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

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

INTRODUCTION

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

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

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

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

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

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

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

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

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

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

FORCE-OF-ONCHOCERCIASIS-INFECTION MODEL

General considerations and definitions

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

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

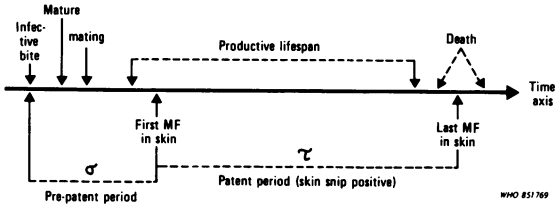

Fig. 1. Lifespan of *O. volvulus* in the human host (MF = microfilaria).

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

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

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

Model for the pre-control situation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Post-control model in adults after interruption of transmission

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

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

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

$$= 1-\exp\{-\beta\,(\sigma+\tau-y)\}$$

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

and

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

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

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

EPIDEMIOLOGICAL TRENDS PREDICTED BY THE MODEL

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

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

Epidemiological trends by age: $\beta = 0.4$

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

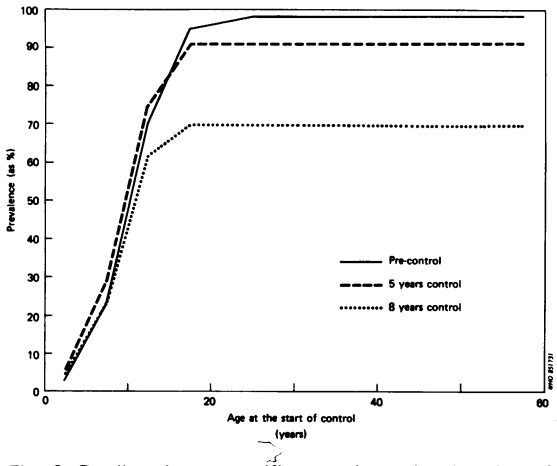

Fig. 2. Predicted age-specific prevalence by duration of control.

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

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

Relative trends by age in the intensity of infection

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

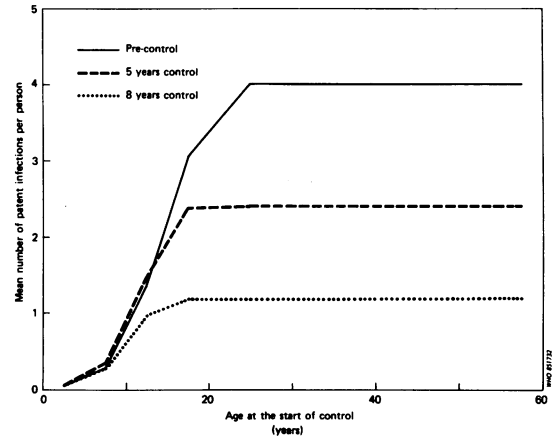

Fig. 3. Predicted age-specific mean number of patent infections by duration of control.

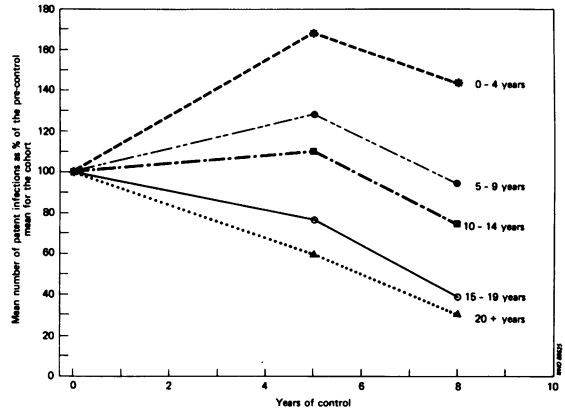

Fig. 4. Predicted relative trend in the mean number of patent infections by age cohort.

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

Epidemiological trends in adults by endemicity level

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

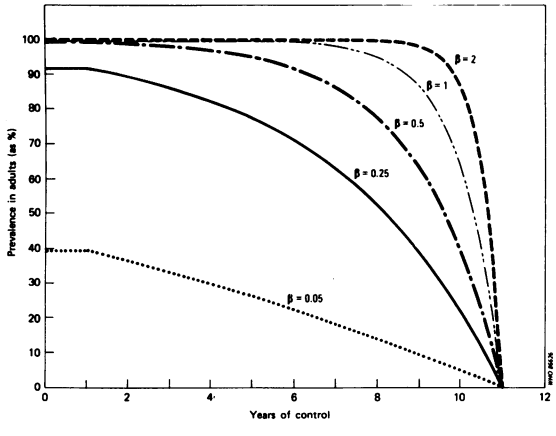

Fig. 5. Predicted trend in prevalence in cohorts of adults by endemicity level.

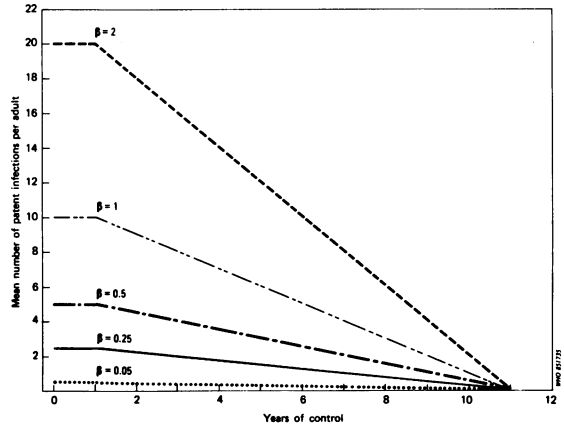

Fig. 6. Predicted trend in the mean number of patent infections in cohorts of adults by endemicity level.

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

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

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

The sample population studied

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

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

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

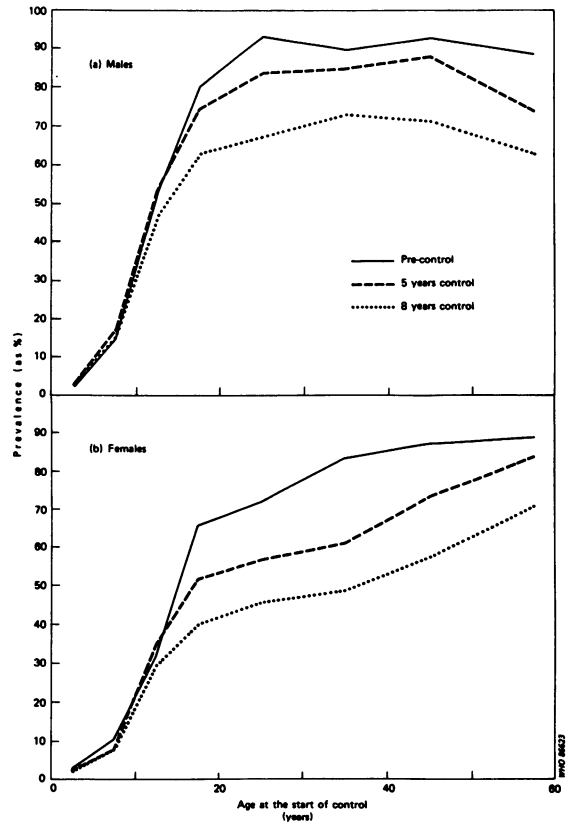

Fig. 7. Observed age-specific prevalence in males and in females by duration of control.

Epidemiological trends by age for the total sample population

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

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

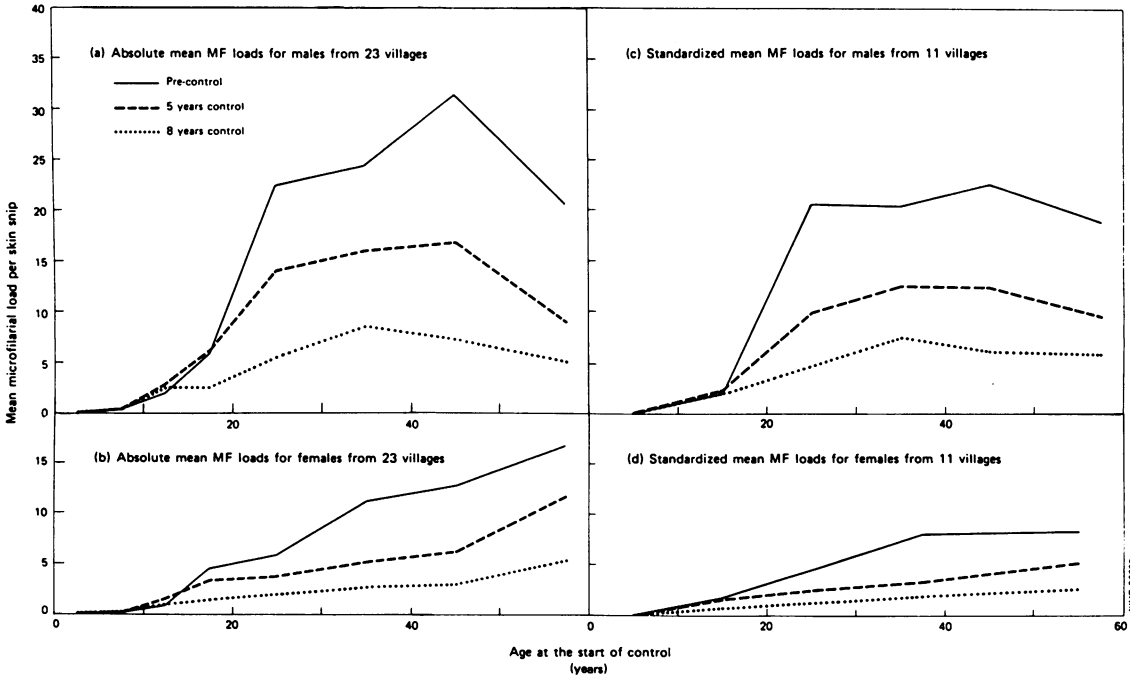

Fig. 8. Observed age-specific mean microfilarial (MF) load in males and in females by duration of control.

observed trends in the mean microfilarial load.

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

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

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

Intensity of infection after standardization. A disadvantage of pooling the data from 23 villages (Fig. 8a and 8b) is that the results may be affected by variations in the age distribution of the populations of the different villages. Overrepresentation of certain age groups in villages with a very high or a very low endemicity level may cause artificial irregularities in the epidemiological patterns by age. To correct for this we repeated the analysis after standardization for endemicity, but it was only possible to do this for the 11 largest villages, which had at least

some individuals in each of the age cohorts, and even then slightly larger age groups had to be used. The average endemicity level for these 11 villages was lower than for the local sample because the smallest villages, which were excluded, usually had the highest endemicity of onchocerciasis.

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

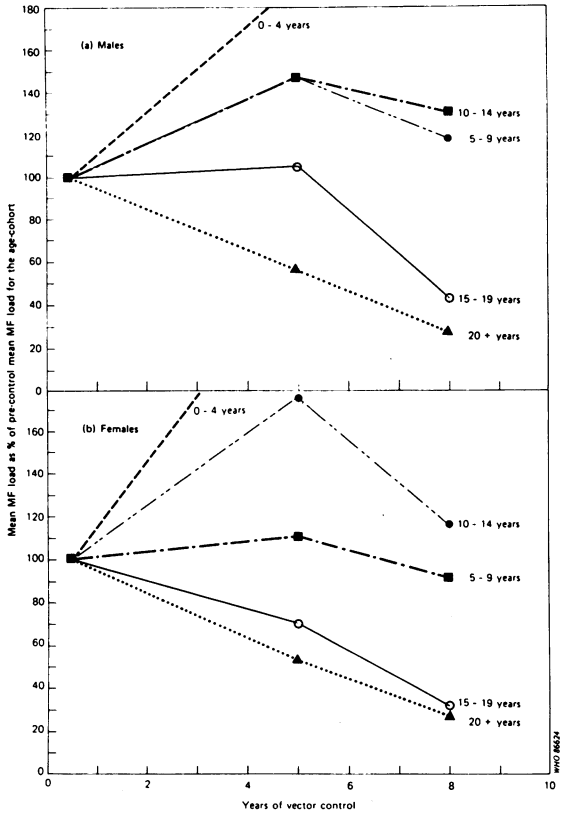

Fig. 9. Observed relative trend in the mean microfilarial (MF) load in males and in females by age cohort.

Relative trends by age in the intensity of infection

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

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

Since the microfilarial loads level off after the age of 20 years in both pre- and post-control surveys, the trends for adults are presented as one cohort for each sex. However, the hypothesis of an age-independent post-control trend for adults was further tested with an analysis of variance on the logarithm of the ratio between the post- and pre-control microfilarial count plus one per person. No significant differences were found between the adult 10-year age groups (5 years of control, $P=0.33$; 8 years of control, $P=0.19$) or between the sexes (5 years of control, $P=0.33$; 8 years of control, $P=0.51$), facts which provided further justification for pooling the results for the whole population with an initial age of more than 20 years. The observed post-control trends for both males and females agree very well with the predictions of the model. Indeed the observed trends are even

more directly linear than the predicted trend and do not clearly show the delaying effect of the pre-patent period.

Epidemiological trends in adults by endemicity level

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

Trend in prevalence in adults. The observed trends in prevalence in adults by endemicity level are shown in Fig. 10. The pre-control prevalences for the three groups with the highest endemicity levels are very similar and are all close to 100%, thus demonstrating the limitations of the prevalence as a measure of endemicity. Only for the group with less than 5 microfilariae per snip, a group poorly represented among OCP indicator villages, is the pre-control prevalence distinctly lower. The post-control prevalence figures

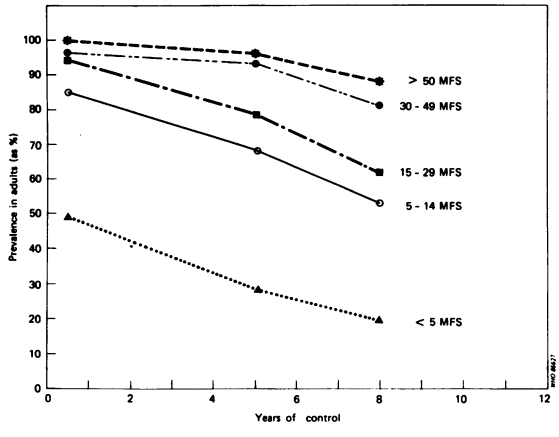

Fig. 10. Observed trend in prevalence in cohorts of adults by endemicity level (MFS = number of microfilariae per skin snip).

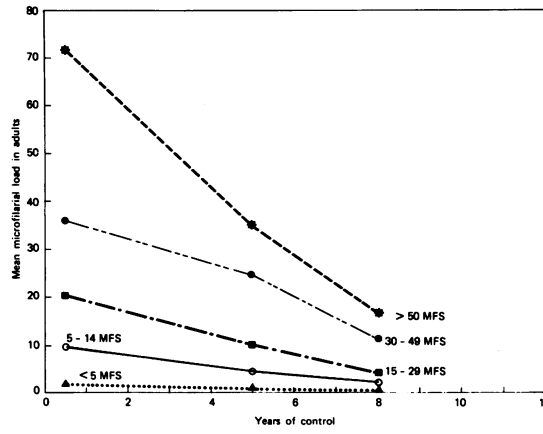

Fig. 11. Observed trend in the mean microfilarial load in cohorts of adults by endemicity level (MFS = number of microfilariae per skin snip).

observed during the first 8 years of control are comparable with the predicted trends (see Fig. 5) and show clearly that the rate of fall in the prevalence depends to a great extent on the initial endemicity level. For the two highest endemicity levels (> 50 and 30–49 mfs) there is virtually no change in the prevalence during the first 5 years of control, and only after 8 years does it begin to drop marginally. For the two next lower endemicity levels (15–29 and 5–14 mfs) the prevalence is already beginning to decrease during the first 5 years of control and the decrease becomes more rapid between the 5th and 8th years. Only in the lowest endemicity group (< 5 mfs) does the prevalence show a nearly linear decrease.

Trend in microfilarial loads in adults. Fig. 11 shows the mean microfilarial loads in adults at each endemicity level before and after control. At all levels of endemicity the mean loads show a decrease during the first 5 years of control and this continues up to year 8. For four of the endemicity levels the decrease is nearly linear and only in the group with a mean of 30–49 microfilariae is the decrease somewhat slow during the first 5 years of control. The figures for the individual subpopulations in this group showed that the slower decrease was mainly due to a different trend in one village, for which both the male and female subpopulations were classified in this endemicity group. In this village the mean microfilarial load actually increased between the pre-control survey and the 5-year follow-up, although the trend between the 5th and the 8th years of control was comparable to the other subpopulations in this group. One possible explanation of this discrepancy may be that the pre-

control data for this village were of poor quality and that the pre-control mean load had been underestimated. The largest absolute decrease was seen in the group with the highest endemicity level (>50 mfs) for which the prevalence had remained nearly constant during 8 years of control. All the regression lines show a tendency to converge on a zero point after about 10–11 years of control and the general trend is very similar to that predicted by the model (see Fig. 6).

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

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RÉSUMÉ

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

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

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

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

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

REFERENCES

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