Computer Methods and Programs in Biomedicine, 31 (1990) 43–56
Elsevier

COMMET 01059

Section II. Systems and programs

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

A.P. Plaisier [1], G.J. van Oortmarssen [1], J.D.F. Habbema [1], J. Remme [2] and E.S. Alley [2]

[1] *Department of Public Health and Social Medicine, Medical Faculty, Erasmus University Rotterdam, 3000 DR Rotterdam, The Netherlands, and* [2] *Onchocerciasis Control Programme, B.P. 549, Ouagadougou, Burkina Faso*

ONCHOSIM is a computer program for modelling the transmission and control of the tropical parasitic disease onchocerciasis, or river blindness. It is developed in collaboration with the Onchocerciasis Control Programme in West Africa (OCP), and is used as a tool in the evaluation and planning of control operations. The model comprises a detailed description of the life history of the parasite *Onchocerca volvulus* and of its transmission from person to person 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. In the program two simulation techniques are mixed. Stochastic microsimulation is used to calculate the life events of individual persons and inhabitant parasites, while the dynamics of the *Simulium* population and the development of the parasite in the flies are 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.

Disease control; Parasitic disease; Microsimulation; Onchocerciasis; Simulation model

1. 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 [1]. 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 [2]. This makes the disease 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 [1].

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. 1.

Adult inseminated female parasites produce millions of microfilariae (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 microfilariae from the skin. A fraction of these microfilariae avoids to be digested and becomes an L1-stage larva soon after the

Correspondence: A.P. Plaisier, Department of Public Health and Social Medicine, Medical Faculty, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

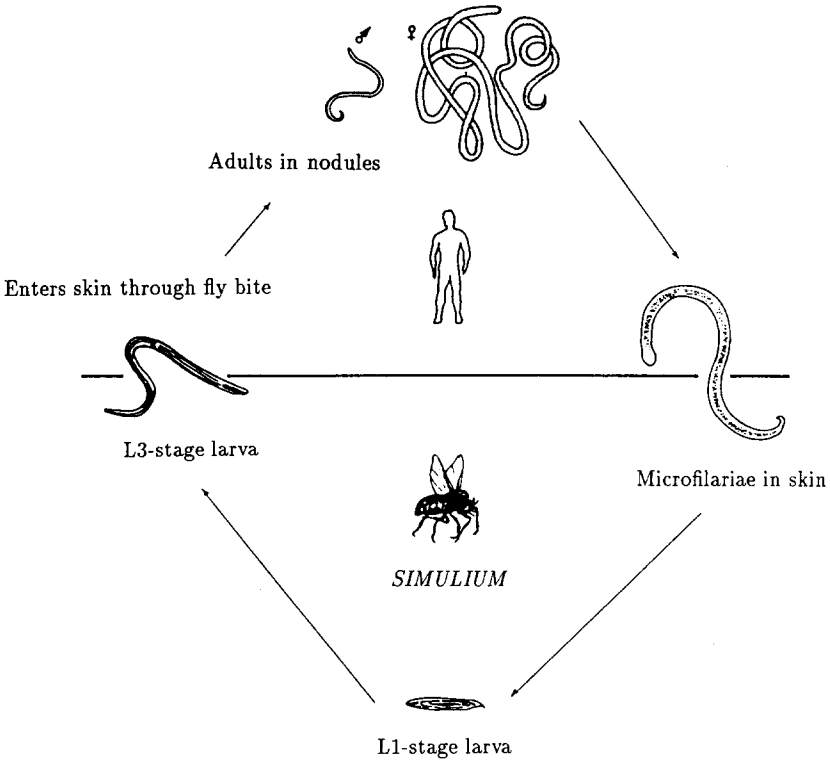

Fig. 1. Transmission and life cycle of *O. volvulus*.

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 blood meal, 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 microfilariae. Male worms are mobile and capable of mating with females in several nodules [3]. Microfilarial lifespan is estimated between 6 months and 3 years [4]. For microfilariae engorged in a fly it takes about 6–9 days to develop into the infective L3 stage [5]. Following inoculation into man, the parasite is prepatent for about 1–1.5 years [6]. The total lifespan of the worm has been estimated to be about 10–12 years on average [7,8].

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 (OCP) in West Africa, which started its activities in 1975, has proven that this method can be very successful. After 12 years of larviciding, it had achieved control of the disease in 90% of the original Programme area [9]. 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) [10], and community trials have shown that it is sufficiently safe to be used in mass treatment [11]. Until now no signifi-

cant long-term effect on the viability of the mature parasite has been observed. Regular administration of ivermectin should prevent visual decline and mass treatment has shown to lower the level of transmission [12].

Extensive entomological and epidemiological evaluation data have been collected in the OCP, and it became obvious that a biomathematical 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 [7], 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 analyse 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

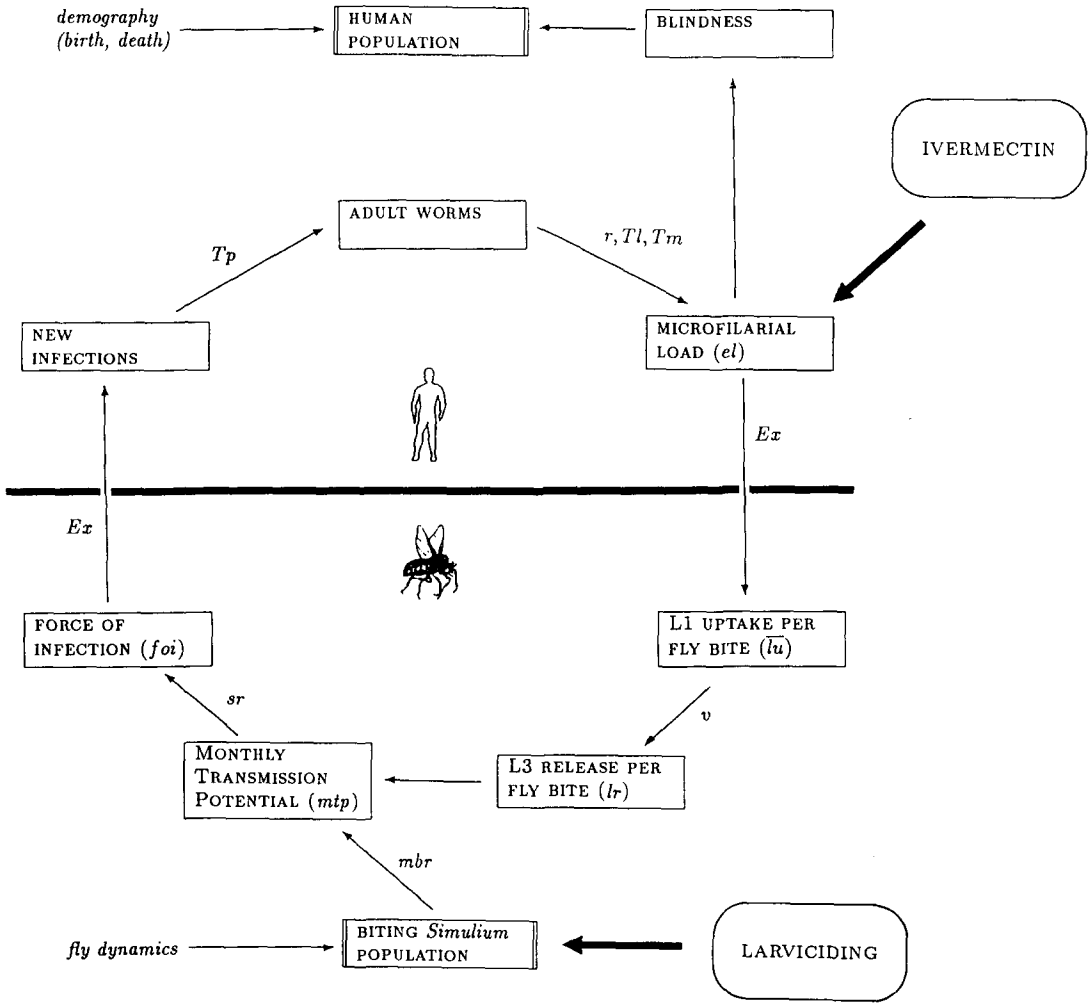

Fig. 2. Schematic representation of the structure of the model.

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 offspring 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. 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 in the 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, fixed value)
A 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 blood meals
Fly fecundity	Number of nulliparous flies resulting from a single brood of a *Simulium* fly
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 calendar month)
Fly immigration	Monthly biting rate caused by immigrating flies (for each calendar 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 L3 larvae that survives one gonotrophic cycle
Larval release	Fraction of 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

TABLE 1 (continued)

Parameter	Model specification
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

P.d.f. = probability distribution function.

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 submodels. One submodel deals with the human population and calculates the life history of the parasite in the human host. This is a stochastic submodel. The other part is a deterministic submodel which calculates the fly dynamics and the fate of the parasite in the fly. In order to carry out simulations with the model, the computer program ONCHOSIM has been developed.

2. The model

The model describes the transmission and control of onchocerciasis in an endemic focus. In Fig. 2 the structure of the model is presented schematically, with reference to the life cycle of *O. volvulus*. The most important parameters are summarized in Table 1.

2.1. The process of infection

During a blood meal of a *Simulium* fly a person can become infected with the parasite *Onchocerca volvulus*. This is indicated in Fig. 2 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 [7,13].

Beside these systematic differences, there are numerous other factors which determine exposure, such as attractivity to the flies and behavioural 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).

2.2. 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 prob-

ability distribution. After the prepatent period a female worm can start producing microfilariae if there are also mature male worms. Female worms need to mate regularly [3]. 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 microfilariae during her life. Since the exact number of microfilariae originating from one female is unknown, we introduce *mo*, the relative microfilarial offspring. This *mo* reflects the contribution of a female worm to the total microfilarial load in the human body. It is a relative measure with a maximum value of 1.

Following the onset of microfilariae production, *mo* will build up to an equilibrium value. As microfilarial longevity is fixed, this build-up phase requires a period equal to *Tm*. The equilibrium level of *mo* depends on the rate at which microfilariae 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 microfilarial load (see Section 2.7). 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 microfilarial load of a person. This microfilarial load is denoted with *el*, the effective parasite load, 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*.

2.3. Blindness

Dependent on the microfilarial load a number of microfilariae will penetrate the tissues of the skin and the eye. Immunological response to dead microfilariae 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 microfilarial load [14], and in the prevalence of blindness which is highest among old persons. In the model, the risk of getting blind is a function of the microfilarial load (denoted by *el*) accumulated over time.

In agreement with reported excess mortality among persons with eye lesions [15,16], in the model a reduction factor is applied to the residual life expectancy of blind individuals.

2.4. Skin load and infection of flies

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

$$sl = cw \times el \qquad (4)$$

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

Microfilariae in the skin can be engorged by biting and blood sucking *Simulium* flies. Following uptake in the flies, only a fraction of the microfilariae 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 microfilarial 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, see also [5] and [17]).

The probability that a fly will bite a certain individual depends on his exposure (*Ex*, see equa-

tion 1) and the following relationship is used to calculate the average L1 uptake of a fly:

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

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

2.5. 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 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:

$$lr = v \times \overline{lu} \quad (6)$$

In combination with a given monthly biting rate (*mbr*, see Section 2.6) the monthly transmission potential (*mtp*) can be calculated as follows:

$$mtp = lr \times mbr \quad (7)$$

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 [7]) which is here defined as the expected number of new infections per person per month:

$$foi = sr \times mtp \quad (8)$$

For each person i, it follows that

$$foi_i = Ex_i \times foi \quad (9)$$

The person i is assumed to become infected according to a Poisson process with rate foi_i [18].

2.6. Fly dynamics and intervention by larvicide application

The monthly biting rate (*mbr*) is calculated as the sum of the daily biting rates per person (*dbr*) 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* [19].

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 blood meal, 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.

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.

2.7. 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 microfilariae. 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 microfilarial 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 [11].

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 microfilarial load varied from 100% reduction to no reduction at all [12]. Therefore, this microfilarial 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 encorporated by the option to specify a percentage reduction of the relative productivity (r) as a function of the number of treatments a worm underwent.

2.8. *Measuring onchocerciasis*

2.8.1. *Epidemiological measures*

In routine epidemiological surveys, skin snips are taken from each person and the number of viable microfilariae per snip is counted during microscopic examination of the snip. At least two factors may cause a difference between the average skin microfilarial load (sl) and the number of microfilariae 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 some 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 [7]) 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 persons in whom the accumulated efffective parasite load exceeds a given threshold level (see Section 2.3).

2.8.2. *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.

3. 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) 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;
(2) 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 subprogram.

3.1. Vectorial part

The vectorial sub program consists of an initialisation part in which v (the transmission probability of an L1 larva, see Section 2.5) 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 Section 2.6). 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 (Section 3.2).

3.2. Epidemiological part

3.2.1. 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 low-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 Section 2.3);
(7) v the time since the last ivermectin treatment;
(8) v the instantaneous reduction in microfilarial load at the last ivermectin treatment;
(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;
(3) v the time since the last mating;

(4) v the number of ivermectin treatments the worm experienced during her life.

For male worms only the first two characteristics are needed.

3.3. Simulation procedure

3.3.1. 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 injection 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 Section 2.5).

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.

3.3.2. 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_t, see Section 2.5) and the birth of new humans.

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

$$\Delta T = \frac{-\ln u}{\sigma} \tag{12}$$

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 ΔTs exceeds 1 month.

If we follow the fate of a single worm in a given human, then the events that will occur after infection with that worm 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 become 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).

3.4. 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 *CMFL*, prevalence of blindness and the *ATP*.

Roughly, in the utilization of the program, three phases can be distinghuised: 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 microfilariae 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. 3 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*).

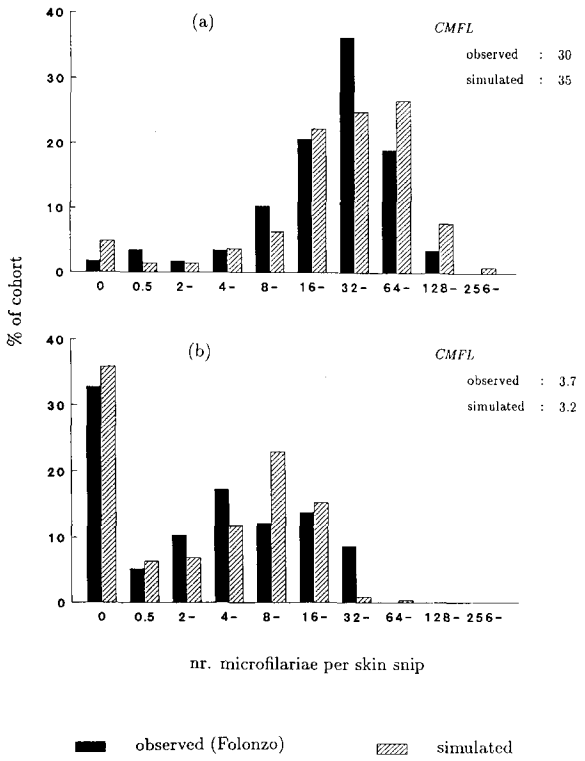

Fig. 3. Example of the simulated distribution of microfilariae per skin snip compared with the observed distribution in Folonzo (Burkina Faso) at the start of control (*a*) and after 10 years of larviciding control (*b*). Data apply to a cohort of persons that were older than 20 years at the start of control.

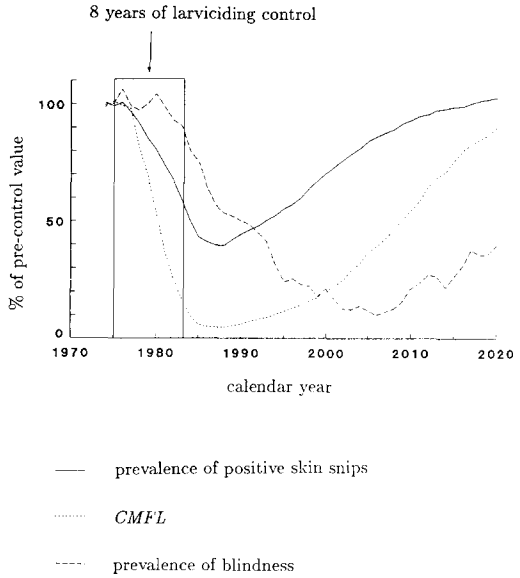

Fig. 4. Example of simulated decline in the prevalence of positive skin snips, the *CMFL* and the prevalence of blindness during 8 years of larviciding control, and of the recrudescence after stopping control too early.

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 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. 4 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.

4. 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 [20] 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 bioclimatic zones. However, it was soon pointed out that this work was based on several incorrect and misleading assumptions [21]. Partial models have been developed for certain aspects of the transmission, such as the fly dynamics [22] and the development and migration of parasite larvae in the fly [23].

A mathematical description of onchocerciasis transmission has been provided by Dietz [24] (see also the discussion in [25]). Dietz develops 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 a 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. [7] 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. 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 microcomputer configurations should make ONCHOSIM a valuable tool for research workers and decision makers in the field of onchocerciasis control.

Acknowledgements

We would like to thank Dr. E.M. Samba, Director OCP, for his support of our work. Important contributions to the development of the model were made by R.H.A. Baker, K.Y. Dadzie, G. De Sole, K. Dietz, J. Grunewald, M. Karam, D. Kurtak, D. Mulder, B. Philippon, J.F. Walsh and G. Zerbo. The development of the ONCHOSIM model was carried out on the basis of a Technical Service Agreement, number 08/181/85, provided by the World Health Organisation, on behalf of the Onchocerciasis Control Programme (OCP).

References

[1] WHO Expert Committee on Onchocerciasis, third report, Technical Report Series 752 (World Health Organisation, Geneva, 1987).

[2] A. Prost and N. Prescott, Cost-effectiveness of blindness prevention by the Onchocerciasis Control Programme in Upper Volta, Bull. WHO 62 (1984) 795–802.

[3] H. Schulz-Key and M. Karam, Periodic reproduction of *Onchocerca volvulus*, Parasitol. Today 2 (1986) 284–286.

[4] B.O.L. Duke, The effects of drugs on *Onchocerca volvulus*, I. Methods of assessment, population dynamics of the parasite and the effects of diethylcarbamazine. Bull. WHO 39 (1968) 137–146.

[5] B. Philippon, Etude de la transmission d'*Onchocerca volvulus* (Leuckart, 1893) par *Simulium damnosum* (Theobald, 1903) en Afrique tropicale, Travaux et documents de l'O.R.S.T.O.M. 63 (1977).

[6] A. Prost, Latence parasitaire dans l'onchocercose, Bull. WHO 58 (1980) 923–925.

[7] J. Remme, O. Ba, K.Y. Dadzie and M. Karam, A force-of-infection model for onchocerciasis and its application

in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area, Bull. WHO 64 (1986) 667–681.

[8] M. Karam, H. Schulz-Key and J. Remme, Population dynamics of *Onchocerca volvulus* after 7 to 8 years of vector control in West Africa, Acta Trop. 44 (1987) 445–457.

[9] WHO, Twelve years of onchocerciasis control in Western Africa, World Health Stat. Annu. (1987) 19–22.

[10] K. Awadzie, K.Y. Dadzie, H. Schulz-Key, H.M. Gilles, A.J. Sulford and M.A. Aziz, The chemotherapy of onchocerciasis. XI. A double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in Northern Ghana, Ann. Trop. Med. Parasitol. 80 (1986) 433–442.

[11] G. De Sole, J. Remme, K. Awadzi, S. Accorsi, E.S. Alley, O. Ba, K.Y. Dadzie, J. Giese, M. Karam and F.M. Keita, Adverse reactions after mass treatment of onchocerciasis with ivermectin. Combined results from eight community trials, Bull. WHO (in press).

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

[13] A. Renz, H. Fuglsang and J. Anderson, Studies on the dynamics of transmission of onchocerciasis in a Sudan-savanna area of North Cameroon, IV. The different exposure to *Simulium* bites and transmission of boys and girls and men and women, and the resulting manifestations of onchocerciasis, Ann. Trop. Med. Parasitol. 81 (1987) 253–262.

[14] K.Y. Dadzie, J. Remme, A. Rolland, B. Thylefors, The effect of 7–8 years of vector control on the evolution of ocular onchocerciasis in West African savanna, Trop. Med. Parasitol. 37 (1986) 263–270.

[15] A. Prost and J. Vaugelade, La surmortalité des aveugles en zône de savane ouest-africaine, Bull. WHO 59 (1981) 773–776.

[16] B. Kirkwood, P. Smith, T. Marshall and A. Prost, Relationships between mortality, visual acuity and microfilarial load in the area of the Onchocerciasis Control Programme, Trans. R. Soc. Trop. Med. Hyg. 77 (1983) 862–868.

[17] B.O.L. Duke, Studies on factors influencing the transmission of onchocerciasis, II. The intake of *Onchocerca volvulus* microfilariae by *Simulium damnosum* and the survival of the parasites in the fly under laboratory conditions, Ann. Trop. Med. Parasitol. 56 (1962) 255–263.

[18] A.M. Law and W.D. Kelton, Simulation Modeling and Analysis, pp. 206–210 (McGraw-Hill, New York, 1982).

[19] J.F. Walsh, J.B. Davies, R. Le Berre and R. Garms, Standardization of criteria for assessing the effect of *Simulium* control in onchocerciasis control programmes, Trans. R. Soc. Trop. Med. Hyg. 72 (1978) 656–657.

[20] A.R. Mills, A quantitative approach to the epidemiology of onchocerciasis in West Africa, Trans. R. Soc. Trop. Med. Hyg. 63 (1969) 591–602.

[21] B.O.L. Duke, Quantitative appoach to the transmission of *O. volvulus*, Trans. R. Soc. Trop. Med. Hyg. 64 (1970) 311–312.

[22] M.H. Birley, J.F. Walsh and J.B. Davies, Development of a model for *Simulium* s.l. recolonization dynamics at a breeding site in the Onchocerciasis Control Programme area when control is interrupted, J. Appl. Ecol. 20 (1983) 507–519.

[23] D. Jerwood, T. Lewis and F.W.O. Saporu, Modelling the migration of *Onchocerca volvulus* in Simuliids, using a simple compartmental process, Biometrics 40 (1984) 313–322.

[24] K. Dietz, The population dynamics of onchocerciasis, *in*: R.M. Anderson (ed.), Population Dynamics of Infectious Disease, pp. 209–241 (Chapman and Hall, London – New York, 1982).

[25] R.M. Anderson and R.M. May, Helminth infections of humans: mathematical models, population dynamics and control, Adv. Parasitol. 24 (1985) 1–101.

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 [12]. In these tables 'MFS' means microfilariae in skin snips.

-- THE ONCHOSIM PROGRAM --

January 1975, OCP_reference_village, sim EO 13334

	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	0.06	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= Mean 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	1	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= Mean 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