Two 'model-villages' are considered. One with an extremely high and the other with a medium high pre-control endemicity level. These endemicity levels are similar to that of Tiercoura and Folonzo (both in Burkina Faso) which we considered in previous work (Plaisier *et al.*, 1991a,b) and which had a pre-control CMFL (Community Microfilarial Load; i.e., the geometric mean Mf load in adults) of 70 and 30 Mf per skin-snip respectively. For these villages, which we will denote as HIGH and MED respectively, observations of pre-control fly biting rates are lacking. Using observations in the Pru-river, close to the highly endemic Asubende region in Ghana (Remme *et al.*, 1989b; Alley *et al.*, 1994) we estimate the Annual Biting Rate (ABR) in the absence of vector control within Tiercoura (HIGH) at 27,000 bites per person per year (for adult men) and within Folonzo (MED) at 16,000. The maximum exposure to fly-bites is reached at the age of 15 years. Women are, on average, 30% less exposed than men. The variation coefficient of bites / person within a specific age and sex group is estimated at 0.39 for Tiercoura and 0.54 for Folonzo. Since we have previously found that the variation in biting rate within a village is a risk factor for recrudescence (Plaisier *et al.*, 1991b), we will also simulate a 'Tiercoura-like' village with a higher exposure variation coefficient of 0.58.

Simulation of control strategies

A control strategy is described by the number of years vector control (v), the number of annual ivermectin treatments (i), and the treatment coverage (c) assuming that this will be constant for the whole period. A large number of combinations of v (range: 0 to 15 years), i (range: 0-25), and c (range: 45%-75%) are simulated. The result of each simulation run is summarized as 'recrudescence' (1) or 'no recrudes-

cence' (0). We conclude that 'recrudescence' occurs when 50 years after stopping control the CMFL is higher than 10 Mf/skin-snip (Mf/s) (Plaisier *et al.*, 1991b). Due to the stochastic nature of the model, the simulation of a certain control strategy may one time result in recrudescence and another time not. It is assumed that there is no importation of the infection from elsewhere (by humans or flies). Thus, recrudescence is exclusively the result of local transmission. An example of a control strategy followed by recrudescence is shown in Fig. 22a. An example successful control is given in Figure 22b. Both are based on a single simulation, and the possibility of other results from repeat simulations cannot be excluded.

Statistical analysis of simulation results

Because of the variability of simulation outcomes, statistical analysis is required to efficiently relate the recrudescence risk to the strategy characteristics. Since recrudescence is a binary outcome variable (yes=1, no=0) risk estimates were obtained by means of logistic regression (using SPSS). In their most complete form, the regression equations comprise the dependent variables v and $i \times c$, their square and cubic forms (e.g., v^2, $i \times c^3$), as well as linear, square, and cubic combinations (e.g., $v^3 \times i^2 \times c$). The strategy variables i and c always appear as a combination because $i = 0$ implies the absence of ivermectin treatment regardless the value of c, and vice versa. Estimation of regression coefficients is always started with only the linear and square terms. Insignificant terms are removed from the equations (likelihood-ratio test; $P > .1$), while possible significant cubic terms are added ($P < .05$). The Wald-criterion (Clayton and Hills, 1993) is used to select the terms eligible for inclusion or exclusion. Regression equations are derived for each of the model villages and for the alternative assumptions on drug efficacy. The resulting equations, each based on 3000 to 6000 simulations, enable a straightforward calculation of the risk of recrudescence for a given v, i, and c. The reverse (e.g., given i and c, how long must vector control be done to reduce the risk to .01) is done numerically. For several control strategies in different villages the goodness-of-fit of the equations has been tested by comparing the risks (indirectly) predicted by the regression model with those (directly) obtained by repeatedly simulating the same strategy (100x) and counting the number of occurrences of recrudescence. In all cases the indirect and direct estimate were in close agreement.

Results

Fig. 23 shows how the risk of recrudescence depends on combinations of annual ivermectin treatment and vector control in village HIGH. It is assumed that the

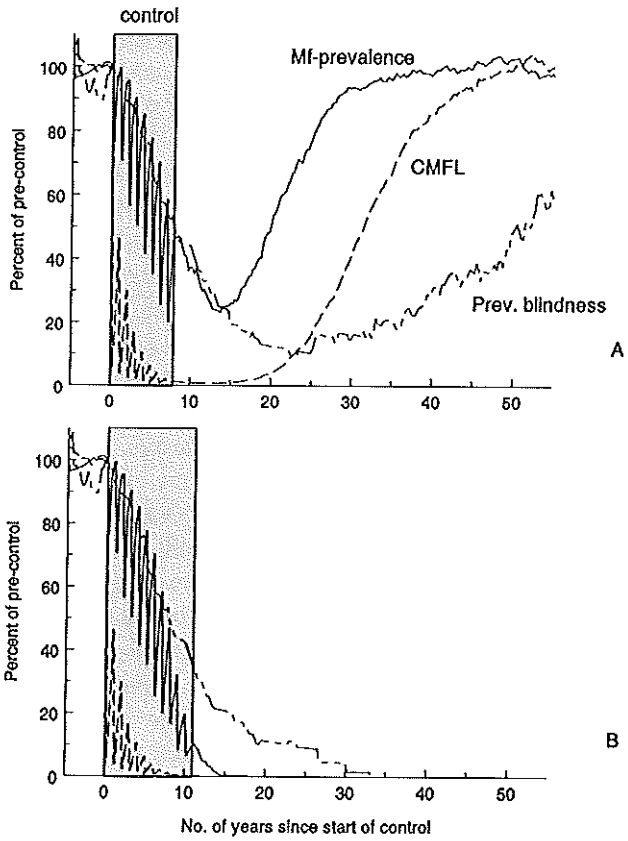

Figure 22 **Simulated trend in Mf-prevalence, CMFL, and blindness prevalence during combined vector control and annual ivermectin treatment (coverage 65%) in a highly endemic area (model village HIGH). Program output (simulated surveys) is given at three month intervals. The upper graph (A) shows recrudescence after 8 years of combined control. The lower graph (B) gives an example of 11 years of control which appeared to be sufficient to prevent recrudescence. In both simulations it is assumed that vector control and annual treatment start at the same time and have the same duration.**

average treatment coverage is 65% and that both control methods start in the same year. The lines in the figure represent 'iso-risk' lines, connecting those strategies that result in equal recrudescence risks (.01, .1, .5, and .99). Below or left of each line (less vector control or less annual treatments respectively) the risk is higher

than indicated, otherwise it is lower. In the absence of ivermectin treatment (points on the Y-axis) approximately 13 years of vector control are required to reduce the recrudescence risk to .01. If larviciding is combined with annual ivermectin treatment throughout the control period, then a total duration of 11 years of control is sufficient to achieve the same result (intersection point of solid and dashed line). The iso-risk lines shown in Fig. 23 diverge at increasing number of annual treatments. In the absence of treatment, the risk of recrudescence changes from ~0 to ~1 when the duration of vector control is shortened from 13 to 10.5 years. With 11 ivermectin treatments, the same change in risk occurs over a much wider range of vector control durations: from 11 to 6 years. If treatment is continued for 25 years then even in the absence of vector control the recrudescence risk is reduced to .5. However, still 6 years of larviciding are required to reduce the risk further to below .01. The explanation for the divergence of iso-risk lines is that, compared to vector control, community treatment involves more chance factors, both with respect to the participation of persons (coverage, compliance) and the effect of treatment. As the number of treatments increase, so does the role of these chance factors, leading to more variability in the calculation of recrudescence risks.

The effect of alternative treatment coverage-levels in HIGH is shown in Fig. 24a. In this figure only the .01 iso-risk lines are shown. Especially for longer periods of treatment the importance of the treatment coverage is considerable. High coverage levels allow more prominent reductions in the duration of vector control. For example, if annual treatment continues for 10 years at a coverage of 45%, then vector control can be shortened with only slightly more than one year as compared with the situation without treatment. With a coverage level of 75%, a saving of almost two years can be achieved. Fig. 24b demonstrates that the effectiveness of control strategies is highly dependent on the pre-control endemicity of the area. In the village MED a period of 20 years of annual treatment with a coverage of 65% is sufficient to eradicate the parasite without the help of vector control; in village HIGH a supplement of at least 8 years of vector control would be required to achieve the same. Shorter periods of treatment (10 - 15 years) allow considerably higher reductions in the duration of vector control in MED than in HIGH.

Simulation results for a village with a pre-control endemicity level like HIGH, but with more individual variation in fly biting rates (more exposure heterogeneity) indicate that in such heterogeneous villages the allowed reductions in larviciding ('savings') are only little less than for more homogeneous HIGH villages. For example, with 10 treatments (cov. = 65%) in the standard HIGH village the duration of vector control can be reduced by 22 months, while in a heterogeneous HIGH-village this is 19 months. However, in these latter villages we have found that at least 14 years of vector control would be required if this were the only

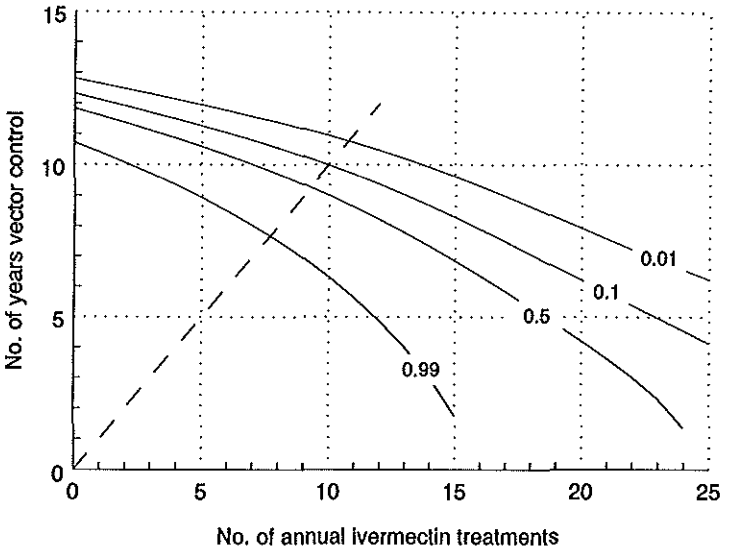

Figure 23 **Iso-risk lines, representing combinations of vector control and ivermectin treatment (coverage = 65%) resulting in equal recrudescence risks. Predictions are made for a village with an extremely high pre-control endemicity level (model village HIGH). It is assumed that both strategies start in the same year. The dashed line represents strategies in which treatment and larviciding also stop in the same year.**

means of control. In the standard HIGH this is 13 years.

Considerably lower savings are calculated under the assumption that an ivermectin treatment is less efficacious than estimated (25% reduction of female worm fecundity instead of 35%). Now 10 years of treatment at a coverage of 65% allow only 15 months reduction of vector control. Under all circumstances, there is more than a proportional increase in savings with the number of annual treatments. This is apparent from the concave shape of the lines in Figs. 23 and 24. For example, 10 treatments (cov. = 65%) in HIGH result in a saving of 22 months. By adding 5 treatments the saving increases with 16 months. Adding another 5 treatments increases the allowed reductions in vector control even with 20 months.

Table 12 gives savings under the assumption that vector control and annual ivermectin treatment are always done together (same starting moment, same duration; e.g., a 'duration' of 10.5 years of treatment means 11 treatments). From this table we could derive the general guideline that if annual treatment is given to on average 65% of the population then the total duration of control can be 1.5 to 2 years less

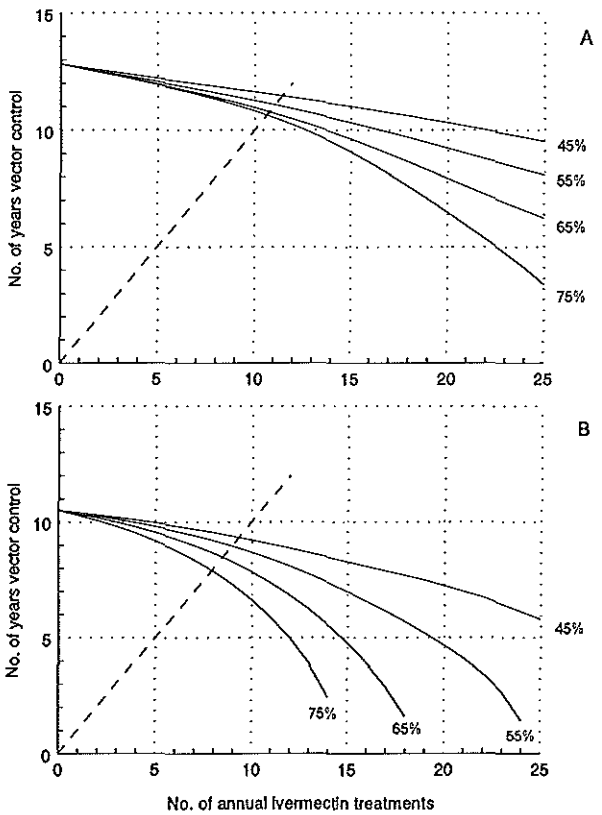

Figure 24 .01 iso-risk lines for combinations of annual treatment and vector control in the model villages HIGH (A) and MED (B), representing villages of extremely high and medium high pre-control endemicity. The different solid lines represent different levels of treatment coverage. The dashed line represents strategies in which treatment and larviciding stop in the same year.

than in the absence of treatment.

Discussion

The model predictions shown in this paper reflect the anticipated effects of the current practice of OCP in its extension areas. The primary aim of adding iver-

Table 12 **Number of months by which the duration of vector control can be shortened as a result of annual ivermectin treatment in several circumstances (villages), assuming that both control methods start and stop at the same moment. Savings are such that the risk of recrudescence after stopping control (larviciding and treatment) remains less than 1%.**

Village (endemicity level)	Vector control alone (years [months])[a]	Treatment coverage (%)			
		45	55	65	75
HIGH	12.8 [154]	16[b]	20	24	26
MED	10.5 [126]	14	18	24	31
HIGH[c]	13.5 [162]	15	20	23	25
HIGH[d]	12.8 [154]	13	16	18	20

[a] No. of years [months] of vector control required to reduce the recrudescence risk to below 1%

[b] Interpretation: if vector control and annual treatment are combined throughout the control period and the treatment coverage is 45%, then the total duration of control can be 16 months shorter than a strategy which relies on vector control alone (i.e. 138 instead of 154 months).

[c] Village HIGH with more exposure variability.

[d] Assuming a lower efficacy of ivermectin (25% irreversible reduction of female worm fecundity per treatment; standard = 35%).

mectin treatment to the usual larviciding activities was the prevention of morbidity during the early years of vector control, when the intensity of infection is still so high that new cases of blindness or severe ocular lesions cannot be excluded. Indeed, ivermectin has proven to be an efficacious drug for the treatment and prevention of ocular onchocerciasis (Dadzie *et al.*, 1991; Abiose *et al.*, 1993). However, as combined control continues, a question of major operational relevance is to what extent the reduction of the community Mf load as a consequence of repeated ivermectin treatment allows an earlier cessation of vector control. On the basis of statistical analysis of simulation results obtained with the ONCHOSIM model, we conclude that in a situation where vector control is accompanied by annual ivermectin treatment, the required duration of control can be reduced with at least one year (in case of low coverage of ~45%) up to two years (coverage ~65%) when compared to strategies which rely on vector control alone (see Table 12). Compared to the original guideline of 14 years of vector control (Plaisier *et al.*, 1991b), this implies that when at least 65% coverage can be assured and when there is no importation of infection from elsewhere, a duration of 12 years of

combined control would be sufficient to prevent recrudescence even in areas of very high endemicity like our model village HIGH.

The strength of the combination strategies is highly dependent on the treatment coverage. The attainable coverage depends on a variety of factors. An important determinant is, of course, the efforts of the control programme to include as many persons as possible. There are, however, unmanageable factors which relate to a person's ability or willingness to participate. The original guidelines for treatment are that pregnant women, women during the first week of lactation, and children below 5 should be excluded from treatment (De Sole *et al.*, 1989a). These exclusion criteria are taken into account by considering an age/sex-specific compliance profile (see appendix). Though this limits the effectiveness of one particular treatment round, in the framework of a long term treatment programme the impact will be moderate: children below 5 years harbour low numbers of worms, while pregnant or breast-feeding women may receive the drug in subsequent rounds (nine months pregnancy plus one week lactation falls within the interval of one year). More important will be persons who are permanently excluded because of chronic diseases (mainly related to the nervous system, e.g., epilepsy) or who have a limited ability or willingness to participate. In terms of the model, this latter group has a low 'compliance-index' (see appendix). Among those with a low compliance there will be persons with a considerable Mf load (even after a period of control), and they will have a relatively high contribution to transmission when vector control ceases. It is, therefore, advisable not only to attempt to reach a high coverage (65% - 75% seems to be attainable, even in situations of 'community self treatment'; OCP, 1994b), but also to trace people who tend to miss treatments systematically.

All results of this study are based on the assumption that larviciding and ivermectin treatment start in the same year. However, in some parts of the extension areas large scale treatment started with a delay of two years. Therefore, for the model village HIGH we have calculated recrudescence risks for several time-lags. We have found that up to a time lag of 4 years - which is more than in any of the areas - no observable difference with a synchronous start could be found in the sense that .01 iso-risk lines are virtually on top of each other. However, a time lag may result in a longer total duration of control. Applied to the guideline of 12 years of combined control, a time lag of two years implies an increase of the total duration to 14 years.

Of course, the conclusions of our study are as sound as are the underlying assumptions. In a previous study (Plaisier *et al.*, 1991b) we showed how uncertainty about model parameters is reflected in the outcome of the recrudescence analysis. The guideline of 14 years as a minimal duration of vector control in an area without importation of infection (through infective flies or infected migrants) is largely

based on 'unfavourable' assumptions on the parasitic life span, the efficiency of the *Simulium* vector in transmitting the parasite at low skin Mf densities, and the heterogeneity of the exposure to fly bites. The present study is mainly concerned with potential savings in terms of reducing the vector control efforts by the addition of ivermectin treatment. Most of the uncertainty about the estimates of these savings is related to the efficacy of the drug. We have previously found that in a schedule of annual administration, each treatment causes an irreversible reduction of ~35% of the fecundity of female parasites (Plaisier *et al.*, 1995). However, the confidence interval for this estimate ranges from 25% to 40%. The impact of a lower efficacy of 25% has been explicitly tested. From Table 12 we learn that with this unfavourable assumption the savings are only 1.5 years when the treatment coverage is 65%. However, both this 1.5 years of saving and the 14 years of the original guideline are based on unfavourable assumptions on model parameters. When both are combined (14-1.5=12.5) we end up with an extremely pessimistic view of the potential of mixed strategies, and therefore there is no need to revise the guideline of 12 years of combined control.

The conclusions of our analysis are not only determined by assumptions on specific model-parameters, but also largely by assumptions on the effectiveness of vector control and the circumstances in the areas where control is carried out. We always assume that prior to control there is a stable endemic situation and that the pre- and post-larviciding fly biting rates are equal. It is imaginable that the observed pre-control endemicity (CMFL) is an underestimation of the potential endemicity, for example because of the Sahelian droughts of 1968-1974, preceding the start of OCP (McMillan, 1995). Furthermore, we assume that there is no transmission throughout the whole period of vector control and that there is no immigration of infected flies and infected persons. It is clear that in many places these strong conditions are not met. Reinvasion of (infected) flies has been reported frequently (Garms *et al.*, 1979; Philippon *et al.*, 1990). Though importation of the infection by human migration is not (yet) an important problem (most migratory movements are from areas where river blindness was not endemic to the river-valleys where the disease is eliminated; see McMillan, 1995), explorative computer-simulations have demonstrated that a few infected migrants settling in a village of limited size considerably raise the risk of recrudescence. It is clear from these considerations that the guidelines as presented in this paper may be applied only after critical review of the situation. A thorough study of the local circumstances and the history of control (especially control failures) should all be included in a rational decision making.

Appendix

Calculation of the individual treatment probability

The primary characteristic of a certain ivermectin mass treatment w is the coverage C_w (fraction of the population treated). However, a difficulty in calculating individual chances of participation is that there are several exclusion criteria for the drug. Moreover, compliance to treatment differs from person to person. Exclusion criteria can be either permanent (chronic illness) or transient (children below 5 and pregnant or breast-feeding women). We define the eligible population as the total population *minus* a fraction fc (= .05) which is permanently excluded from treatment (in the model from birth to death). The coverage among the eligible population is now given by:

$$C'_w = C_w / (1 - fc) \tag{1}$$

The transient contra-indications and other age- and sex-related factors are taken into account in the age- and sex-specific relative compliance $c_r(k,s)$ for each age-group k and sex s. Based on OCP data we use:

age-group (k)	0-4	5-9	10-14	15-19	20-29	30-49	50+
$c_r(k, \delta\delta)$	0.00	0.75	0.80	0.80	0.70	0.75	0.80
$c_r(k, ♀♀)$	0.00	0.75	0.70	0.74	0.65	0.70	0.75

Note that in $c_r(k,s)$ only the *ratio* between the values for the different groups is relevant.

Now, the coverage $c(k,s,w)$ in each of the age- and sex-groups at treatment round w is calculated as:

$$c(k,s,w) = \frac{c_r(k,s) \times N(w)}{\sum_{s=1}^{2} \sum_{k=1}^{n_a} c_r(k,s) \times N(k,s,w)} \times C'_w \tag{2}$$

with: $N(k,s,w)$ Number of individuals eligible to treatment in age-group k and with sex s at treatment round w.

$N(w)$ Total number of eligible individuals at treatment round w.

Finally, the probability to participate in treatment round w for an eligible person i of age-group k and sex s is given by:

$$Ptr_{i,w} = co_i^{\frac{1-c(k,s,w)}{c(k,s,w)}} \tag{3}$$

with: co_i Personal compliance index. This is considered as a lifelong property and is generated from a uniform distribution on [0,1].

Note that for all k and s the average value of $Ptr_{i,w}$ equals $c(k,s,w)$.

Chapter VI

General Discussion

This thesis describes the use of a model for onchocerciasis, or river blindness. The objectives were: (1) to develop, quantify and validate a model for the transmission and control of onchocerciasis in West African savanna and (2) to use this model for aiding decision making in OCP.

Though the second objective, the practical application of the model, is the most important justification of putting money and efforts in a research project like this, the first objective outweighs the second both in terms of time investments and number of pages in this thesis (Chapters II, III, and IV). Specific questions within the first objective included the estimation of the reproductive lifespan of *Onchocerca volvulus* and the estimation of the effects of ivermectin when given at a standard dose. Answering these specific questions was essential for the fruitful application of the model in evaluating and prediction.

Within the second objective (aiding decision making), specific questions were (a) how long should vector control be continued to reduce the risk of recrudescence to very low levels after ceasing operations, and (b) can this required duration of control be shortened in areas where larviciding is accompanied by annual ivermectin treatment. The guidelines derived from addressing these questions (see Chapter V) have had important implications for decision making within OCP (Samba, 1994; Aron and Silverman, 1994; Goodman, 1995; Molyneux, 1995; WHO, 1995).

In this discussion, first the contributions computer simulations made to decision making in OCP will be summarized (section VI.1). These contributions not only comprise the results presented in Chapter V. ONCHOSIM has frequently been used to aid the understanding of epidemiological trends in areas or villages with a specific history of control or control failures (Habbema *et al.*, 1992). Furthermore, once the guidelines for the prevention of recrudescence were adopted, it was recognized that surveillance strategies need to developed for the early detection and control of recrudescence if it unfortunately occurs. Model simulations have helped in designing such strategies, and in section VI.1 the, as yet unpublished, results will be introduced.

It is obvious that the quality of model predictions highly depends on the quality of the model and the suitability of the modelling technique. Section VI.2 considers the

extent to which the applied methodology - stochastic microsimulation - was crucial for the use of the model as an operational tool. Advantages and disadvantages of this technique will be discussed. A very important issue is the validity of the model with regard to both the overall structure and the parameter quantification. In section VI.3 first the different steps in the development of a model and of ONCHOSIM in particular will be presented. Next it will be discussed to what extent this development resulted in a valid model. Though in Chapter III the quantification of the reproductive lifespan and related parameters are already discussed extensively, all model assumptions made thus far and the way alternative assumptions would most likely affect the predictions of the model will be reviewed. Finally, the current and future use of the model, both within and outside the OCP context, will be presented.

VI.1 Contribution to policy making in the OCP

The required duration of vector control

By focusing on the trend in the intensity of infection within a cohort of adults, Remme *et al.* (1986) demonstrated that 8 years after the start of OCP, vector control had a significant impact on the parasite population. The force-of-infection model used in this study predicted a gradual reduction in the intensity of infection to insignificant values after 11-12 years of control. By explicitly considering variability in the lifespan of *O.volvulus* predictions with a host-parasite model (a micro-simulation model developed by the Dept. of Public Health, which can be considered as a precursor of ONCHOSIM; see I.4) suggested that both the prevalence and intensity of infection will have declined to very low values (Remme *et al.*, 1990a) between 13 an 15 years of larviciding. Both model based analyses and predictions were highly relevant for the question of how long the costly control operations should be continued to prevent recrudescence of infection and disease after allowing blackflies to re-colonize their original breeding sites. Though by 1989-1990 the efficacy of Ivermectin was being studied in many clinical and community trials, there was too much uncertainty about its impact on transmission to rely on its possible use in controlling recrudescence. Hence, stopping vector control untimely could, in the long term, lead to complete re-establishment of an endemic situation.

Section V.1 extensively discusses the required duration of a control strategy based on larviciding alone, knowing that blackflies will immediately return to their former breeding sites and start to bite the human population as before control. Through a large number of simulations with ONCHOSIM, covering both the uncertainty in important model parameters (like the reproductive lifespan of the parasite and the efficiency of blackflies to transmit infective stages at low human Mf levels) and the variability in endemic levels in the OCP communities, it was shown that 14 years of vector control should be sufficient. This 14 years has been adopted as a general guideline and has led to cessation of larviciding in those parts of OCP's original area - i.e., the area where control started in 1975 - where epidemiological trends were consistent with the predictions and where no problems with vector control (e.g., as a result of large-scale reinvasion) were reported in the past (EAC, 1991). Noticing that, in view of the rather strong underlying assumptions (100% effective vector control), these guidelines may not be applied uncritically, in the OCP there is a continuous awareness of the potential occurrence of recrudescence in the central area.

Combining vector control with ivermectin treatment

Since 1990 (between 0 to 2 years after the start of larviciding) in the southern and western extension of OCP Ivermectin is administered annually in most of the endemic communities with a CMFL[14] of above 10 Mf/s (EAC, 1991), mainly to achieve a better control of morbidity. This addition of ivermectin distribution is a fortunate reason for reconsidering the guideline on the duration of vector control discussed above. Section V.2 addresses the question whether and to what extent this combination of ivermectin treatment and larviciding could be a reason to shorten the originally planned period of 14 years of control. This question became increasingly important since the results of the trial in Asubende suggested that Ivermectin is not a microfilaricide *sensu stricto* (section IV.1) and a model based analysis demonstrated a considerable irreversible effect on the reproductive potential of female parasites (section IV.2). On the basis of a multitude of simulations of these combination strategies in communities with a range of endemicity levels we conclude that, provided vector control had been and will continue to be highly effective and treatment coverage-levels of around 65% can be maintained, 12 years of control should be sufficient to prevent recrudescence even in the most afflicted communities. This finding gives support to the conclusion that the present strategy of OCP should be continued until the year 2002 (Molyneux, 1995). However, also this guideline can never be a panacea and should be accompanied by intensive surveillance. A complication in this respect is that by suppressing Mf loads, Ivermectin treatment troubles the evaluation of the effects of vector control (EAC, 1995). This is especially a problem when the exact treatment time is not known or when a treatment round is spread over a longer period of time.

Post-larviciding surveillance strategies

In the OCP central area larviciding was only ceased in a river basin when after 14 years (i) according to the entomological evaluation there had been no significant transmission during the control period, (ii) the epidemiological trends in all indicator villages in the river basin were consistent with the model predictions, and (iii) no children born since the start of control had become infected. It was, however, realized that in spite of this careful decision making, the threat of recrudescence remained. Hence, strategies had to be developed for the detection of recrudescence.

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[14] Community Microfilarial Load; i.e. the geometric mean no. of Mf / skin-snip in adults ($\geq$20 yrs.).

Such strategies should on the one hand be based on sound expectations of the dynamics of the infection during recrudescence, both in the human population (trends in intensity, prevalence, and incidence) and in the vector population (infectivity of flies). On the other hand they should be based on the anticipated possibilities to control the recrudescence either by restarting larviciding or by starting ivermectin treatment. Using model predictions of the infection dynamics, a short-term and a long-term strategy for the detection and control of (potential) recrudescence was agreed upon. The short-term strategy is based on entomological data: should infectivity of the (returned) vector exceed an unacceptable value, then larviciding should be restarted. The long-term strategy is based on epidemiological data: should the Mf counts in the population exceed a certain threshold, or should the incidence of new Mf positive cases be too high, then large-scale treatment with ivermectin should be started to prevent further progress.

Entomological surveillance

In order to validate whether the decision to stop had been correct, special entomological studies were undertaken of vector infectivity levels during the first two years after cessation of vector control. A difficulty in these entomological studies was to determine which vector infectivity levels were to be considered as insignificant and which levels reflected an unacceptable risk of transmission. This question was studied in a number of ONCHOSIM simulations of epidemiological situations with a medium to very low risk of recrudescence. These simulations indicated that, if the number of flies with L3 larvae in the head (F3h) was in the order or 0.9 to 1.3 per 1000 parous flies, the risk of recrudescence was negligible. However, in simulations where vector infectivity reached 1.4 to 2.2 F3h per 1000 parous flies, there were several cases of recrudescence. These results provided a basis for the following operational guidelines: if the observed infectivity levels are significantly lower than 1 F3h per 1000 parous flies, the entomological evaluation confirms the correctness of the decision to stop vector control, and no further entomological evaluation would be required at the site in question. If vector infectivity is significantly higher than 2 F3h per 1000 parous flies, the risk of recrudescence is unacceptable and vector control should be started again. In the range between 1 and 2 F3h per 1000 parous flies it is difficult to take a decision on the basis of the model predictions alone, and additional information on the specific local situation should be taken into account. These guidelines were used to develop sequential decision charts for the entomological evaluation (Remme *et al.*, 1995).

Epidemiological surveillance

A definite indication of the occurrence of recrudescence can only be obtained from

epidemiological data (Mf counts in skin snips). The timing of post-control epidemiological surveillance is a complicated issue and it is important to know: (i) when should such post-control data be collected and (ii) when do such data indicate 'recrudescence'. In section V.1 we showed that in general recrudescence is a relatively slow process. Therefore, to distinguish a 'real' recrudescence from either an occasional new infection or previously undetected old infections, one should preferably postpone epidemiological surveys until significant Mf levels are to be expected. On the other hand, model simulations have indicated that, if recrudescence has proceeded too far, it is very difficult to control it by means of mass treatment with ivermectin. Simulations also indicated considerable variation in the dynamics of recrudescence: sometimes infection prevalence increases rapidly, sometimes it remains on the same level for quite a long time. These considerations have led to the conclusion that post-larviciding surveillance should be based on a longitudinal approach and consist of a series of surveys at regular intervals. The first surveys (planned shortly after cessation of larviciding) will detect cases of fast recrudescence at a moment that they can still be controlled by ivermectin. Slowly progressing cases of recrudescence can be detected by later surveys. Given this approach, two crucial questions emerge: what is a suitable interval between surveys and what should be used as an indicator of recrudescence.

The way in which these questions are addressed is illustrated in Fig. 25. The basis of this example is 300 simulations of 12.5 years of vector control a highly endemic village (CMFL = 70 Mf/s) resulting in 110 cases[15] of recrudescence. Immediately after detection of recrudescence a campaign of 10 years of annual ivermectin treatment is started with a constant population coverage of 65%. The detection is based on a series of surveys at three years intervals, the first being done at the moment of cessation of larviciding. Fig. 25a shows what happens if an annual incidence of Mf positive skin-snips among adults ($\geq$ 20 yrs.) of 1.5% is used as an indicator of recrudescence. Already at the 2nd survey 40 cases are detected and after 15 years (6 surveys) only a few remain undetected. The finding that only after 30 years all cases are detected illustrates the variation in the dynamics of recrudescence. For none of the recrudescence cases detection comes too late to be controlled by ivermectin treatment (all closed circles are on the X-axis). Though this is certainly a safe strategy, it is probably not the most cost-effective one: in almost 40 situations ivermectin treatment is started without need. In these situations ('false alarms') the incidence exceeded 1.5% but no real recrudescence followed. The effect of increasing the threshold incidence from 1.5% to 2.5% is showed in Fig.

[15] 'Case' is here used for a village (or community, river basin) and not for an individual patient.

25b. Now the number of false alarms is negligible, but in one case the detection of recrudescence came too late to be controlled by ivermectin. This latter phenomenon becomes a considerable problem when the incidence-threshold is increased from 2.5% to 3.5% (Fig. 25c).

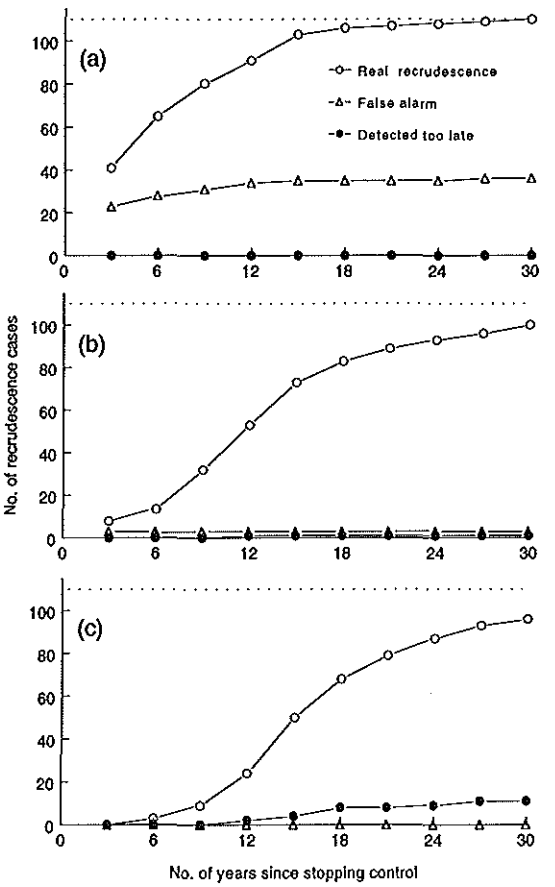

Figure 25 Detection of post-larviciding recrudescence with 3-yearly surveys. Threshold for annual incidence of Mf in skin-snips among adults: (a) 1.5%, (b) 2.5%, (c) 3.5%. See text for details.

From this example, it becomes clear that the design of post-control surveillance is based on the balance between too late detection and unnecessary control. Safe strategies comprise frequent surveys and the starting of ivermectin treatment at low values of the incidence (or prevalence) of infection. Such safe strategies run the risk

of many false alarms and unnecessary starting of a treatment strategy. By contrast, low-cost strategies comprise infrequent epidemiological surveys and high threshold values for indicators of potential recrudescence. As a consequence some cases of recrudescence may be missed or detected too late. Noticing that the possibility of recrudescence control relies on the strength of the treatment strategy that can be put into action, we have tried to find optimal strategies. As a criterion for an optimal strategy we concluded that there should be less than 1% cases of too late detection and a minimum number of instances where treatment is started unnecessarily. By comparing optimal strategies for a number of realistic ivermectin treatment strategies, the Expert Advisory Committee of the OCP recommended post-control surveys should be carried out at three years intervals and that a strategy of at least 10 years of annual treatment should be started if the annual incidence of Mf/s among adults exceeds 2% (EAC, 1991).

VI.2 Methodological issues

The construction of a model - variables, parameters, and their interrelation - and the exploration of the characteristics of this model - such as the prediction of trends during interventions - are two different things. The development and validity of the ONCHOSIM *model* will be dealt with in section VI.3. Here we will discuss the modelling methodology used for the implementation of ONCHOSIM. The features of this methodology - *microsimulation* - are extensively presented in section II.1 and in Habbema *et al.* (1996). Here we will give a justification for the choice of this technique and list a number of (potential) disadvantages.

Why microsimulation

Choosing a modelling methodology is based on a number of considerations. A decisive factor is often the modelling tradition of the research group. For example, a group with a reputation in the use of analytical modelling will most likely start with employing this technique. Other factors include the availability of (powerful) computers and the time and resources allocated to the modelling effort. However, by far the most important factor is (or should be) the objective of modelling. Generally, when models serve to study the behaviour of a (biological) system and to determine the sensitivity of certain parameters, a tractable analytical approach is to be preferred. There are a lot of good examples of the use of analytical models for investigating the dynamics of infectious diseases. An overview can be found in textbooks like Anderson and May (1991) and Scott and Smith (1994). When models are to be used for predicting the impact of a variety of interventions in specific endemic situations, it is mostly better to use simulation techniques. In this section we will list a number of considerations which supported the decision to construct a simulation model, or more precisely a *microsimulation* model, for analyzing the data of OCP and predicting the impact of control. We will also make clear that, after all, this was a good choice.

1. *Need for a detailed model*
In view of the envisaged use it was necessary to develop a model which reflects as good as possible the biologic, demographic, and epidemiologic situation in the onchocerciasis endemic areas covered by OCP. Noticing that the understanding of past trends and the prediction of future trends under the larviciding strategy was sharply determined by the life-history of the parasite (Remme *et al.*, 1986, 1990a), it was essential that the model was suitable to test a variety of assumptions on this life-history, including the mean and variation of the reproductive lifespan of *O.volvulus*, the age-dependent production of microfilariae, the variability in this Mf

production, and mating of parasites. For a realistic model - both in view of the quality of the outcomes and in view of the acceptance by users within OCP - it was further essential to include known facts like the excess-mortality among blind persons, the non-linear relation between human infection and vector infection, and variability in the exposure to fly-bites. Finally, to enable a detailed testing of the model, it should produce output with the same degree of detail as the results of epidemiological surveys, such as longitudinal output for cohorts of persons. Including all these details into one model makes it extremely difficult, if not impossible, to use analytical techniques for evaluating such a model.

2. *Flexibility*
It was further essential that, once a basic model was developed and tested, it was relatively easy to extend it on the basis of new evidence or in view of new questions. An example of such an extension is the more detailed modelling of the life-history of microfilariae (considering monthly age-classes). This extension was essential to enable a more realistic simulation of the short-term effect of ivermectin. In general, analytical approaches are too rigid to allow for major extensions and require a complete revision of the model.

3. *Estimation of recrudescence risks*
By simulating discrete events (birth and death, acquisition and death of parasites) in a finite human population (e.g., a village of 300 persons) the stochastic nature both of infection and disease and of the impact of control is mimicked. This property of microsimulation has been utilized to calculate the risk of recrudescence of infection after stopping of control (Chapter V). When after a certain period of effective vector control the flies are allowed to return then it is a combination of stochastic elements which will determine whether recrudescence will occur or not: the remaining worm load in the population, the distribution of the worms over the population and the associated mating chances, the distribution of individual biting rates, etc. Especially when the average worm load approaches critical values below which no endemic situation can be maintained, a certain simulated control period will sometimes be followed by recrudescence and sometimes not. Thus, by repeatedly simulating a range of larviciding periods it is possible to relate the recrudescence risk to the duration of control. This type of risk-calculations are much more complicated when relying on analytical methods. With analytical modelling it is at most possible to identify a breakpoint (worm load) below which no recrudescence will occur and associate this breakpoint with a certain duration of control: below this breakpoint it will *never* occur, above the breakpoint it will *always* occur.

4. *Prediction of effects of complicated strategies*:
A final reason in favour of microsimulation was the need to evaluate a large number of control strategies in a variety of endemic circumstances. These strategies include vector control, chemotherapy (ivermectin), and a combination of both. The endemic circumstances include different levels of infection and different levels of variation in individual biting rates. Furthermore, it was essential that the effects of specific complications could be studied such as the reinvasion of flies during the control period and the immigration of infected individuals during control or during the period after cessation of control. Microsimulation is particularly suited to mimic such highly specific events.

It is the *combination* of these considerations which was decisive. For example, for the isolated question of how long the parasite persists when transmission is interrupted, we explored a simplified model which gave similar results (Van Oortmarssen, unpubl.).

Disadvantages of microsimulation

The most important drawbacks of microsimulation models are the 'black-box' nature of such models, the stochastic variability in model output and the related difficulties involved in fitting the model to data, and the efforts required for the development and management of the complex computer programs.

1. *Black box*
In the absence of restrictions imposed by calculus and algebra, (micro)simulation models like ONCHOSIM easily grow to levels of complexity which hamper understanding of the behaviour of the model, i.e., the relation between model output and the assumptions made in the model. Understanding the behaviour of the model requires extensive and time consuming sensitivity analyses. In analytical approaches the relation between model calculations and model parameters is mostly much more transparent.

2. *Variable outcome*
Though very useful for the calculation of recrudescence risks, the stochastic nature of the microsimulation model is also a disadvantage. A single simulation of a control strategy in a population of around 200-300 individuals represents only one possible outcome of that strategy and can never be used for far reaching conclusions about the effectiveness of that strategy. Variability in model outcomes is especially

cumbersome in attempts to fit the model to data in order to estimate parameters (see Chapter III and section IV.2). The goodness-of-fit of a set of assumptions can only be accurately determined by repeating simulations many times or, similarly, simulating large numbers of individuals. The consequence of simulating small populations is a considerable probability of either not rejecting a poorly fitting set of assumptions or rejecting good fitting assumptions. Related to this, standard optimization routines developed for deterministic models, such as the Downhill-Simplex method employed in section IV.2, cannot be applied without making adaptations for dealing with stochastic results. Finally, simulation of limited populations (discrete numbers) considerably hampers the use of maximum likelihood procedures for fitting the model. This is especially a problem in attempts to fit the model to data on repeated measurements, like the repeated skin snip examination of the treatment cohort in section IV.2. Other modelling approaches are better suited for this task. An illustrative example is the statistical model developed by De Vlas *et al.* (1992, 1993) for describing variations in repeated egg counts in *Schistosoma mansoni* infections. This model links a (negative binomial) probability distribution of worm numbers with a distribution describing the variability of egg counts in a person with a certain worm load. For given values of these distribution parameters, the probability that a person exhibits a certain series of egg counts in repeated observations can be calculated. With a maximum likelihood procedure the model parameters can then be estimated by fitting the model to observations of repeated egg counts. In microsimulation the number of simulated individuals is generally too small to generalize their combination of features to likelihoods. For example, the individuals in treatment cohort 1 of section IV.2 were examined 9 times during the ivermectin trial. Even if we represent their skin-snip count at each survey by a frequency distribution with only three categories (e.g., 0-3, 4-15 and $\geq$16 Mf/s), then the total number of possible series of skin-snip outcomes equals $3^9=19{,}683$. Arriving at an estimate of the likelihood to be in either of these states requires the simulation of a population of millions of individuals *for each parameter quantification tested.* This was the main reason for fitting the model to the marginal distributions: a total χ^2 was derived as the sum of χ^2s for the goodness-of-fit to the Mf count distribution of each of the surveys. This implies the assumption that successive observations are independent. Since observations were done on the same persons (cohort), this is - a-priori - not a tenable assumption. However, we have demonstrated that the explicit model assumption of dependency of observations (i.e., persons systematically respond good or poor to ivermectin) did not result in a significantly better fit. This is - a-posteriori - a justification of this approach.

3. *Complex computer programs*
A final disadvantage experienced with microsimulation is the complex computer programs that have to be developed and maintained. The total ONCHOSIM package, including the simulation-core and programs for processing output, consists of more than 20 highly interlinked modules (files with C-code) which together comprise around 10,000 lines of source code. Debugging of such a program is an arduous task and programming errors may sometimes remain undetected for quite some time.

In conclusion, microsimulation has proven to be a very powerful modelling technique, but before constructing a microsimulation model the following considerations should be made:

(i) to gain insight in the system under study (the transmission of an infectious disease in a population) it is recommendable to start with constructing a more tractable analytical model or deterministic simulation model. Once the limits of these techniques are reached, one could consider the additional benefits of a comprehensive microsimulation approach.

(ii) the construction of a stochastic model and its implementation in a microsimulation program is a time consuming enterprise which relies on the availability of a powerful computing equipment and programming skills. Though the availability of computers becomes a less important limitation in developed countries it can still be pressing elsewhere.

(iii) validation of a stochastic individual based model by fitting it to data is hampered by the random output produced by the model and the difficulty in using maximum likelihood procedures.

VI.3 State of the art of ONCHOSIM

Evolution of the model

In the development of a model, several evolutionary stages can be distinguished. A schematic overview of these stages is given in Fig. 26 (see also Habbema *et al.*, 1995). As the arrows in this flow diagram suggest, one can be in several stages at the same time and certain loops may be passed several times. For the development of ONCHOSIM there were clear objectives (*problem identification*): for a balanced decision making, predictions had to made of the long-term impact of current and future control strategies of the OCP. Thanks to two previous modelling enterprises (Remme *et al.*, 1986; 1990a), the second phase - *investigation of knowledge* - could be focused on those aspects that were related to transmission (which was lacking in these models), especially the relation between human infection and the mean uptake and development of larvae by the vector, and the impact of control by ivermectin treatment (Chapter IV). The *model design* was entirely tailored to the anticipated use as an epidemiological model for long term predictions. For that reason, short-cuts were made in the entomological part of the model. In the absence of vector control a fixed value is used for the biting rate in each calendar month. Hence we only consider seasonal variation and not, for example, year to year variation. Also the probability that an engorged L1-stage larva will be released as an infective L3-larva (the transmission parameter v, see section II.2) is constant. On the contrary, a detailed description of the life-history of the parasite in the human host was included to enable a realistic calculation of epidemiological trends during vector control and chemotherapy. By far the largest investments were made in the, highly interlinked, phases of *model quantification* (assigning values to parameters on the basis of available knowledge) and *model validation* (adapting parameter values in order to fit the model to observations); see Chapter III and section IV.2. Although in this respect many uncertainties remain (see below), the close agreement between predicted and observed trends in the OCP area stimulated extensive use of the model in *prediction and optimization* of future control; see Chapter V and section VI.1. Although no considerations were made about resource use, the results presented in these chapters can be considered as an attempt to optimize control: what is the minimal control effort to meet a certain goal (prevention or timely detection of recrudescence). By extensively discussing model predictions with OCP staff and by stressing the conditions under which predictions are valid or invalid, major contributions have been made to *decision making* (see above). Although depicted as a final phase, *transfer of the simulation program* has been a continuous process. In fact the first complete version of the computer program (shortly after model design) was immediately transferred to OCP headquarters in Ouagadougou and tested on

their equipment. Since then, numerous updates have been sent and experiences exchanged. Recently, triggered by many requests outside OCP, a user-friendly version of ONCHOSIM has been developed which can be used for research, teaching and training.

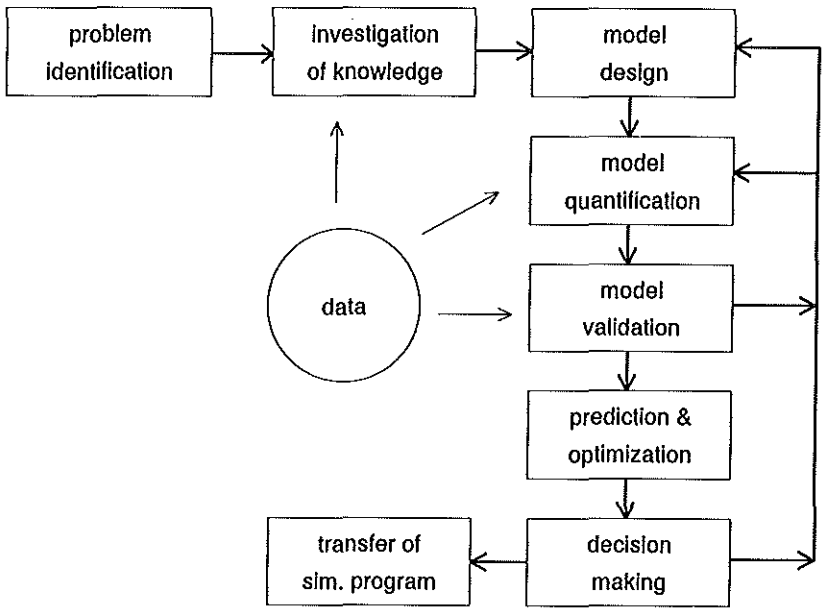

Figure 26 Stages in the development of a model (see Habbema *et al.*, 1995).

The most important lesson learned from the development of ONCHOSIM and its application within OCP is that models can only become effective tools if there is continuous feedback both from those who could benefit from model calculations (the decision makers) and from the experts in the epidemiology of the disease under study. In terms of the schedule of Fig. 26: wandering back to 'earlier stages' (e.g., from model validation to model design) is not only inescapable but, in fact, crucial. Flexibility and the willingness to revise initial ideas are essential ingredients for applied modelling. In section VI.2 we have shown that this was an important reason to choose microsimulation as modelling technique.

ONCHOSIM and current knowledge

The flow diagram of Fig. 26 reveals that predictive models should be data-driven. A valid model not only incorporates as much as possible field or laboratory evidence on certain processes, but should also be able to reproduce observed trends in the area to which the model applies. For ONCHOSIM this area is the West African savanna. Parameter estimates have been derived for the *O.volvulus* strain and *S.damnosum* species typical for this area. For other areas, such as the African rain forest or Cental and Southern America, the same model structure can be used, but parameter estimates will be different, and additional research is required to apply the model there (see WHO, 1995 for a discussion of geographical differences).

Here, we will briefly discuss the validity of the present structure and quantification of the model (see Ch. II) in the light of current knowledge. We will especially highlight those aspects that are known to be crucial for the model predictions presented in this thesis.

Reproductive lifespan

As reported in Ch. III the reproductive lifespan of *O.volvulus* has been estimated on the basis of trend in skin-snip counts in three representative villages in the core area of OCP. It has been argued that this estimate depends on a number of other parameters, such as the age-specific Mf production, mating of worms, and the lifespan of microfilariae. Together, these parameters constitute the *effective* duration of the infection. Confounding parameters for this effective duration and its variability are the between-person variation in exposure to fly-bites (resulting in variation in worm loads), the mean Mf production (in terms of the average contribution of a female worm to the Mf density in a skin-snip), the selected type of probability distribution for the lifespan (Weibull), the variability in the contribution to the Mf count between parasites (e.g., because of the variable distance of parasites to the skin-snip site, or because of genetic differences in fecundity), and the assumption on skin-snip sampling variability (Poisson distribution). Two of these parameters (mating and fecundity-variation) have only been included in the model because there is overwhelming evidence that they play a role in the production of Mf by *O.volvulus* (Schulz-Key and Karam, 1986; Karam *et al.*, 1987; Schulz-Key, 1990; Duke *et al.*, 1990a). All other parameters appeared essential to arrive at a good fit to the longitudinal series of Mf count distributions used in the analysis. We further found (see Chapter III) that, except for the age-trend in the fecundity, varying these parameters did not result in major changes in the estimate for the lifespan. Though this points to a reasonably robust estimate for this parameter, one possible problem could still be the tail of the probability distribution. It cannot be excluded that more parasites

survive to old ages than indicated by the Weibull model. These long survivors may be important risk factors for recrudescence after stopping vector control.

Worm load versus Mf production

A problem with a parasitic disease like onchocerciasis is that adult worms in the human host cannot be counted, at least not on a routine basis. Though nodulectomies shed some light on potential worm loads (see e.g., Duke, 1993), a certain Mf density can either be caused by a single or few highly productive worms, or by a large number of lowly productive worms. Though not the most sensitive variable in the model (it is the microfilariae which cause the trouble), especially *under*estimating the worm load (which is equivalent to *under*estimating the probability that an inoculated L3-larva succeeds in becoming an adult worm: the success-ratio, *sr*) may result in an underestimation of the risk and speed of recrudescence after withdrawal of vector control: the lower the worm load, the lower the mating chances, the lower the Mf production. Using the follow-up data in the same three villages as mentioned in Chapter III, we have attempted to arrive at a 95% confidence interval for both the success-ratio and the fecundity (represented by the parameter *cw*, see section II.2). Translated into a range of possible worm loads in a hyperendemic village, we found that this could range from 10 to 27 female worms per person *on average* (i.e., including persons with low or zero worm loads; unpubl. analysis). There is some evidence that this range is in accordance both with nodulectomy results and with calculations based on the *in vivo* release of Mf. These latter calculations resulted in an estimate of 16 female worms per patient (geometric mean; Schulz-Key, 1990). Nodulectomy of patients from Liberia and Burkina Faso (Albiez *et al.*, 1988b) revealed 20 to 40 female worms per person. Since, these observation only included nodule carriers (i.e., a biased sample), this range is an overestimation of the mean worm burden in the population. In an attempt to link the level of transmission of infective larvae to the human parasite load, Duke (1993) - using data from various sources - estimated that the ratio between the Annual Number of Potentially Productive Female Worms (APPF) and the Annual Transmission Potential (ATP; no. of L3-larvae transmitted per year) is around 0.002. Given the definition of this ratio (only *female* worms), the value should be compared with 0.5 x our *sr*. Since we estimate *sr* at 0.0015, this model parameter is a bit lower than the findings of Duke, but given the totally different routes followed to arrive at the estimates, they are in fact remarkably well in agreement.

Parasite density regulation

In the absence of any density regulating mechanism, parasite numbers will increase to infinity if one female worm is able to replace herself by more than one female

worm in a next generation (i.e., if the so called basic reproductive number R_0 exceeds unity; see Anderson and May, 1991). Density regulation of *O.volvulus* is observed to occur in the vector: at increasing numbers of engorged Mf, a decreasing proportion is developing to later larval stages (Basáñez *et al.*, 1995). On the basis of a xenodiagnostic experiment with persons from Asubende (Ghana), a good estimate could be made of the relationship between human Mf density (measured by the mean of 3-4 skin-snips) and the number of first stage larvae developing in engorged flies (Basáñez *et al.*, 1995; section V.1 - appendix). The saturated relationship resulting from this experiment is by far the most important density regulating mechanism in the ONCHOSIM model.

Another, much weaker, regulating mechanism is the excess-mortality of blind persons, i.e., the early death of persons with a high accumulation of infection. In the model we assume that, at the moment a person goes blind, his life-expectancy is reduced with 50% on average (range 0-100%, uniformly distributed). This percentage is in agreement with Prost & Prescott (1984) who estimate that, while the normal life-expectancy at the average age of the onset of blindness is approximately 23 years, for blind persons this is only about 9 years.

To our knowledge, there is no strong evidence for any other density regulating mechanism within the human host, such as density dependent production of Mf or resistance to super-infection of infected persons. In a recent review of immunological aspects of *O.volvulus* infection, Ottesen (1995) concludes that, while infection is accompanied by prominent antibody responses, the primary force driving the immune system is the need to prevent inflammatory reactions against the huge numbers of microfilariae dying in the skin or elsewhere. The simple observation that in hyperendemic areas prevalence rates among adults are close to 100% provides quite some evidence that neither immune-reactions against worms or Mf nor resistance to new infections play an important role in the regulation of parasite numbers. This lack of evidence, combined with the fact that the model could very well explain both the observed age related prevalence and density patterns as well as the frequency distributions of Mf counts, support the assumption that density regulation in the human host can be neglected.

Should this assumption turn out to be wrong, then two consequences can be anticipated. Firstly, if either the survival of L3 to adult worms or the fecundity of adult worms is reduced at a high parasite load, then in a situation of recrudescence (when worm loads are brought down through control) higher rates of acquisition of new parasites or a higher Mf output will occur than predicted by the model. Hence, in this case both the risk and the dynamics of recrudescence have been underestimated. A second possibility is that in an uncontrolled situation high worm loads and high Mf densities are maintained because of a down-regulated immune system

(immunological tolerance). It cannot be excluded that after reducing the worm load to insignificant values, or in children born in a situation without transmission, strong immune-responses against new infections occur. Such strong responses will than most likely result in a much more rapid development of morbidity in skin and eyes. At the same time they are likely to either reduce the establishment of parasites or limit the appearance of Mf in the skin. Hence, if this is true, both the risk and dynamics of recrudescence have been overestimated.

Pre- and post-control fly biting rates

Since the start of larviciding in the OCP in 1975, a sophisticated system of entomological monitoring was set up, with fly catching sites at all important rivers and tributaries and a weekly briefing of important variables such as the biting rate and the infectivity of the flies (Philippon *et al.*, 1990). However, prior to OCP, no other programme could afford such an extensive evaluation, and sufficient comparative pre-control entomological data are not available for the whole area. Hence, it is not possible to link the pre-control epidemiological situation in most of the indicator villages to the prevailing biting rates in or around these villages. Such comparative data are only available for the Pru river and the village of Asubende and surrounding villages (Ghana). For this area six years of fly collections enabled us to estimate, for each calendar month, the level of the Monthly Biting Rate (MBR). After linking these figures with the epidemiological situation in this area, the biting rate in other villages is derived by applying an appropriate multiplication factor (mostly < 1) to these MBR-values (this multiplication factor is denoted the *relative biting rate, rbr*; see section II.2). This is of course a very indirect estimate of the pre-control biting rate and the quality of the estimates strongly rests upon the assumption of the absence of parasite density regulation in the human host. A possibly more serious threat to the validity of this approach is the assumption that these estimated biting rates have been constant for a period sufficient to establish an equilibrium epidemiological situation in the villages. Though one can only speculate about the implications for *O.volvulus* transmission, during the decade prior to the start of OCP there have been several severe droughts in the Sahel region (McMillan, 1995). Especially along streams which normally do not flow during the dry season, this may have resulted in considerably lower biting rates. These suppressed biting rates, in turn, may have caused a gradual reduction in the parasite density in the villages. Hence, the observed pre-control endemicity level in these villages may be an underestimation of the *potential* endemicity and the biting rate estimated for these villages may be an underestimation of the *potential* biting rate. In such areas, the biting intensity after stopping control could be much higher than estimated, and this could result in higher risks of recrudescence than predicted by

the model. In anticipation of this problem we have derived the guideline for the required duration of vector control for the highest endemicity levels encountered in the OCP area.

Morbidity

In the model highly simplifying assumptions are made with respect to morbidity. The only sign of morbidity considered is complete blindness (operationally defined as the inability to count fingers at a distance of three metres with the better eye). No provision is made for ocular lesions or for skin disease. The restriction to blindness alone is mainly because (i) it is this aspect of morbidity which is the only reason for large scale control of the West African savanna type of onchocerciasis, and, consequently, reduction in blindness is the most important marker for the success of control; (ii) in West African savanna blindness is a much greater public health problem than skin disease; (iii) ocular pathology, leading to a variety of lesions of the (anterior and posterior segment of the) eye is complicated and not well understood. In the model, blindness is assumed to the consequence of the accumulation of infection in a person. This implies that, on average, highly exposed and heavily infected persons go blind early in their lives, while modestly infected persons develop morbidity at older ages. Lightly infected persons will probably die from other causes before they reach their 'blindness' threshold. This concept is in agreement with observations that both on an individual level (Anderson *et al.*, 1976) and on a community level (Remme *et al.*, 1989a; McMahon *et al.*, 1988) there is a high correlation between intensity of infection and (the risk of) blindness. Furthermore, with this simple assumption we were able to reproduce the age specific prevalence of blindness in most of the villages we considered.

Relating the risk of blindness to the accumulation of infection[16] is equivalent to assuming that there is *only* progression and *no* regression of ocular disease. Trials with ivermectin have demonstrated that this assumption deserves revision. After two treatments in the Asubende trial (see Chapter IV) a slight improvement of early anterior lesions was found (Dadzie *et al.*, 1991). It is, therefore, possible that we underestimate the long term impact of repeated ivermectin treatment on the incidence of blindness.

The impact of control

Both the estimation of the reproductive lifespan of *O.volvulus* (Ch. III) and the predictions of recrudescence risks (Chapter V) rely upon the assumption that larviciding has resulted in a complete interruption of transmission. In Chapter III we have

[16] The area under the infection-intensity curve of an individual.

argued that this assumption is not unrealistic for the villages on which the estimates have been based. It is unlikely that the low levels of transmission, observed during the first years of OCP operations in some of the breeding sites, may have a large impact on our estimates. However, we have stated several times that the estimated recrudescence risks are only applicable to those areas where transmission during control is negligible. In this respect, especially dangerous will be transmission during the later years of larviciding, since this results in relatively young parasites at the moment that cessation of operations is being considered.

Chapter IV reports a detailed analysis of the impact of annual ivermectin treatment on the Mf counts in a cohort of patients. This analysis convincingly shows that the observed trends are compatible with the assumption that treatment at a dose of 150 μg/kg eliminates all Mf and permanently reduces the fecundity of female worms with 35% (95% confidence interval 25%-40%). Given the thoroughness of this analysis (taking into account the indirect effect of treatment on transmission) and the agreement with the results of nodulectomies, we believe that these are robust estimates. However, in section V.2 we have shown that the impact of a treatment strategy in a village or area not only depends on the effect of the drug in a patient, but also on the treatment coverage and compliance. The compliance pattern presented in the appendix of section V.2 reflects the observed pattern in the Asubende trial. The effectiveness of community treatment will decrease (considerably) if the proportion of persons which systematically escape treatment (passively or actively) increases.

The above considerations make clear that, as a result of the investments made to bring the model in agreement with current knowledge and data, credible predictions could be made of the impact for the control strategies of OCP. However, model validity has biological, statistical, and public health aspects. Statisticians will, rightly, stress that a number of parameters are not identifiable if only skin-snip data are being used. We have already discussed that parameters governing the worm load are largely exchangeable with parameters governing the (cumulative) Mf output of worms, and that the effective duration of an infection comprises more parameters than the two (mean lifespan and lifespan variation) estimated on the basis of the observed trends. However, biologists (as well as clinicians and epidemiologists) will counter that even though ONCHOSIM is a complex model, it is still too simplistic in several aspects, especially with respect to the vector-parasite dynamics, and that much uncertainty remains about parameter values used in the predictions. One could, therefore, state that ONCHOSIM is much like a compromise between these viewpoints. Though not exhaustive, guidewe have attempted to statistically explore the uncertainty of several assumptions in the model. On the other hand, we have

included quite a number of parameters and variables in order to gain confidence in the model from experts in the field, and because they may be important in view of the use of the model for predictions.

The final and most important criterion for validity is, however, the quality of the predictions of the (long term) epidemiological and public health impact of interventions. Given the time-frame of these predictions, judging the quality of the model in this respect is too premature. In the majority of river basins where vector control has stopped in agreement with model based guidelines, no new infections have been encountered and old infections are dying out. However, recent surveys in the Bougouriba river basin (Burkina Faso) demonstrate that five years after stopping larviciding there was a significant increase in the prevalence of Mf. In this river basin epidemiological and entomological surveillance is now being intensified and research has been initiated to detect the source of this recrudescence. If the recrudescence turns out to be purely local, then this is an important reason to put additional efforts in once more reviewing the model and the validity of assumptions.

VI.4 The future of ONCHOSIM

In this thesis we have only reported the use of ONCHOSIM in the context of the OCP. However, a start has been made to utilize the model for addressing problems with a wider perspective. One of these problems is the possible emergence of resistance of *O.volvulus* against ivermectin. Since it is likely that both within and outside OCP ivermectin will be administered on a large scale for many years, it is very important to gain insight into the likelihood of spread of resistance. This should be studied both on the level of the genetics of resistance and on the level of parasite population dynamics. Recently, ONCHOSIM has been extended with a sub-model for the dynamics of resistance. Important parameters of this sub-model are the initial resistance allele frequency (at the onset of treatment), the location of the resistance alleles (autosomal vs. X-linked), and the phenotypic expression of resistance alleles (dominant vs. recessive). The model is currently being used to investigate whether spread of resistance is likely and how this depends on the model parameters and the treatment strategy.

A second application of the model concerns the prospects of a future *macro*filaricidal drug for the local elimination of the infection. By using ONCHOSIM it is not only possible to compare such future drugs by varying the efficacy in terms of the fraction of parasites killed per treatment, but also to investigate the impact of several patterns of compliance. Tentative simulation results suggest that even a very effective drug (75% of the parasites killed per treatment) will fail to eliminate the infection if a small fraction (10%) of the population systematically escapes treatment.

As mentioned before, ONCHOSIM has been developed and quantified for the savanna form of *O.volvulus*, which is most prominent in the OCP area and which is associated with severe blindness. However, over 50% of all infected persons live in areas where blindness is not common (e.g., over 4,5 million cases in Zaire; WHO, 1995), but where onchocercal skin disease is the most important health problem (Remme, in press). A recent report of the Pan-African Study Group on Onchocercal Skin Disease (WHO-TDR, 1995) revealed that several kinds of skin lesions impose a burden of severe itching and other symptoms that have important psychosocial effects. This study is an important basis for the recently launched African Programme for Onchocerciasis Control (APOC) which aims 'to establish, within a period of twelve years, effective and self-sustainable community based ivermectin treatment throughout the remaining endemic areas in Africa and to eliminate the disease by vector control in selected foci' (Remme, 1995). Undoubtedly, in the framework of this initiative a number of operational questions will emerge related to

the time, efforts, and costs involved in elimination of disease both during and after the programme. To use ONCHOSIM for addressing these questions a thorough study is required both of the area specific parasite dynamics and of the natural history of the several forms of skin-disease.

Apart from the current and future use of ONCHOSIM in the framework of (collaborative) research projects, recently a user-friendly version of the package has been prepared for the use by other researchers in the field of onchocerciasis control and for teaching and training. This user-friendly package comprises the ONCHOSIM computer program itself, a user-interface for parameter quantification and a user's manual[17].

[17] An order-form for the package can be obtained from the author.

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Summary

This thesis describes the development and application of a quantitative model for onchocerciasis. Onchocerciasis, or river blindness, is a parasitic disease caused by the filarial nematode *Onchocerca volvulus* and is transmitted by flies of the genus *Simulium* (blackflies). Prolonged infection may lead to visual decline and complete blindness. Since 1975, the Onchocerciasis Control Programme in West Africa (OCP) aims to eliminate the disease in sub-saharan Africa by larviciding of *Simulium* breeding sites (vector control) and large scale chemotherapy with the drug ivermectin.

The objectives of the work reported in this thesis were: (1) to develop, quantify, and validate a model for the transmission and control of the disease in West African savanna, and (2) to use this model for aiding decision making in OCP.

Within OCP modelling had been used as a tool to interpret epidemiological trends observed during the first 8 years of vector control. This revealed that, while the prevalence of infection (% with microfilariae in the skin) is a very insensitive measure for evaluating the success of control, the observed trend in the intensity of infection (average density of microfilariae) was compatible with what one expects for a long lived parasite and indicated complete interruption of transmission in most of the evaluation areas. In collaboration with the Department of Public Health, Erasmus University Rotterdam, a more sophisticated simulation model was developed which could take account of variability in the reproductive lifespan of the *O.volvulus* parasite. This latter model, which has been extensively used as a routine tool for predicting trends in areas with varying levels of endemicity, was the basis for the development of ONCHOSIM, which is the principal subject of this thesis. Opposite to its predecessors, ONCHOSIM describes the full transmission cycle of the parasite, including the role of blackflies as vector.

The model, which is presented in chapter II, comprises a detailed description of the life-history of *Onchocerca volvulus* and of its transmission by *Simulium*-flies. The effects of different control strategies, based on larvicide application and chemotherapy (ivermectin), on the transmission and on the disease symptoms can be evaluated and predicted. ONCHOSIM is a hybrid of two simulation techniques. The human and parasite parts of the transmission cycle, including the impact of ivermectin treatment, is based on stochastic microsimulation model, which means that chance and variation play an important role and that the individual is the basic unit. Apart from birth and death, events in the life of a simulated person are acquisition of (new) parasites, the onset of blindness, participation in population treatment, etc. Together the simulated persons and inhabitant parasites constitute a hypothetical population of an endemic village. The part of the model describing dynamics of the *Simulium*-population and the development of the parasite in the flies is simulated

deterministically. Output of ONCHOSIM conforms to the format in which data collected by the OCP are reported. This enables detailed checking of model-specifications against empirical data. Output can also consist of summarizing key indices for the intensity of onchocerciasis infection, which is especially useful for comparing the effectivity of control strategies. Section II.1 describes the first version of the model and computer program; section II.2 provides a complete formal description of the model as it evolved during its application in OCP, including quantification of the model parameters.

ONCHOSIM is a comprehensive model with many parameters. For a number of crucial parameters no or very limited information was available, and their estimates should rely on indirect observations. In view of the aim of OCP to eliminate the infection from an area through interruption of transmission by controlling the vector (initially, the only means of control), a very important model-parameter is the reproductive lifespan of the parasite in the human host. Therefore, the first step in model quantification comprised the estimation of this reproductive lifespan and related parameters. The procedure and results are described in chapter III. Model predictions based on different lifespan quantifications were compared with the results of longitudinal surveys in 4 villages where control lasted for 13 to 14 years. At each of these surveys skin-snips (piece of skin in which Mf can be observed) were collected from the population. Good fits between predicted and observed trends in microfilarial loads could be obtained for all villages. By combining the estimates for three of these villages, it is concluded that the mean reproductive lifespan of the savanna strain of *O.volvulus* is in the range 9-11 years, and that 95% of the parasites reach the end of reproduction before the age of 13-14 years.

Other model parameters which are crucial for making credible predictions of the effectiveness of interventions are related to the control strategies themselves. The effects of vector control are simply described by a certain reduction in the fly biting rate. In agreement with entomological evaluation data, a reduction to zero is assumed in most of the predictions for the central OCP area. The effect of ivermectin treatment is much more complicated. The drug is known to be very efficacious against the microfilariae, but the result of clinical trials suggested that there might also be an effect on the adult parasites. Furthermore, patients were known to differ in their response to the drug. Testing hypotheses about the effects of the drug should preferably be based on data from community trials (covering a lot of patients) with repeated treatments to look for the existence of cumulative effects. Such a data-set and its use in validating the sub-model for the effects of treatment on the parasite is reported in chapter IV. The first section (IV.1) describes a community trial of five annual treatments in the holo-endemic focus of Asubende (Ghana). The general observed pattern was a marked reduction of microfilarial loads

shortly after each treatment followed by a steady repopulation of the skin until a subsequent round. The overall reduction of microfilarial loads observed between the baseline survey and one year after the last treatment was 90% for the whole examined population and over 93% for a cohort which received the drug at all five treatment rounds. The study further highlights that already a single treatment with ivermectin has a significant medium term impact on microfilarial loads. Microfilarial counts hardly increased after 14-16 months of treatment and stabilized around 55% of pretreatment counts 2 to 4 years after a single treatment.

The observation that post-treatment Mf levels remain lower than before treatment gave support to the hypothesis that ivermectin is not a microfilaricide *sensu stricto* but that there is also an effect on the reproductive capacity of adult worms. To test this hypothesis, and in particular to find out whether this effect on worms is transient or irreversible, the data from the Asubende trial have been re-analyzed with the help of ONCHOSIM (see section IV.2). Testing of hypotheses and estimation of the relevant parameters have been carried out by comparing model calculations with skin microfilaria counts collected from 114 patients for which either a complete series of observations during the whole trial period exist or who have been re-examined two years after a single treatment. The results of this model based analysis strongly suggest that treatment with ivermectin has three effects: Firstly, except in 3% of treatments, microfilariae are completely eliminated shortly after treatment. Secondly, during 10 to 11 months female parasites recover from treatment and gradually resume Mf production. Thirdly, after recovery the Mf production stabilizes at a level which is 30% lower than before treatment. This latter irreversible effect of treatment, earlier only found after multiple treatments at intervals of less than 6 months, has important implications for public health strategies designed to eliminate onchocerciasis as a significant health hazard.

Within the second objective of this thesis, the use of the model for aiding decision making in OCP, two questions of interest were: (1) How long should vector control be continued in the central area of OCP to prevent recrudescence of the disease after cessation of operations; (2) Could this required duration of control be shortened in areas where vector control was accompanied by large scale ivermectin treatment. Both questions are addressed in chapter V. Ivermectin was registered for human use in 1987 and, hence, in those areas where OCP started control between 1975 and 1977 the drug did not play an important role in reducing transmission. For these areas the policy was that larviciding alone should accomplish the elimination of the parasite.

Section V.1 reports how, by repeatedly simulating periods of vector control in the range of 9 to 15 years, the ensuing risk and dynamics of recrudescence of the infection in an area has been predicted for various conditions. In these simulations,

uncertainty about a number of important confounding parameters was explicitly taken into account. These parameters include the pre- and post-control fly biting rate in the area, variation in exposure between individuals, the parasite lifespan, and the relation between skin microfilarial load and vector infection. The model predicted that, in the absence of immigration of infected humans or invasion of infected flies, 14 years of full scale vector control are required to reduce the risk of recrudescence to less than 1%. The risk depends in particular on the vector biting rate and this has implications for the planning of post-larviciding surveillance. The predictions suggest that recrudescence will be a relatively slow process, its rate depending on the duration of vector control. Even if vector control were stopped too early after some 12 to 13 years in a highly endemic area, it would take more than two decades before the intensity of infection in the community reaches levels of public health importance. This latter result only holds true for recrudescence as a result of purely local transmission. A faster increase could be expected in case of importation of the infection through immigrant humans or flies.

In contrast to the original OCP area, in the extension areas aerial larviciding has been supplemented with annual ivermectin treatment, mainly to achieve a better control of morbidity. The purpose of the study reported in section V.2 is to determine whether and to what extent the addition of ivermectin allows an earlier cessation of vector control than originally recommended for the prevention of recrudescence. In this study, simulation results were analyzed by means of logistic regression to obtain estimates of the recrudescence risk for certain combinations of the duration of vector control, the number of annual treatments, and the percentage of the population treated per round (coverage). Model predictions suggest that, dependent on the pre-control endemicity of the area and the treatment coverage, large scale annual treatment allows considerable reductions in the required duration of vector control. Taking into account the uncertainty about the efficacy of ivermectin, the guideline is derived that, provided the coverage is at least 65% and importation of infection from elsewhere is absent, 12 years of combined control will be sufficient to reduce the risk of recrudescence to below 1% even in the most afflicted areas.

The conclusion seems justified that the development and application of ONCHOSIM has both contributed to a better knowledge of the dynamics of the parasite and the effects of interventions, and to decision making about control policies within OCP. Apart from the applications mentioned in chapter V, the model has also been used to aid the design of strategies for the detection and control of recrudescence, should it unfortunately occur in one of the areas of OCP. The use of ONCHOSIM has not been restricted to practical questions of OCP. Recently, the model has been extended to enable assessment of the risk of resistance to ivermectin

in situations where the drug is used intensively for long periods of time. Further, anticipating the development of a macrofilaricide (a drug which kills adult worms), simulations of population treatment with several hypothetical drugs have been carried out. These simulations revealed that effectiveness of chemotherapy based interventions not only depends on the efficacy of the drug, but also largely on the pattern of compliance with treatment. To enable the use of ONCHOSIM outside OCP, a user-friendly version of the computer program has been developed. Together with the reported usefulness of modelling for disease control, this distribution version of the model may stimulate similar initiatives for other parasitic diseases.

Samenvatting en conclusies

Dit proefschrift handelt over de ontwikkeling en toepassing van een computer model waarmee de verspreiding en bestrijding van *onchocerciasis* of *rivierblindheid* kan worden nagebootst. Voordat het eigenlijke onderwerp aan de orde komt zullen we eerst de nodige achtergrondinformatie geven.

Onchocerciasis is een parasitaire ziekte die als endemie[18] voorkomt in grote delen van Afrika (met name het westen en midden) en in Zuid en Midden Amerika. De parasiet *Onchocerca volvulus* is een worm waarvan het vrouwtje een lengte van 20 tot 50 cm bereikt. De wormen leven groepsgewijs in onderhuidse knobbels. In de mens produceert een volwassen vrouwtje miljoenen nakomelingen die microwormen of *microfilariën* worden genoemd. Het zijn deze microfilariën (Mf) die de ziekteverschijnselen veroorzaken. Zij migreren naar de huid en geven daar aanleiding tot ondraaglijke jeuk en (onder andere door krabben) huidafwijkingen. Om aan te tonen of iemand geïnfecteerd is (een produktieve vrouwelijke worm heeft) wordt een kleine huidbiopt (een skin-snip) genomen en wordt onder de microscoop gekeken of daar microfilariën in zitten. Hoewel de huidproblemen zeer vervelend kunnen zijn, waren de belangrijkste reden om deze parasiet te bestrijden de oogafwijkingen die het gevolg zijn van het binnendringen van microfilariën in de oogbol. Deze oogafwijkingen hebben in eerste instantie een verminderd gezichtsvermogen of een verminderd blikveld[19] tot gevolg. Uiteindelijk kunnen ze tot volledige blindheid leiden. Microfilariën kunnen niet zonder meer tot volwassen worm uitgroeien. Daartoe moeten ze eerst worden opgeslokt door een vlieg die een bloedmaaltijd nuttigt van een mens met microfilariën in de huid. In zo'n vlieg (van het geslacht *Simulium*, ook wel 'blackflies' genoemd) kan een microfilaria overgaan in het larvestadium. De larve wordt na enige dagen infectieus. Als een vlieg met infectieuze larven opnieuw een bloedmaaltijd gebruikt (bij een willekeurige andere persoon) dan kunnen deze larven worden overgedragen op die persoon en uitgroeien tot een nieuwe volwassen worm. De rijping tot worm duurt ongeveer een jaar. De naam *rivierblindheid* heeft te maken met de broedplaatsen van de *Simulium*-vlieg (de vector[20]). Voor hun ontwikkeling zijn de vliegen-larven afhankelijk van het zuur-

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[18] Er is sprake van een endemie als een ziekte, in afwezigheid van bestrijdings-maatregelen, altijd in een gebied aanwezig is en een aanzienlijk aantal mensen treft. Indien een ziekte met kortere of langere tussenpozen kortstondig toeslaat wordt er gesproken van een epidemie.

[19] Het blikveld is datgene wat met 'vanuit de ooghoeken' ziet. Bij onchocerciasis kan dit sterk verminderd zijn zodat het lijkt alsof men door een koker of een sleutelgat kijkt.

[20] Een organisme dat een infectie (parasiet) van de ene mens op de andere overbrengt wordt 'vector' genoemd. Bij onchocerciasis is dit een vlieg. Bij malaria een mug. Bij schistosomiasis (bilharzia) een waterslak.

stofrijke water van snelstromende rivieren.

Bestrijding van de ziekte kan op twee manieren. Door de vlieg te bestrijden kan worden voorkomen dat deze de parasiet overdraagt (vector-bestrijding). Door medicijnen toe te dienen die de microfilariën (of zelfs de volwassen wormen) doden kan worden voorkomen dat patiënten blind worden en wordt tevens de overdracht (transmissie) verminderd[21]. Vector-bestrijding geschiedt vrijwel uitsluitend door met behulp van chemicaliën het larve-stadium van de vlieg in de rivier te doden. Hiervoor zijn een aantal zgn. *larviciden* beschikbaar die betrekkelijk veilig zijn voor de overige diersoorten in het water. Voor behandeling van patiënten is het medicijn *ivermectine* beschikbaar. Dit oraal toe te dienen medicijn elimineert vrijwel alle microfilariën met één enkele dosis en vermindert de produktiviteit van de volwassen vrouwtjes. Door ivermectine jaarlijks toe te dienen kan het ziekteproces een halt worden toegeroepen.

Sinds 1975 wordt de ziekte in West Afrika op grote schaal bestreden door het *Onchocerciasis Controle Programme in West Africa* (OCP), een ziekte-bestrijdings programma dat gecoördineerd wordt door de Wereld Gezondheids Organisatie (World Health Organization, WHO) en dat gefinancierd wordt door een aantal westerse landen waaronder Nederland. Tot 1987, het jaar waarin ivermectine werd geregistreerd voor gebruik als medicijn voor onchocerciasis, werd de bestrijding uitsluitend gedaan door met behulp van helikopters en vliegtuigen larviciden in de belangrijkste rivieren van de 7 deelnemende landen[22] te deponeren. Dit bleek zeer succesvol en leidde tot een teruggang in het aantal geïnfecteerde personen en een sterke daling in de mate waarin mensen geïnfecteerd zijn (het aantal parasieten per persoon). Tevens werden er nog maar zelden patiënten volledig blind. Het probleem van het OCP was (en is) echter dat de bestrijdings-activiteiten zich over een lange periode moeten uitstrekken willen ze een duurzaam effect op de volksgezondheid hebben. De maximale levensduur van de volwassen parasiet werd aanvankelijk op 20 jaar geschat, en men moest er dus voor zorgen dat gedurende 20 jaar geen nieuwe infecties ontstonden om er zeker van te zijn dat de parasiet uit het gebied werd uitgeroeid[23]. Dit betekent een even zo lange periode van intensieve vliegen-bestrijding, en dat kan alleen maar door grote investeringen in hoogwaardige

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[21] Indien een persoon geen microfilariën meer heeft kan een bijtende vlieg ook niet meer geïnfecteerd worden. Als veel personen behandeld worden zal dit dus gunstige gevolgen hebben voor de totale infectie-druk in een gebied.

[22] Burkina Faso (voorheen Opper Volta), Mali, Ivoorkust, Ghana, Togo, Benin en Niger. Later zijn hier ook (delen van) Senegal, Guinee, Guinee-Bissau en Sierra Leone bijgekomen.

[23] Immers, zo'n nieuwe infectie (lees: parasiet) kan weer 20 jaar actief blijven.

technologie (gespecialiseerde helikopters, nieuwe larviciden), door een strakke verticale organisatie, en door een goed gekwalificeerde staf uit diverse disciplines (entomologen[24], (oog-)artsen, epidemiologen, economen, (bio-)statistici, managers, etc.) niet alleen voor het plannen en uitvoeren van de bestrijding maar ook voor het evalueren van de effecten.

Met name dit laatste, het evalueren van de effecten van bestrijding, is niet eenvoudig in het geval van een infectieziekte die het gevolg is van het samenspel van drie organismen: de mens, de vlieg en de parasiet. Gegevens verzameld gedurende de eerste 8 jaren van het OCP gaven bij oppervlakkige beschouwing niet zo'n heel florissant beeld van de bestrijdings resultaten. Er was weliswaar een teruggang in het percentage geïnfecteerde personen[25] (*Mf-prevalentie*), maar deze werd toch onbevredigend geacht. Gestimuleerd door deze bevindingen zijn de gegevens nogmaals geanalyseerd, maar ditmaal met behulp van een speciaal voor dit doel ontwikkeld wiskundig model. Dit model beschrijft het verloop van een parasieten-populatie (met gemengde leeftijden) in de bevolking onder de veronderstelling dat er op een gegeven moment (= de start van het OCP) geen nieuwe infecties meer bijkomen en er dus alleen nog maar parasieten kunnen doodgaan. De berekeningen van dit model werden vergeleken met de waargenomen trends en daaruit bleek dat de geringe teruggang in Mf-prevalentie gedurende de eerste jaren volstrekt in overeenstemming is met wat verwacht mag worden bij een parasiet met een lange levensduur en waarvan de meeste patiënten er (veel) meer dan één hebben. De belangrijkste conclusie was dan ook dat *prevalentie* (% geïnfecteerden) een ongevoelige maat is voor het succes van bestrijding. In plaats daarvan dient men te kijken naar de trend in de *intensiteit* van infectie (het gemiddelde aantal microfilariën per skin-snip). Modelberekeningen suggereerden tevens dat de gemiddelde levensduur van de parasiet ongeveer 10 jaar is, hetgeen een stuk korter is dan de eerder genoemde 20 jaar.

Aangezien de levensduur van de parasiet (of nog beter: de duur van het reproduktieve leven van volwassen vrouwtjes) zeer bepalend is voor de noodzakelijke duur van ziekte-bestrijding, werd het noodzakelijk geacht een tweede model te ontwikkelen dat deze reproduktieve levensduur in groter detail beschrijft. Omdat met name de *variatie* in deze levensduur van belang is, was het niet mogelijk het eerste (zgn.

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[24] Insekt-kundigen.

[25] Het percentage mensen met een positieve skin-snip (ofwel een skin-snip waarin tenminste één microfilara wordt aangetroffen).

'*force-of-infection*') model uit te breiden[26] en werd een nieuw model ontwikkeld dat gebaseerd was op de techniek van *microsimulatie*. Bij microsimulatie worden hypothetische *individuele* mensen en (in dit geval) *individuele* parasieten nagebootst en in de tijd gevolgd. Mensen worden op een gegeven moment geboren, krijgen op gezette tijden nieuwe parasieten die een bepaalde tijd leven, en sterven op een gegeven moment. Die gebeurtenissen en de momenten waarop ze plaatsvinden worden bepaald door waarschijnlijkheids-verdelingen[27]. Een belangrijke waarschijnlijkheids verdeling in het nieuwe model is de verdeling van de levensduur van *O.volvulus*. Het microsimulatie model (gedoopt als '*host-parasite*' model; ofwel gastheer-parasiet model) werd voornamelijk voor twee doeleinden gebruikt: (1) een betere schatting verkrijgen van de reproduktieve levensduur van de parasiet (dit komt uitvoerig aan de orde in hoofdstuk III[28]); (2) voor verschillende endemiciteits niveaus[29] de trend in prevalentie en intensiteit voorspellen en de voorspellingen vergelijken met waarnemingen in verschillende dorpen. Met dit laatste kon men veel makkelijker dan voorheen die gebieden op het spoor komen waar de bestrijding niet bevredigend was. Model voorspellingen suggereerden dat na 14 tot 15 jaar bestrijding zowel intensiteit als prevalentie tot vrijwel nul zouden zijn gereduceerd.

Dit laatste gaf aanleiding tot de brandende vraag: hoe lang moeten de zeer kostbare bestrijdings-activiteiten van het OCP nog doorgaan om de oorspronkelijke doelstellingen te halen: (1) het elimineren van onchocerciasis als gezondheids probleem en (2) er voor zorgen dat de infectie niet terugkeert na afloop van de

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[26] Het *force-of-infection* ('infectie-druk') model is een puur wiskundig model waarvoor een analytische oplossing te herleiden valt. Indien men ingewikkelde veronderstellingen wil toetsen wordt het bijbehorende model dikwijls te ingewikkeld om nog op te lossen en moet men de toevlucht nemen tot numerieke technieken of *simulatie* technieken.

[27] Een waarschijnlijkheids-verdeling geeft aan welke waarden een bepaalde variabele kan aannemen (bijv. de levensduur van een parasiet, of de tijd tussen opeenvolgende nieuwe infecties bij een bepaalde infectie-druk) en hoe waarschijnlijk elk van die waarden is.

[28] In hoofdstuk III wordt weliswaar de opvolger van het host-parasite model gebruikt (ONCHOSIM) maar dit model is voor wat betreft de beschrijving van de parasitaire levensduur identiek.

[29] Met het endemiciteits niveau (of kortweg de endemiciteit) wordt de ernst van de infectie in een dorp of gebied bedoeld. Het wordt vooral in relatieve zin gebruikt: hoog- vs. laag-endemisch. Voor onchocerciasis wordt de regel gehanteerd dat een dorp met een Mf-prevalentie van meer dan 60% hoog-endemisch (hyper endemic) wordt genoemd.

bestrijding[30]. Ook voor het beantwoorden van deze vraag achtte men het zinvol om modelberekeningen uit te voeren. Echter, in beide eerdere modellen speelde de verspreiding van de ziekte via de vlieg geen rol. Beide modellen beschreven de trends gedurende de *af*wezigheid van de vector terwijl er juist berekeningen nodig waren voor de implicaties van de terugkeer van de vlieg. Daarom werd er een nieuw model ontwikkeld dat de complete transmissie van onchocerciasis beschrijft en waarmee de effecten van zowel vector-bestrijding als medicijn-behandeling op de transmissie kon worden nagebootst. Dit model, ONCHOSIM, is gebaseerd op dezelfde microsimulatie-techniek als het host-parasite model. Dit proefschrift beschrijft de ontwikkeling en toepassing van ONCHOSIM.

ONCHOSIM

ONCHOSIM is een *stochastisch microsimulatie model*. Het is *stochastisch* omdat kansen en variabiliteit een belangrijke rol spelen. Het is een *simulatie* model omdat numerieke technieken gebruikt worden om berekeningen te doen met het model. Het is een *micro*simulatie model omdat het gebaseerd is op het nabootsen van individuele levens-geschiedenissen (van mensen en parasieten). Het model wordt beschreven in hoofdstuk II. Een strikt formeel-wiskundige beschrijving wordt gegeven in sectie II.2. Doordat daar ook alle gebruikte parameter-waarden worden vermeld kan deze sectie - in theorie - worden gebruikt om ONCHOSIM te reproduceren. Een semi-formele (meer verhalende) beschrijving wordt gegeven in sectie II.1. Deze sectie geeft niet alleen een overzicht van parameters en variabelen, en hoe deze gerelateerd zijn, maar beschrijft ook hoé het model geïmplementeerd is in een computer programma[31]. Een van de belangrijkste stochastische factoren in ONCHOSIM is de variatie in de frequentie waarmee personen door vliegen gebeten worden. De mate waarin dit varieert noemen we *exposure heterogeniteit*. Door het model te

[30] Ervaringen met vroegere, meer lokale, bestrijding leerden dat vrijwel onmiddellijk (op z'n laatst het volgende natte seizoen) na het stoppen van vector-bestrijding de *Simulium* vliegen hun vroegere territoria weer in gebruik nemen en dus ook weer mensen gaan bijten. Het is dan dus zaak dat die mensen geen of bijna geen microfilariën meer in hun huid hebben.

[31] Formeel zijn 'model' en 'computer simulatie programma' (zie titel van sectie II.1) twee verschillende dingen: het model beschrijft de samenhang tussen parameters (bijv. de gemiddelde levensduur van een worm-parasiet) en variabelen (bijv. het aantal wormen in een mens) terwijl het computer programma gebruikt wordt om op basis van dit model berekeningen en voorspellingen te doen. In de praktijk worden de begrippen door elkaar gehaald en beide met 'model' aangeduid.

fitten[32] aan evaluatie gegevens van verschillende dorpen is gebleken dat verschillen tussen dorpen verklaard kunnen worden uit verschillen in de gemiddelde bijtfrequentie (die op zich weer bepaald wordt door onder andere de produktiviteit van de *Simulium* broedplaatsen en de afstand van het dorp tot een broedplaats) en verschillen in exposure heterogeniteit.

Reproduktieve levensduur van Onchocerca volvulus
Het bovengenoemde fitten van ONCHOSIM aan evaluatie gegevens is op een gedetailleerde manier uitgevoerd met de gegevens van 4 dorpen in het centrale OCP gebied (waar vanaf 1975 vliegenbestrijding is toegepast). In deze dorpen is gedurende 14 jaar met tussenpozen van 2 tot 7.5 jaar een skin-snip genomen van een zo groot mogelijk deel van de bevolking (een epidemiologische survey). Voor de analyse van deze gegevens is voor ieder dorp eerst een cohort gevormd van personen die bij de eerste survey volwassen waren (20 jaar en ouder) en die aan alle onderzoeken hebben deelgenomen. Voor iedere survey zijn de gegevens van zo'n cohort weergegeven in de vorm van een frequentie-verdeling van microfilaria tellingen[33]. Precies hetzelfde soort frequentie verdelingen kan ook door ONCHOSIM worden geproduceerd, en door de mate van overeenstemming tussen berekende en waargenomen verdeling (m.b.v. een χ^2-criterium) te bepalen kan een bepaalde veronderstelling worden getoetst. De te toetsen veronderstellingen betroffen de gemiddelde reproduktieve levensduur van *O.volvulus* en de mate waarin deze levensduur tussen parasieten varieert. Door een reeks van waarden te toetsen aan de gegevens van de vier dorpen kon worden geschat dat de gemiddelde levensduur varieert tussen 9 tot 11 jaar terwijl de variabiliteit van de levensduur dusdanig is dat 95% van de parasieten sterft vóór de leeftijd van 13 tot 14 jaar. De schattings procedure en de resultaten worden gepresenteerd in hoofdstuk III.

Parasitologische effecten van ivermectine
Voor een goed voorspellend model is het niet alleen van belang dat het model een adequate beschrijving geeft van de dynamiek van de parasiet in de vlieg en de mens. Het is ook van groot belang dat betrouwbare veronderstellingen worden gedaan over

[32] Het fitten van een model is het proces waarbij voor parameters een dusdanige numerieke waarde wordt gezocht dat de uitkomst van het model zo goed mogelijk overeenstemt met waarnemingen. Dit toekennen van waarden wordt meestal met een standaard procedure gedaan. Bij één of twee parameters kan het vaak ook door 'trial and error'. Voor de mate van overeenstemming tussen model en waarnemingen bestaan statistische criteria.

[33] In het OCP heeft men de gewoonte om personen in te delen volgens een geometrische reeks, d.w.z. personen die 0, 1, 2-3, 4-7, 8-15, 16-31, 32-63, 64-127, 128-255, en meer dan 256 Mf per skin-snip hebben.

de effecten van bestrijdings-maatregelen. Voor de effecten van vector bestrijding ligt dat vrij eenvoudig. Het doden van vliegen-larven heeft maar één effect en dat is een verminderd aantal beten. Voor het centrale OCP gebied is voor de meeste rivieren vastgesteld dat de bijt-frequentie tot nul is gereduceerd. Voor de effecten van ivermectine behandeling ligt het een stuk ingewikkelder. Vóór de registratie van het medicijn was al door veldstudies komen vast te staan dat ivermectine meer doet dan alleen maar microfilariën doden. Na behandeling duurde het enige tijd voor er weer Mf in de huid konden worden aangetoond en ook langere tijd daarna bleef de Mf-spiegel lager dan vóór behandeling. Dit deed vermoeden dat ivermectine ook een effect heeft op de produktie-capaciteit van de vrouwelijke worm. Daarbij is dan natuurlijk de vraag van welke aard dit effect is. Is het tijdelijk en produceert de worm na verloop van tijd weer normaal, of is het een permanent effect, misschien wel omdat een zeker percentage van de wormen wordt gedood. Om deze vraag te onderzoeken zijn een aantal mogelijke effecten van toediening in ONCHOSIM 'ingebouwd' en getoetst door modelberekeningen te vergelijken met de resultaten van een grote veldstudie in Asubende (een cluster van dorpen aan de Pru-rivier in Ghana). In deze veldstudie werd gedurende 5 jaar jaarlijks aan zoveel mogelijk dorpsbewoners ivermectine toegediend. Na elke behandeling werd tenminste één keer, maar soms wel drie keer een epidemiologische survey gedaan waarin het aantal Mf per skin-snip bepaald werd. Sectie IV.1 geeft een uitvoerige beschrijving van de organisatie van de veldstudie en van de resultaten van de surveys. Het bleek dat onder de personen die in alle 5 ronden het medicijn geslikt hadden, de Mf-telling één jaar na de laatste behandeling gemiddeld nog maar 7% was van de telling vóór de eerste behandeling. Ook het effect van één enkele behandeling was al aanzienlijk: 2 tot 4 jaar erna is de Mf-telling nog maar 55% van de telling vóór behandeling. De analyse van deze gegevens met behulp van ONCHOSIM is beschreven in sectie IV.2. Uit deze analyse komt naar voren dat de trends in de Mf-tellingen uitsluitend verklaard kunnen worden met de veronderstelling dat elke behandeling de produktiviteit van vrouwelijke wormen permanent reduceert met ongeveer 30% (of dat elke behandeling 30% van de vrouwelijke wormen doodt). Het is duidelijk dat dit gegeven van groot belang is voor de verwachte effectiviteit van massa-behandeling[34] met ivermectine.

[34] Bij massa-behandeling wordt het medicijn aan zoveel mogelijk mensen in een bepaalde gemeenschap (dorp) toegediend zonder eerst vast te stellen of men wel echt geïnfecteerd is. Dit is natuurlijk alleen maar zinvol als een ziekte hoog-endemisch is (bijna iedereen heeft het) en het is alleen maar toegestaan als het medicijn geen ernstige bijwerkingen heeft. De tegenhanger is doelgerichte behandeling, waarbij eerst een diagnose wordt gedaan en pas daarna wordt behandeld.

De vereiste duur van vector bestrijding

Zoals gezegd was de eerste reden voor de ontwikkeling van ONCHOSIM de ondersteuning bij de beslissing over de noodzakelijke duur van vector bestrijding. Bestrijding van de vlieg moest zolang worden volgehouden dat het risico op een opleving van de infectie in de populatie (*recrudescence*) na terugkeer van de vliegen verwaarloosbaar klein was. Men realiseerde zich daarbij dat te vroeg stoppen op termijn kon leiden tot een volledig ongedaan maken van al de inspanningen en kosten die men zich al getroost had. Met behulp van ONCHOSIM is het recrudescence-risico berekend voor verschillende periodes vector bestrijding (van 9 tot 15 jaar). Deze berekening is gedaan voor twee (voormalig) hyper-endemische dorpen in het centrale OCP gebied. Eén van die dorpen (Tiercoura, Burkina Faso) had vóór aanvang van de bestrijding een van de hoogste infectie-niveaus ooit vastgesteld in de OCP. Daarnaast werden bij de simulaties ook nog de meest ongunstige (maar met het oog op waarnemingen nog net realistische) veronderstellingen gedaan over de levensduur van de parasiet[35] (zie hoofdstuk III), de efficiëntie waarmee vliegen microfilariën kunnen opnemen bij lage Mf-dichtheden in de huid van de mens[36], en de mate waarin de blootstelling aan vliegenbeten varieert in het dorp[37]. Voor een bepaalde duur van vector bestrijding in een dorp (en een bepaalde combinatie

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[35] Die veronderstelling die er vanuit gaat dat 5% van de wormen ouder kan worden dan 15 jaar.

[36] Deze 'efficiëntie' is een belangrijke factor in de transmissie van de parasiet. Uit experimenten - zie de appendix bij sectie V.1 - is gebleken dat het aantal *O.volvulus* larven dat zich na een bloedmaaltijd in de vlieg ontwikkelt op een kromlijnige manier samenhangt met de Mf-dichtheid in de huid van de mens waarvan de bloedmaaltijd genuttigd wordt. Bij afwezigheid van Mf in de huid ontwikkeld zich uiteraard geen larve in de vlieg. Bij toenemende Mf-dichtheid neemt het aantal larven in de vlieg aanvankelijk sterk toe, maar bij hoge Mf-dichtheid wordt die toename steeds geringer. Bij dichtheden hoger dan 150 Mf per skin-snip stijgt het aantal larven nauwelijks meer (verzadiging). In model-termen is dit het belangrijkste dichtheids regulerende proces. De statistische analyse van de genoemde experimentele gegevens leidde tot een schatting van de wiskundige relatie waarmee dit kromlijnige verband beschreven kon worden. Zoals met de meeste biologische waarnemingen is er echter niet slechts één zo'n relatie denkbaar. Naast de relatie die het best past zijn er ook nog andere mogelijk. Bij één van die andere mogelijkheden is de vlieg beter in staat om larven tot ontwikkeling te brengen bij lage (bijna nul) Mf-dichtheden in de huid. Die mogelijke relatie is uitgekozen als 'ongunstige' veronderstelling bij de berekening van het recrudescence risico.

[37] Er kan wiskundig worden aangetoond dat variatie in blootstelling (exposure-heterogeneity) stabiliserend werkt op een endemie. Voor een eventuele recrudescence is deze heterogeniteit ook een belangrijke risico factor. Immers bij een grote variatie heb je een aantal mensen die relatief veel wormen bevatten en die ook na vele jaren bestrijding nog steeds relatief veel Mf in de huid hebben. Zij kunnen bij terugkeer van de vliegen de hele infectie weer op gang brengen.

van bovengenoemde factoren) werd het recrudescence risico berekend door deze strategie 50 keer te simuleren en vervolgens te tellen in hoeveel gevallen het model een recrudescence liet zien[38]. Sectie V.1 laat zien dat in het hoogst geïnfecteerde dorp het risico snel daalt als bestrijding langer duurt dan 12 jaar. Echter, pas tussen 13 en 14 jaar bestrijding reduceert het risico tot bijna nul. De analyse gaf aanleiding tot de richtlijn dat 14 jaar vliegenbestrijding voldoende is om het recrudescence risico tot minder dan 1% terug te brengen, zelfs onder de meest ongunstige omstandigheden wat betreft endemiciteit en andere risico factoren. Twee belangrijke randvoorwaarden bij het hanteren van deze richtlijn zijn dat de vector bestrijding 100% effectief is geweest (geen vliegenbeten tijdens de bestrijding) en dat er geen immigratie heeft plaatsgevonden van ofwel geïnfecteerde personen of geïnfecteerde vliegen. Het model voorspelt ook dat, mocht recrudescence toch optreden, het tenminste 20 jaar duurt voordat de intensiteit van infectie een niveau bereikt dat gevaar oplevert voor de volksgezondheid.

De vereiste duur van gecombineerde bestrijding

De richtlijn voor de vereiste duur van vector-bestrijding geldt alleen voor die gebieden waar geen andere bestrijdings-maatregelen zijn genomen. Dit is inderdaad het geval voor het centrale (oorspronkelijke) OCP gebied. Echter, tussen 1988 en 1990 is het OCP gebied aanzienlijk uitgebreid zowel in westelijke als zuidelijke richting. In deze *extension areas* is vanaf het begin vector bestrijding gecombineerd met jaarlijkse massa-behandeling met ivermectine, vooral om een snellere afname in morbiditeit[39] te bewerken. Het is duidelijk dat op die manier de infectie niveaus sneller dalen dan met vector bestrijding alleen. Het is daarom van belang om voor deze gebieden aparte richtlijnen te formuleren voor de vereiste duur van, in dit geval gecombineerde, bestrijding. Ook hiervoor zijn simulaties met ONCHOSIM gebruikt. Het bepalen van recrudescence risico's is hier echter aanzienlijk ingewikkelder. Immers, gegeven de endemiciteit en gegeven bepaalde risico-factoren (zie sectie V.1), wordt dat risico nu niet bepaald door één maar door drie factoren: de duur van vector-bestrijding, het aantal massa-behandelingen, en het percentage daadwerkelijk behandelde mensen. In sectie V.2 wordt uitgelegd hoe dit is aangepakt met behulp van de statistische techniek van logistische regressie. Hoewel het niet goed mogelijk is om met zoveel factoren tot een eenduidige richtlijn te komen, kon worden vastgesteld dat in die gebieden waar gedurende de hele periode vector bestrijding en jaarlijkse behandeling worden gecombineerd, en waar steeds tenmin-

[38] Als recrudescence in n gevallen optreedt is het risico $(n/50)\times 100\%$.

[39] Het geheel aan ziekteverschijnselen. Bij onchocerciasis huidafwijkingen, oog-lesies en blindheid.

ste 65% van de mensen behandeld wordt, 12 jaren bestrijding voldoende moet zijn om het recrudescence risico tot bijna nul te reduceren. Ook hier geldt de belangrijke randvoorwaarde dat de vector bestrijding zeer succesvol moet zijn geweest en er geen import van de infectie van buitenaf moet hebben plaatsgevonden. Een andere voorwaarde is dat niet bepaalde personen of groepen van personen systematisch onbehandeld blijven.

Conclusies

1. Het ontwikkelen van een model voor de verspreiding en bestrijding van onchocerciasis (rivierblindheid) is zinvol geweest omdat het heeft geholpen bij de interpretatie van epidemiologische gegevens van het OCP en omdat het heeft geholpen bij een rationele afweging van de effekten van verschillende interventies en daarmee ondersteuning heeft verleend aan de besluitvorming rond interventies.
2. Het feit dat dit model - ONCHOSIM - een microsimulatie model is heeft in belangrijke mate bijgedragen aan de toepasbaarheid van het model op de beleidsvragen. Microsimulatie modellen zijn dermate flexibel dat veronderstellingen aangepast kunnen worden zonder de hele model structuur aan te passen. Tevens kunnen in zulke modellen allerlei complicaties in beschouwing worden genomen (zoals migratie, deelnamepatronen bij massa-behandeling, etc.). en kunnen specifieke strategieën (behandelingen of surveys met onregelmatige intervallen, selektieve behandeling) worden nagebootst.
3. De gedetailleerde analyse met behulp van ONCHOSIM van trends gedurende vector bestrijding in vier dorpen in het OCP gebied heeft geresulteerd in een schatting van de reproduktieve levensduur van de parasiet *Onchocerca volvulus* in de West-Afrikaanse savanne. Deze levensduur is gemiddeld 9 tot 11 jaar terwijl 95% van de parasieten sterft vóór de leeftijd van 13 tot 14 jaar.
4. De analyse van de resultaten van een veldstudie van 5 opeenvolgende jaarlijkse behandelingen met ivermectine heeft aan het licht gebracht dat, behalve het doden van microfilariën, iedere behandeling een permanente reductie van de produktiviteit van vrouwelijke parasieten met 30% tot gevolg heeft.
5. De duur van vector bestrijding die vereist is om een opleving van de ziekte te voorkomen in het savanne gebied van West Afrika is 14 jaar. Deze richtlijn geldt alleen als de bestrijding volledig effectief is en er geen import van de infectie van buitenaf plaatsvindt.
6. Indien vector bestrijding gecombineerde wordt met jaarlijkse massa-behandeling met ivermectine (waarbij steeds tenminste 65% van de bevolking behandeld wordt) kan de vereiste duur van bestrijding worden verkort tot 12 jaar.

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[1] for publications included in this thesis.

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Curriculum vitae

Anton Plaisier werd geboren op 27 november 1961 te Ridderkerk. Hij deed in 1980 eindexamen Atheneum B aan de Reformatorische Scholengemeenschap 'Guido de Brés' te Rotterdam. In 1986 behaalde hij het ingenieursdiploma aan de Landbouwhogeschool (thans Landbouwuniversiteit) te Wageningen in de studierichting populatiebiologie. Het doctoraalprogramma omvatte twee hoofdvakken: Plantenoecologie en Theoretische Teeltkunde, en één bijvak: Informatica. De stage werd voor een deel doorgebracht op het Instituut voor Veredeling van Tuinbouwgewassen (Wageningen). Een tweede onderdeel, uitgevoerd onder verantwoordelijkheid van de vakgroep Theoretische Teeltkunde (Landbouwhogeschool), betrof de uitwerking van een door de World Meteorological Organization wereldwijd verspreide enquête naar de bruikbaarheid van gewasgroeimodellen voor het modelleren van de CO_2-verrijking van de atmosfeer (het broeikaseffect). Sinds maart 1986 is hij verbonden aan het instituut Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam alwaar hij betrokken is bij onderzoek op het terrein van de bestrijding van tropische infectieziekten. Met name heeft hij gewerkt aan het ontwikkelen van een model voor de verspreiding van rivierblindheid en de toepassing van dit model op beleidsvragen van het Onchocerciasis Control Programme in West Africa. Inmiddels is hij ook betrokken bij modelontwikkeling ten behoeve van de bestrijding van lymfatische filariasis. Tevens participeert hij als docent in het keuze-onderwijs Tropengeneeskunde en in de cursus Evaluation of Tropical Disease Control (een module van The Netherlands Institute for Health Sciences). Hij is getrouwd met Joke Zwagemaker en heeft vijf kinderen: Geert, Eline, Willem, Joanne en Thijs.