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THE ROYAL SOCIETY

Population biology of human onchocerciasis

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Human onchocerciasis (river blindness) is the filarial infection caused by *Onchocerca volvulus* and transmitted among people through the bites of the *Simulium* vector. Some 86 million people around the world are at risk of acquiring the nematode, with 18 million people infected and 600 000 visually impaired, half of them partially or totally blind. 99% of cases occur in tropical Africa; scattered foci exist in Latin America. Until recently control programmes, in operation since 1975, have consisted of antivectorial measures. With the introduction of ivermectin in 1988, safe and effective chemotherapy is now available. With the original Onchocerciasis Control Programme of West Africa coming to an end, both the new African Programme for Onchocerciasis Control and the Onchocerciasis Elimination Programme for the Americas, rely heavily on ivermectin self-sustained mass delivery. In consequence, the need for understanding the processes regulating parasite abundance in human and simuliid populations is of utmost importance. We present a simple mathematical framework built around recent analyses of exposure- and density-dependent processes operating, respectively, within the human and vector hosts. An expression for the basic reproductive ratio, R_0, is derived and related to the minimum vector density required for parasite persistence in localities of West Africa in general and northern Cameroon in particular. Model outputs suggest that constraints acting against parasite establishment in both humans and vectors are necessary to reproduce field observations, but those in humans may not fully protect against reinfection. Analyses of host age-profiles of infection prevalence, intensity, and aggregation for increasing levels of endemicity and intensity of transmission in the Vina valley of northern Cameroon are in agreement with these results and discussed in light of novel work on onchocerciasis immunology.

Keywords: onchocerciasis modelling; infection age-profiles; parasite aggregation; regulatory processes; *Simulium damnosum sensu lato*; Cameroon

1. INTRODUCTION

Human onchocerciasis is the infection caused by the parasitic filarial nematode *Onchocerca volvulus* being transmitted from person to person by the bites of the blackfly *Simulium* vector. The parasite's developmental cycle (figure 1) comprises the long-lived adult stages (male and female worms living in subcutaneous palpable nodules (onchocercomata) or in deeper and inaccessible bundles, with an average female reproductive life span of about ten years); the embryonic, skin-dwelling microfilariae (Mf) with a mean life expectancy of 15 months (responsible for most of the pathology associated with onchocerciasis and the stage infective to vectors); larvae that do not multiply but attain infectivity to humans within the fly in roughly one week (L1 to L3), and immature stages (L4 and juvenile adults) that reach sexual maturity and start producing Mf within humans in approximately one year (Duke 1991, 1993). Because the vectors breed only in fast-flowing streams and rivers and one of the worst clinical manifestations of onchocerciasis is partial or total visual impairment, human onchocerciasis is also known as 'river blindness'. Although ocular damage is the most serious complication, the skin is the principal site of infection and of subsequent cutaneous lesions (Murdoch *et al*. 1993), the organ involved in the transmission of the parasite to and from vectors, and the means currently used for parasitological diagnosis by detection of Mf in skin snips. However, microfilarial load (mean number of Mf per milligram of skin or per snip) constitutes only an indirect and crude approximation to the true parasite burden per host. In general, it is considered that Mf load is roughly proportional to adult worm burden (Duke 1993).

In tropical Africa the parasite is prevalent over broadly continuous areas of savanna and forest in the west and over more patchy zones in the east, the West African savanna parasite populations being more pathogenic to the eye than their forest equivalents (Duke & Anderson 1972; Zimmerman *et al*. 1992). However, blinding strains are also found in forest–savanna mosaic and pure forest areas of Central Africa (WHO 1987). There are smaller onchocerciasis foci on the south-western coast of the Arabian peninsula and in tropical Central and South America (WHO 1987). The estimated total number of persons living in endemic areas and thus exposed to the risk of acquiring the parasite is 86 million. Of them, 18 million are infected, approximately 300 000 suffer from onchocerciasis-induced blindness and a similar number

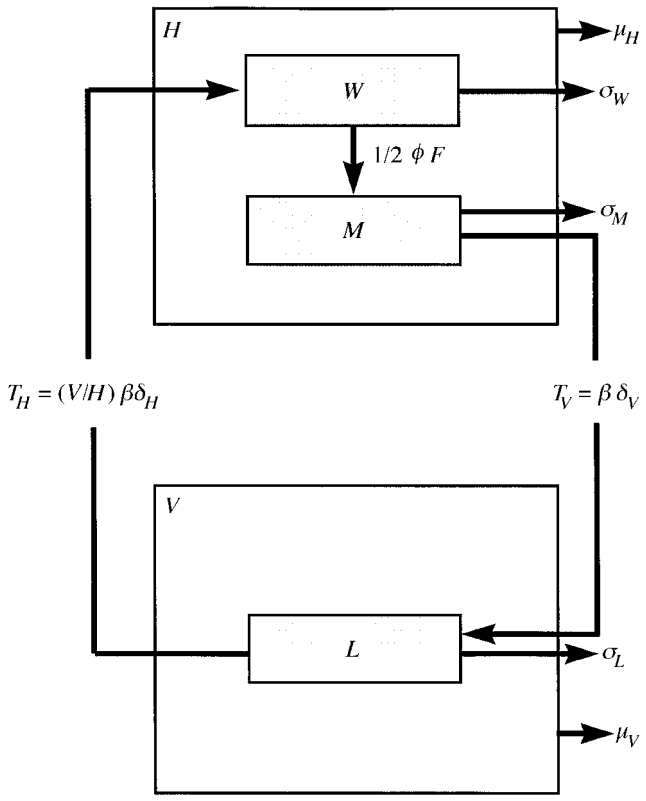

Figure 1. Flow diagram for the life-cycle of *O. volvulus*. There are two compartments, H, the human host population and V, the vector population. Within the human host there are W adult worms (50% of them are females) that produce M skin microfilariae per milligram of skin by mating with probability ϕ and per capita fecundity F. Within the simuliid vector there are L infective larvae. T_H and T_V are, respectively, the transmission rates from vector to human and from human to vector as described in table 1. Mortality rates, μ_H, μ_V, σ_W, σ_M, and σ_L are also described in table 1.

suffer from severe visual impairment. Africa and Yemen account for 99% of those infected and 99.6% of the blind, whereas the remainder are found in Latin America (Duke 1990). In the worst afflicted regions, the impact of the disease can be so extreme that fertile valleys are depopulated with serious socio-economic consequences (Prost *et al.* 1979; Nwoke 1990; Evans 1995). For this reason, river blindness has been the subject of extensive research and high expenditure control efforts mainly channelled through the Onchocerciasis Control Programme (OCP), initiated in 1974 and extended in 1986 to cover 11 countries of the Sudano–Guinean savanna belt of West Africa (WHO 1996). This programme, until recently solely based on vector control, is now supplemented in some areas with the annual use of ivermectin, a mainly microfilaricidal drug (Molyneux 1995). However, the endemic countries not included in OCP account for 84% of the total number of people infected with *O. volvulus* in Africa. As a result, a new African Programme for Onchocerciasis Control (APOC) has recently being launched in the remaining endemic areas. This initiative relies mainly on community-directed ivermectin treatment with vector control in selected foci (Remme 1995). The simuliid vectors in West Africa belong to the *S. damnosum sensu lato* species complex (Crosskey 1990). A similar chemotherapy scheme is in operation in Latin America under the auspices of the Onchocerciasis Elimination Programme for the Americas (OEPA), where the main vectors are *S. ochraceum s.l.* in Mexico and Guatemala; *S. exiguum s.l.* in Colombia and Ecuador, and *S. guianense s.l.* in the Amazonian focus between Venezuela and Brazil (Shelley 1991).

Like most macroparasitic infections, onchocerciasis is an endemic, stable, resilient and usually chronic condition in the affected communities, in which reinfection is the 'norm' and parasite prevalence may reach high levels. These characteristics are probably due, on the one hand, to the existence of density-dependent regulatory constraints on parasite population growth, and on the other hand, to the human host's inability to mount a strong protective immune response, or to do so only after many years of exposure. However, disease is not synonymous with infection but more typically with high intensity of infection (Anderson & May 1985*a*; Maizels *et al.* 1993). Since *O. volvulus* does not multiply within the human or fly hosts to increase worm numbers directly, the growth of parasite populations is basically controlled by immigration (=infection) and death processes operating at the level of the individual host. The average rates at which these immigration–death processes take place will determine observed age-profiles of infection prevalence and intensity in host populations. In human communities, mean Mf intensities may be higher in males than females (but not always), increase with age in both sexes, reach a plateau in the 15–30 year age-group and decline in the elderly (processes such as parasite-induced host mortality due to blindness, acquired immunity, and age-dependent changes in exposure, infection rate, or parasite mortality and/or fecundity could generate such patterns). Alternatively, infection may increase steadily with age and decrease only in the oldest (50+ year) age-groups (Kirkwood *et al.* 1983*a*). Broadly speaking, the former pattern is associated with transmission regimes that tend to be seasonal and less intense, whereas the latter seems to occur in places where transmission is heavy and virtually perennial.

Microfilarial prevalence and intensity, in fact two statistics of the probability distribution of worm numbers per host, are commonly nonlinearly related, such that for hyperendemic localities ($\geqslant$60% of people infected), large changes in intensity are associated with slight modifications in prevalence (Anderson & May 1985*a*; Remme *et al.* 1986). The same relationship applies to the proportion of flies with larvae and the mean larval load per fly (Basáñez *et al.* 1994, 1995). Both are the result of highly overdispersed distributions of parasite numbers per human or vector host, which have successfully been described by the negative binomial distribution (Cheke *et al.* 1982). This aggregation may contribute to stabilize the interaction between *O. volvulus* and its definitive and vector hosts by limiting the detrimental impact of the infection to that fraction of the host population harbouring high worm loads, and by making it possible for regulatory processes to influence the larger proportion of the parasite population concentrated in a few individuals (Anderson & May 1978). However, and possibly due to the scarcity of suitable animal models in which to reproduce or mimic the parasite's life cycle (with perhaps the exception of chimpanzees (Duke 1980; Soboslay *et al.*

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1991; Irvine *et al*. 1997), mangabey monkeys (Eberhard *et al*. 1991) and *O. ochengi* in its cattle host (Trees 1992)), the question still remains as to precisely where and how in this cycle the key constraints, regarded to be crucial in regulating parasite population growth, operate. This question obviously has important theoretical and practical implications. In consequence, a number of researchers have explored the properties of a variety of analytical and simulation mathematical models of the transmission dynamics of the parasite which make various assumptions regarding the processes thought to govern onchocerciasis population biology (Dietz 1982; Wada 1982; Remme *et al*. 1986; Davies *et al*. 1987; Davies 1993; Plaisier *et al*. 1990). Although some progress has been made in understanding those regulatory constraints operating within the simuliid vector (Basáñez *et al*. 1994, 1995, 1996), little progress has been made to date in exploring those acting within the human host.

This paper starts by summarizing the properties of a simple model for the transmission dynamics of *O. volvulus* developed by Basáñez (1996), whose outputs are equilibrium values of worm density per human and fly host at the community level. Intensity is used to predict prevalence assuming an overdispersed parasite distribution among hosts. We proceed to present host age-profiles of infection prevalence and intensity for increasing levels of endemicity, and their accompanying patterns of parasite aggregation, in an attempt to detect evidence supporting the operation of density dependence by the so-called 'ecological approach' (Fulford *et al*. 1996). Finally, we discuss the significance of both model results and empirical data in relation to possible mechanisms determining the regulation and stability of the host–parasite interaction. Because of its major public health importance, we concentrate on the population biology of West African savanna parasites transmitted by savanna members of the *S. damnosum* complex, namely, *S. damnosum sensu stricto* and *S. sirbanum*, with particular reference to Cameroon, a country situated outside the OCP, and therefore only recently benefiting from control interventions.

2. REGULATORY PROCESSES IN ONCHOCERCIASIS

In the sections that follow, the term average intensity of infection in humans and flies always refers to arithmetic means as the arithmetic mean is an unbiased estimator of the true mean (Fulford 1994), one of the two parameters which can characterize the negative binomial distribution (the other being k, the aggregation parameter), and the measure of central tendency used in most epidemiological and entomological surveys from West Africa in general and Cameroon in particular (Anderson *et al*. 1974*a*,*b*; Duke *et al*. 1975; Walsh *et al*. 1978; Renz & Wenk 1987; Renz *et al*. 1987*b*).

(a) *Within the simuliid host*

Basáñez *et al*. (1994) have reported that there is no strong density dependence when the relationship is examined between microfilarial load in the skin (M = mean no. Mf mg^{-1}) and microfilarial intake by the vector (m = mean no. Mf per fly). Therefore, the proportion of Mf mg^{-1} ingested per bite, a_V, can be considered to be virtually constant regardless of skin load. However, the relationship observed in fly-feeding experiments between microfilarial input, m, and infective larval output (L = mean no. L3 per fly) at the end of the extrinsic incubation period, can be described by a saturation-type curve (limitation) in simuliid species lacking a toothed cibarium, such as *S. damnosum s.l.* (Basáñez *et al*. 1995). In consequence, the proportion of ingested Mf that succeed in attaining the infective stage within the simuliid, s_V, is a monotonically decreasing function of mean microfilarial intake (figure 2*a*), and via the previously described relationship, of skin density. Basáñez *et al*. (1996) have also found evidence supporting the operation of parasite-induced mortality of infected flies under experimental conditions. The data suggest that the parasite stages mainly responsible for fly death are the ingested Mf. A linear relationship between per capita vector mortality rate and mean microfilarial intake is shown in figure 2*b* with intercept μ_V (background mortality rate of uninfected vectors), and slope α (excess mortality rate per ingested Mf).

(b) *Within the human host*

Dietz (1982) presented, for West African savanna villages, a relationship between the annual transmission potential delivered by *S. damnosum s.l.* (ATP = no. of L3 potentially received per person per year in a particular locality, Duke (1968)) and the corresponding mean intensity of skin microfilarial infection (M) in the village. According to Dietz's function, overall mean Mf load would increase with ATP at two different rates, the former corresponding to a fast linear increase when ATP $\rightarrow 0$, and the latter to a slower, but also linear, increase as ATP $\rightarrow \infty$. This relationship seemed to hold over the wider range of ATP values obtained when Basáñez (1996) expanded the original data set to include additional information of Cameroonian savanna villages from Duke *et al*. (1975) and Renz *et al*. (1987*b*). An alternative assumption, namely a saturation-type curve, was also fitted to the available data describing a relationship between intensity of transmission and mean Mf load that would level off for high values of the transmission potential (Basáñez 1996).

The relationship between ATP and M could be encapsulating regulatory processes affecting parasite establishment, parasite mortality, parasite fecundity and parasite-induced human mortality, among others. Although density-dependent regulation of *O. volvulus* microfilarial production has been suggested by Schulz-Key (1990), other authors have not found sufficient evidence supporting this (Duke 1993). In the cattle host, increasing adult worm burdens of *O. ochengi* are not accompanied by similar increases in Mf loads, yet this is not due to a reduced productivity index, defective embryogenesis or delayed release of Mf, but perhaps to immunologically mediated microfilarial mortality (Trees *et al*. 1992). A relationship between intensity of infection, blindness and higher death rates among the blind has been documented in human onchocerciasis (Prost & Vaugelade 1981; Kirkwood *et al*. 1983*b*; Prost 1986). In other filarial species such as *W. bancrofti* in humans and *B. pahangi* in the cat model, there are strong indications in favour of the operation of exposure-dependent, and possibly

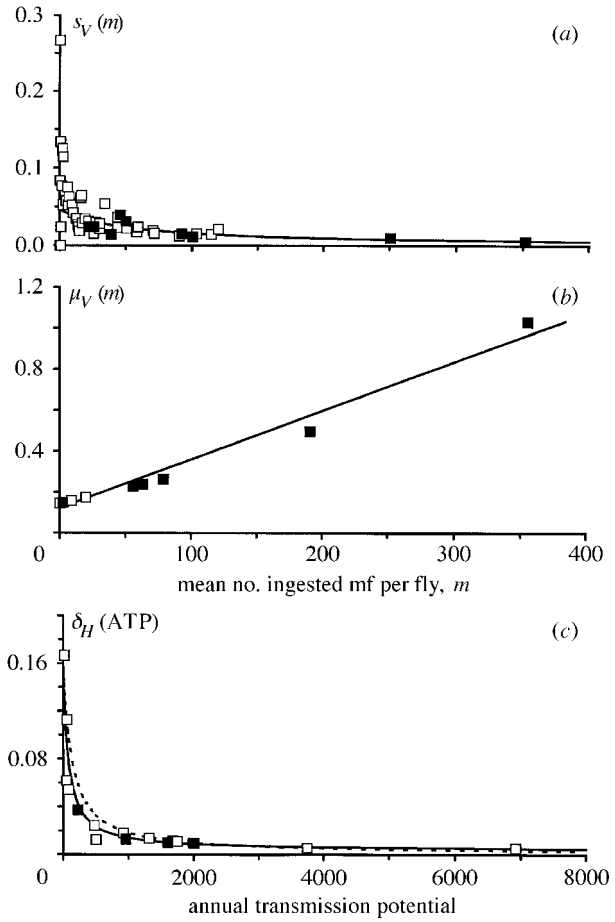

Figure 2. Density dependence functions incorporated in the model described by equations (1), (2), and (3) in the text. (*a*) The estimated (markers) and fitted (solid line) proportion of *O. volvulus* ingested Mf reaching the infective stage (s_V) within savanna species of *S. damnosum s.l.* The estimated fraction of successful parasites is the mean no. of L3 larvae per fly (L) divided by the average no. of ingested Mf per fly (m). The fitted function is $s_V(m) = s_{V_0}/(1+cm)$ with $s_{V_0} = 0.0463$ (s.e. $= 0.0097$, $p < 0.0001$) and $c = 0.0196$ Mf^{-1} (s.e. $= 0.0067$, $p = 0.0047$). Open and solid markers correspond, respectively, to data from Ghana and Burkina Faso–Côte d'Ivoire (Basáñez *et al.* 1995). (*b*) Average per capita mortality rate (calculated as the reciprocal of the life expectancy at cessation of engorgement, $1/e_0$) of simuliid vectors lacking a well-developed cibarial armature (μ_V) as a function of mean Mf intake (m). The values of e_0 have been estimated using equations (13) and (14) of Basáñez *et al.* (1996). Fitted line is the expression $\mu_V(m) = \mu_V + \alpha m$ with $\mu_V = 0.1217$ fly^{-1} day^{-1} (s.e. $= 0.0140$, $p < 0.0001$), and $\alpha = 0.0024$ fly^{-1} day^{-1} Mf^{-1} (s.e. $= 0.0001$, $p < 0.0001$). Open and solid markers for, respectively, *S. damnosum s.l.* (Cameroon) and *S. guianense s.l.* (southern Venezuela) as described in Basáñez *et al.* (1996). (*c*) The estimated (markers) and fitted (solid and dotted lines) proportion of *O. volvulus* infective larvae reaching maturity within the human host (δ_H) as a function of the total number of L3 to which a person is exposed during a whole year (ATP) in onchocerciasis endemic areas of West and Central Africa. Estimated δ_H is calculated as $M_{\text{obs}}/(\text{ATP}\,\gamma)$ with $\gamma = \phi F/[2(\sigma_W + \mu_H)(\sigma_M + \mu_H)]$. Fitted δ_H is the function $\delta_H(\text{ATP}) = (\delta_{H_0} + \delta_{H_\infty} c_{H_i}\text{ATP})/(1 + c_{H_i}\text{ATP})$ with $\delta_{H_\infty} > 0$ for the solid line and $\delta_{H_\infty} = 0$ for the dotted line. Parameter values as follows: $\delta_{H_0} = 0.16$, $\delta_{H_\infty} = 0.0032$ (s.e. $= 0.0004$, $p < 0.0001$), $c_{H_\infty} = 0.0137$ L^{-1} (s.e. $= 0.0014$, $p < 0.0001$, $c_{H_0} = 0.0078$ L^{-1} (s.e. $= 0.0007$, $p < 0.0001$). Open and solid markers represent data from, respectively, northern Cameroon (table 3) and Burkina Faso–Côte d'Ivoire (table 4).

immunologically mediated, constraints on infection rates (Denham *et al.* 1972, 1983; Vanamail *et al.* 1989; Das *et al.* 1990). These mechanisms would act against incoming parasites, not on established worms (Grenfell *et al.* 1991). Nevertheless, observations of *O. ochengi* in the cattle model (Trees *et al.* 1992) suggest that protective responses against larval stages may be incomplete and ineffective in preventing accumulation of adult worms with host age (which serves as a surrogate of cumulative exposure). It could also be argued that there is a maximum microfiladermia that can be harboured by the superficial layers of the skin (the ones reached by the devices used to take snips). A within-host microfilarial population which is increasing with exposure might invade the deep dermis and other body organs and/or fluids, yet remain undetected by standard methods of parasitological diagnosis. In the absence of more extensive data, and in agreement with the hypothesis of immunological tolerance in filarial infections (Maizels & Lawrence 1991), the opinion is favoured that, within the human host, regulation is mainly addressed against the incoming infective larvae and less so against established populations of macro- and microfilariae (Grenfell & Michael 1992). For the purposes of this paper the consequences of both a partial decrease and a total failure of larval establishment within the human host contingent on transmission intensity are explored (figure 2*c*). The former will correspond to an asymptotically linear relationship between M and ATP, whereas the latter would underlie a limitation-type curve between these two variables.

3. THE MODEL

A deterministic framework is used which mimics the rate of change over time in the mean intensity of infection, an epidemiological variable that reflects better the severity of skin and eye disease by comparison with a simple prevalence measure (Remme *et al.* 1986). Although the population biology of the host–parasite interaction will be strongly influenced by the dynamics of the longest-lived adult worm stage (Anderson 1982), model development is guided by the variables most commonly measured in field epidemiological studies, namely, the intensity of microfilarial infection in humans and the number of infective larvae in flies.

(a) *General assumptions and equations*

For the sake of simplicity, the model assumes, as a first stage in its development, populations of human and vector hosts without explicit age-structure and which are constant in size through time; it ignores intrinsic and extrinsic incubation periods in, respectively, the human or vector host, and does not consider heterogeneities in human or vector populations with respect to exposure, susceptibility or immunity to infection. Regulation of parasite population growth is assumed to take place through constraints on parasite establishment within the vector host (Basáñez *et al.* 1995), survival of infected flies (Basáñez *et al.* 1996) and parasite establishment within the human host (Dietz 1982; Basáñez 1996). The model consists of three ordinary, coupled differential equations describing the rate of change with respect to time of the mean number of adult worms per person at time t, $W(t)$;

the mean number of microfilariae per milligram of skin (Mf mg^{-1}) per person, $M(t)$; and the mean number of L3 larvae per simuliid fly, $L(t)$,

$$\frac{dW(t)}{dt}=\frac{V}{H}\beta\left(\frac{\delta_{H_0}+\delta_{H_\infty}c_{H_i}(V/H)\beta L(t)}{1+c_{H_i}(V/H)\beta L(t)}\right)L(t)-(\sigma_W+\mu_H)W(t), \quad (1)$$

$$\frac{dM(t)}{dt}=\left(\frac{1}{2}\phi F\right)W(t)-(\sigma_M+\mu_H)M(t), \quad (2)$$

$$\frac{dL(t)}{dt}=\beta\left(\frac{\delta_{V_0}}{1+c_V M(t)}\right)M(t)-\left(\sigma_L+\mu_V+\alpha_V M(t)+\frac{a_H}{g}\right)L(t). \quad (3)$$

It is assumed that, whereas the proportion of infective larvae released per bite, a_H, is density-independent, the fraction of inoculated larvae becoming established within the human host, δ_H, depends on the transmission potential, $(V/H)\beta L(t)$, i.e. on the total number of infective larvae to which a person is exposed per unit time through blackfly bites received during that time with δ_{H_0} and δ_{H_∞} as, respectively, the proportions of infective larvae reaching maturity when ATP$\rightarrow 0$ and ATP$\rightarrow\infty$. V/H is the vector to human ratio and $\beta(=h/g)$ is the biting rate per fly on humans (h is the proportion of blood meals of human origin and g is the average interval between two consecutive blood meals or mean duration of the gonotrophic cycle). In the case of asymptotic proportionality between M and ATP, $\delta_{H_\infty}>0$ and c_H is the reciprocal of the ATP value for which $\delta_H(\text{ATP})=(\delta_{H_0}+\delta_{H_\infty})/2$, and hence an inverse measure of the intensity of transmission at which there occurs a reduction in the probability of successful parasite establishment within the human host. In the alternative model ($\delta_{H_\infty}=0$), c_H would be a more straightforward measure of the severity of limitation of parasite establishment within humans. The former will be referred to as c_{H_∞}, to indicate that it will apply when $\delta_{H_\infty}>0$. The latter will be represented by c_{H_0}, corresponding to the case when $\delta_{H_\infty}=0$. Therefore, the subindices $i=0$ or $i=\infty$ of the parameter c_H represent, respectively, limitation or partial decrease of parasite establishment with increasing intensity of transmission. Adult worms will mate with a probability ϕ, half being females (sex ratio = 1.0). Inseminated, fertilized female worms produce Mf with a per capita fecundity rate, λ, which is divided by the total number of Mf-bearing milligrams of skin in an average adult to obtain a per capita, per milligram of skin, fecundity rate F. A fraction δ_V of skin Mf per bite will be ingested by, and succeed in reaching the infective stage within the vector host, with δ_{V_0} as the fraction of Mf that attain infectivity within the fly per ingested Mf when $M\rightarrow 0$, and c_V as a measure of the severity of density-dependent limitation of larval establishment, per ingested Mf. There will be losses of parasites due to adult worm mortality with per capita rate σ_W, microfilarial mortality with rate σ_M, human mortality with rate μ_H, larval mortality with rate σ_L, vector mortality with rate μ_V for uninfected flies, to skin Mf being ingested by the vector (negligible), and to larvae escaping from the fly's proboscis during feeding (since L3 may be released regardless of whether the simuliid is procuring a blood meal from human or animal hosts, this component is represented by the rate a_H/g). The per capita excess mortality of infected flies due to uptake of skin Mf is represented by α_V. All mortality rates are assumed to be constant and equivalent to the reciprocal of the life expectancy of the parasite stage or host in question, therefore, survival times are exponentially distributed. Table 1 defines the model variables and parameters described thus far. Parameter values (average, minimum and maximum) are listed in table 2 with their corresponding sources. Model solutions were obtained using Solver, a numerical integration software package that uses the fourth order Runge–Kutta method (Blythe *et al*. 1990). The input variable was the annual biting rate (ABR) recorded at each locality (tables 3 and 4).

(b) *The basic reproductive ratio and the threshold biting rate*

The basic reproductive number or ratio, R_0, is a measure of the reproductive success of the parasite between one generation and the next for a given host population in a given environment assuming no constraints on parasite population growth. For macroparasites such as *O. volvulus*, R_0 is defined as the average number of female offspring, themselves reaching maturity, produced by an adult female parasite during her reproductive life span in absence of density-dependent regulation (Anderson & May 1991). The expression, derived via local stability analysis of the system (Basáñez 1996), encapsulates all the process rates that determine the flow of a parasite through its life cycle, and defines a theoretical threshold between extinction ($R_0<1$) and persistence of the infection ($R_0>1$),

$$R_0=\frac{\phi F(V/H)\beta^2\delta_{H_0}\delta_{V_0}}{2(\sigma_W+\mu_H)(\sigma_M+\mu_H)(\sigma_L+\mu_V+(a_H/g))}. \quad (4)$$

Equation (4) provides a means to calculate the minimum or threshold biting density (TBR) below which endemic transmission cannot be maintained (R_0 would be less than 1),

$$\text{TBR}=\frac{2(\sigma_W+\mu_H)(\sigma_M+\mu_H)(\sigma_L+\mu_V+(a_H/g))}{\phi F\beta\delta_{H_0}\delta_{V_0}}. \quad (5)$$

(c) *Relationship between microfilarial prevalence and intensity*

Figure 3 shows microfilarial prevalence, p, as a function of mean skin load, M, for an independent data set of 25 North Cameroonian villages studied by Boussinesq (1991) along the Vina valley, where the fitted line corresponds to the expression,

$$p=100\left[1-\left(1+\frac{M}{(k_0M^{k_1})}\right)^{-(k_0M^{k_1})}\right]. \quad (6)$$

Equation (6) assumes that the frequency of the number of Mf per milligram per person follows a negative binomial distribution with parameters M and k, in which the latter (the aggregation parameter) is a power function of the mean (see also figure 9*a*,*b*). This relationship is used to predict infection prevalence among humans from model outputs (table 5).

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Table 1. *Definition of the variables and parameters used in the mathematical model described in equations (1), (2) and (3)*

host and parasite populations	
H	density of human hosts (assumed to be constant)
V	density of vectors (assumed to be constant)
$W(t)$	mean number of adult worms per person at time t
$M(t)$	mean number of Mf per milligram per person at time t
$L(t)$	mean number of infective larvae (L3) per fly at time t
demographic rates	
μ_H	per capita death rate of human host
μ_V	per capita death rate of vector host (uninfected)
ϕ	mating probability (polygamous, dioecious worms)
F	per capita fecundity rate of adult female worms (production of Mf per female per unit time) scaled by the total weight of Mf-bearing skin
$1/2$	proportion of female adult worms
σ_W	per capita death rate of female adult worms
σ_M	per capita death rate of dermal Mf
σ_L	per capita death rate of L3 larvae within the fly host
transmission rates	
$\mathcal{T}_H$	transmission rate from vector to human: $\mathcal{T}_H = (V/H)\beta\delta_H$, with
V/H	the vector to human density
β	the biting rate per fly on humans $= (1/g)h$
$1/g$	the biting frequency (reciprocal of the length of the gonotrophic cycle)
h	the human-blood index (fraction of blood-meals taken on humans)
$(V/H)\beta$	the biting rate per person
δ_H	the proportion of L3 larvae developing into adult worms within the human host, per bite $= a_H s_H$, comprised of
a_H	the proportion of larvae shed per bite
s_H	the fraction of inoculated L3 larvae surviving and reaching maturity within the human host
$\mathcal{T}_V$	transmission rate from human to vector: $\mathcal{T}_V = \beta\delta_V$, with
δ_V	the proportion of Mf mg^{-1} developing into infective larvae within the vector host, per bite $= a_V s_V$, comprised of
a_V	the fraction of Mf ingested per bite per milligram of skin
s_V	the fraction of ingested Mf reaching infectivity within the fly
ABR	annual biting rate: the total number of simuliid bites to which a person is exposed during a whole year, obtained by multiplying $(V/H)\beta$ by 365 because the biting rate per person is usually expressed as a daily rate
ATP	annual transmission potential: the total number of infective larvae potentially received during a whole year by a person exposed to the annual biting rate, equivalent to $(V/H)\beta L(t)$ multiplied by 365
regulation of parasite population abundance (see also table 2) within the human host	
δ_{H_0}	the proportion of L3 larvae developing to the adult stage within the human host, per bite, when $V/H\beta L(t) \to 0$
δ_{H_∞}	the proportion of L3 larvae developing to the adult stage within the human host, per bite, when $(V/H)\beta L(t) \to \infty$
c_{H_∞} $(\delta_{H_\infty} > 0)$	the reciprocal of the ATP value for which δ_H (ATP)$= (\delta_{H_0} + \delta_{H_\infty})/2$
c_{H_0} $(\delta_{H_\infty} = 0)$	the severity of density-dependent limitation of parasite establishment within the human host
within the vector host	
δ_{V_0}	the proportion of Mf mg^{-1} developing to the infective stage within unarmed[a] vectors, per Mf, per bite, when $M \to 0$ (calculated as $s_{V_0} a_V$)
c_V	the severity of density-dependent limitation of larval development within unarmed[a] vectors, per dermal Mf (calculated as ca_V)
α_V	the per capita excess vector mortality induced by the Mf parasite stage (calculated as αa_V)

[a] Unarmed vectors: those simuliid vector species lacking a well-developed cibarial armature, such as *S. damnosum s.l.*

(d) *Model results*

Tables 3, 4 and 5 summarize the epidemiological data and estimated R_0 values for those Central and West African villages for which there are detailed pre-control parasitological and entomological data. Age- and sex-adjusted microfilarial densities and prevalences have been corrected for 24 h incubation of the skin snips (Collins *et al.* 1980; Basáñez *et al.* 1994) in order to facilitate comparisons. Table 3 includes North Cameroonian villages for which the proportion of blood meals taken on humans, h, has been considered to be 0.3 on average (Disney & Boreham 1969; Renz 1987), whereas table 4 comprises data from Burkina Faso and Côte d'Ivoire for which $h = 0.67$ (Toé *et al.* 1994). Table 5 also presents predicted Mf prevalence according to equation (6), expected mean number of adult female worms per person (in the whole body), and observed and predicted mean number of palpable nodules. The latter have been obtained under the assumption that in savanna areas, each palpable nodule indicates a total of 34 live female worms in the body (Duke 1993). The average

Table 2. *Parameter values for onchocerciasis model (values are expressed per year)*

parameter	average value	minimum	maximum	source and reference
population rates				
μ_H	0.02[a]	0.0167	0.025	United Nations 1994
μ_V	26	12	52[a]	Le Berre *et al*. 1964; Millest *et al*. 1992
ϕ	1[a] (as $W^* \rightarrow 10$)	dioecious, polygamous worms		May 1977; Anderson 1982
λ	584 000	475 000	693 500	Engelbrecht & Schulz-Key 1984; Schulz-Key 1990
Mf-bearing mg of skin of an adult	875 000			Duke 1993
F	0.6674[a]	0.5423	0.7926	
sex ratio	1.0[a]			Schulz-Key & Karam 1986
σ_W	0.1[a]	0.0909	0.1111	Plaisier *et al*. 1991
σ_M	0.8[a]	0.5	1.0	Duke 1993
σ_L	52	26	104[a]	Anderson & May 1991
transmission rates and parasite population regulation				
$1/g$	104[a]	91	122	Crosskey 1990
h				
Cameroon	0.3[a]	0.2	0.4	Disney & Boreham 1969; Renz 1987
Burkina Faso and Côte d'Ivoire		0.67	1.0	Toé *et al*. 1994
δ_{H_0}	0.16[a]	0.0756	1.0	Dietz 1982; Davies 1993; this paper
a_H	0.8[a]	0.54	1.0	Duke 1973; Renz 1987
s_H	0.2[a]	0.14	1.0	Duke 1980, 1993
δ_{H_∞}	0.0032	0.0023	0.0042	this paper
c_{H_0}	0.0078	0.0063	0.0094	this paper
c_{H_∞}	0.0137	0.0106	0.0168	
S. damnosum s.l.				
a_V	0.4481[a]	0.3234	0.6226	Basáñez *et al*. 1994
s_{V_0}	0.0463[a]	0.0267	0.0658	Basáñez *et al*. 1995
c	0.0196	0.0063	0.0330	Basáñez *et al*. 1995
α	0.8653	0.7720	0.9585	Basáñez 1996

[a] parameter values used to calculate R_0 and TBR according to equations (4) and (5), respectively.

contribution of an adult female worm to the mean number of Mf per skin snip ($\mathrm{Mf\,ss^{-1}}$), ranged from two to six. Calculations were made for biopsies taken with a Holth-type punch and weighing on average 2.84 mg (Prost & Prod'hon 1978).

The following structural assumptions are tested against observed data in figure 4: density dependence operates only within the vector host ($c_{H_i} = 0$; $c_V > 0$; $a_V > 0$) in figure 4*a*; there is limitation of parasite establishment within both humans and flies plus excess mortality of infected flies ($\delta_{H_\infty} = 0$; $c_{H_0} > 0$; $c_V > 0$; $a_V > 0$) in figure 4*b*, and partial decrease of parasite establishment within humans, limitation in flies and parasite-induced vector mortality ($\delta_{H_\infty} > 0$; $c_{H_\infty} > 0$; $c_V > 0$; $a_V > 0$) in figure 4*c*. When regulation takes place solely in the simuliid, predicted equilibrium microfilarial load (M^*) grossly overestimates observed values (figure 4*a*). The inclusion of constraints limiting parasite population growth within humans improves the predictions (figure 4*b*,*c*). Agreement is better in the case of weaker constraints upon parasite establishment (figure 4*c*), namely, when there is a reduced, yet positive proportion of L3 reaching maturity as the intensity of transmission increases. In figure 5, predicted infective larval load (L^*) is compared with observed values for models with limitation of parasite establishment within humans only ($c_{H_0} > 0$; $c_V = a_V = 0$) in figure 5*a*, whereas in figure 5*b*,*c* assumptions are the same as for figure 4*b*,*c*. Open and solid markers correspond, respectively, to human blood indices, h, of 0.3 and 0.67. Regulatory constraints operating solely within humans result in model outputs that overestimate observed larval burdens in the fly population. Again, predictions improve when regulatory processes are considered to act within both human and fly hosts with best results in figure 5*c*. In general, the assumption of a low proportion of blood meals taken on humans by *S. damnosum* in Cameroonian localities (open circles) provides reasonable results with the exceptions of Bonandiga (Bo) and Touboro (To). Model results suggest that in these villages *S. damnosum* may be more anthropophilic (black circles), in agreement with Renz (1987). Conversely, considering a higher human blood index for the more western localities of Burkina Faso and Côte d'Ivoire (filled diamonds) results in higher than observed larval loads for Fétékro (F). Alternatively, the models may not be considering the true extent of parasite-induced vector mortality taking place in the field. In general, all models overestimate by far parasite loads for the village of Ndiki (N), a reason being that although the annual biting rate recorded in this locality (the single input variable for numerical solutions) is one of the highest for the area, the parous rate of *S. damnosum* is the lowest (see table 3), with the consequence that most flies are actually nulliparous and therefore non-infectious (Duke *et al*. 1975). The model in figure 4*b* underestimates the mean Mf load in Bédara (Bd), but that in figure 4*c* overestimates it (see also Fétékro and Koumbán (K)).

Table 3. *Data set from northern Cameroon used in the estimation of some parameter values (δ_{H_∞} and c_{H_i}) and in the comparison of model predictions with observations*

(The main vectors are savanna siblings of *S. damnosum s.l.*)

	ABR							R_0	
locality	estimated (TBR) or observed	Dietz (1982)	ATP[b]	M_{obs} = mean[c] no. Mf mg^{-1}	L_{obs} = mean no. L3 per fly	proportion of parous flies	reference	this work[d]	Dietz (1982)
North Cameroon, $h = 0.3$ (this paper); $h = 0.5$ (Dietz 1982)									
TBR[a]	681	720	—	—	—	—	—	1.0	1.0
Tcholliré	1000	—	17	9.6	0.017	0.24	Renz *et al.* 1987*b*	1.5	—
Nonozé[e]	2400	—	77	33.6	0.032	0.45	Renz *et al.* 1987*b*	3.6	—
Douffing	2507	2500	55	21.0	0.022	0.32	Renz *et al.* 1987*b*	3.8	3.5
Rey Manga	3053	2200	49	10.2	0.016	0.51	Renz *et al.* 1987*b*	4.6	3.1
Touboro	8960	—	922	56.4	0.103	0.40	Renz *et al.* 1987*b*	13.4	—
Larki	10 700	—	79	14.4	0.007	0.36	Renz *et al.* 1987*b*	16.1	—
Gandi-2	14 152	—	474	39.0	0.033	0.37	Renz *et al.* 1987*b*	21.2	—
Bonandiga	16 850	—	1673	64.2	0.099	0.78	Renz *et al.* 1987*b*	25.3	—
Mbai-Mboum	28 500	—	1750	65.3	0.061	0.42	Duke *et al.* 1975	42.8	—
Mayo Galké	36 157	36 200	1318	60.6	0.036	0.57	Renz *et al.* 1987*b*	54.2	50.4
Ndiki	81 000	—	500	21.0	0.006	0.13	Duke *et al.* 1975	121.5	—
Bédara	174 750	—	6925	119.0	0.040	0.38	Duke *et al.* 1975	262.1	—
Koumbán	176 500	—	3750	67.7	0.021	0.55	Duke *et al.* 1975	264.8	—

[a,b,c,d,e] See footnotes to table 4.

Table 4. *Data set from West Africa used in the estimation of some parameter values (δ_{H_∞} and c_{H_i}) and in the comparison of model predictions with observations*

(The main vectors are savanna siblings of *S. damnosum s.l.* at Nasso, Dangouadougou, and Fétékro, with a few *S. soubrense* in the latter two localities during the rainy season; the vector species at Péndié was almost exclusively *S. squamosum* from 1968 to 1974, pre-OCP.)

	ABR							R_0	
locality	estimated (TBR) or observed	Dietz (1982)	ATP[b]	M_{obs} = mean[c] no. Mf mg^{-1}	L_{obs} = mean no. L3 per fly	proportion of parous flies	reference	this work[d]	Dietz (1982)
Burkino Faso and Côte d'Ivoire, $h = 0.67$ (this paper); $h = 0.99$ (Dietz 1982)									
TBR[a]	306	288	—	—	—	—	—	1.0	1.0
Nasso[f]	2620	2600	222	28.0	0.085	n.d.	Thylefors *et al.* 1978	8.9	9.0
Péndié[f]	9674	9700	959	41.5	0.099	n.d.	Thylefors *et al.* 1978	32.9	33.7
Dangouadougou[g]	21312	21300	1601	54.3	0.075	n.d.	Thylefors *et al.* 1978	72.5	74.0
Fétékro[g]	47993	48000	1948	66.0	0.041	n.d.	Thylefors *et al.* 1978	163.2	166.7

[a]Threshold biting rate calculated with equation (5) with parameter values as those marked with [a] in table 2.
[b]Values for ATP are annual averages weighted by the fraction of time spent by the population at the fly-catching locations around the village (Renz *et al.* 1987*a*).
[c] Arithmetic means: values for Thylefors *et al.* (1978) have been calculated from the original data set by Dietz (1982); those of Renz *et al.* (1987*b*) have been divided by two to transform Mf ss^{-1} into Mf mg^{-1} according to Dietz (1982). All values have been adjusted for age and sex by the authors using the OCP standard population (Moreau *et al.* 1978) and corrected for 24 h incubation of skin snips following Collins *et al.* (1980) and Basáñez *et al.* (1994). Values from Duke *et al.* (1975) are standardized by the direct method.
[d] R_0 has been estimated according to equation (4), with parameter values as those marked with [a] in table 2.
[e] Nonozé is probably not at endemic equilibrium (Renz & Wenk 1987) and, therefore, it is excluded from subsequent analyses.
[f] Burkina Faso.
[g] Côte d'Ivoire.
n.d., not determined.

It may be concluded that in spite of the fact that this preliminary framework does not incorporate many of the characteristic complexities of host–macroparasite interactions, it does seem to capture some essential features of the system at endemic equilibrium, highlighting the relative contributions to parasite population regulation of processes operating in both the definitive and intermediate host. We have thus far ignored explicit age-structure of host populations and heterogeneity of parasite loads. Analysis of the relationship between microfilarial prevalence and intensity at the community level (equation (6) and figure 3) has already pointed out that the distribution

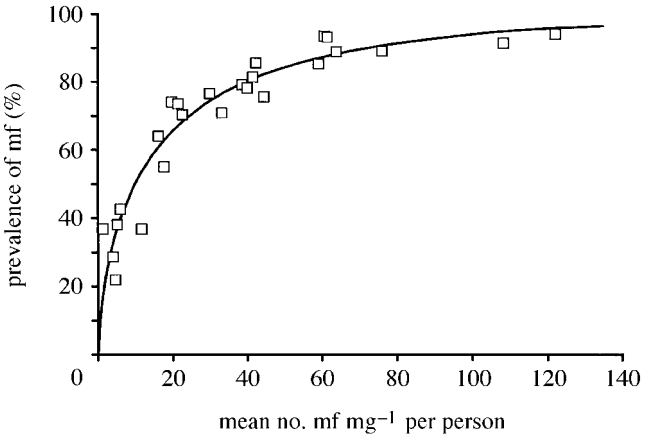

Figure 3. Observed and fitted microfilarial prevalence as a function of mean microfilarial load per person in the community for 25 north Cameroonian villages studied by Boussinesq (1991) and Boussinesq *et al.* (1997) (sample sizes ranging from 19 to 460 per village). The markers correspond to the age- and sex-adjusted Mf prevalence in the community using the whole studied sample (4576 people) as the reference population (direct method). The fitted line is the function given in equation (6) with $k_0 = 0.0553$ and $k_1 = 0.4910$. This fit improved significantly the likelihood of the model when compared to an alternative function in which the aggregation parameter was a linear function of mean Mf burden (log-likelihood ratio statistic = 18.78, $p < 0.0001$).

of microfilarial counts among humans must be highly overdispersed with a variable degree of aggregation (the parameter k is a function of the mean). We now focus on the examination of age-profiles of infection prevalence, intensity, and parasite aggregation in the human host population.

4. AGE-PROFILES OF INFECTION

Observed and expected age-specific patterns of parasite prevalence, intensity and aggregation have been compared in a variety of helminth infections in an attempt to detect, by indirect methods (the so-called 'ecological' approaches, Fulford *et al.* (1996)), evidence of mechanisms regulating or influencing parasite abundance in host populations (Anderson & May 1985*b*). The basic immigration-death model, with constant rate of infection (Λ) and per capita parasite mortality rate (σ), predicts that when net immigration is balanced by net mortality, infection intensity reaches an equilibrium value in the host population given by Λ/σ. In an intensity versus age relationship this translates into mean parasite loads increasing with age at a rate determined by $1/\sigma$ (the parasite's life expectancy) and levelling off once the equilibrium is reached (Anderson & May 1991). Since in the absence of any constraints to parasite population growth worm burden would simply increase exponentially with age without reaching a steady state, any observed pattern in which parasite loads depart from this expectation may be taken as evidence of processes (regulatory, environmental or behavioural) altering the components of the gain and/or the loss terms of the equation. Modifications to the basic immigration-death model that include the possible development of acquired immunity addressed to various parasite stages (resulting in decreased parasite establishment and/or survival and/or fecundity), the operation of parasite-induced host mortality or other forms of density dependence contingent on host age and experience of infection, or the consideration of variable exposure and forces of infection (within and/or between age-classes), predict that age-intensity curves may exhibit a maximum rather than simply levelling off. This phenomenon has commonly (but incorrectly) been referred to in the parasitological literature as convexity (in mathematical terms a convex function has a minimum, not a maximum, Borowski & Borwein (1989)). It is also expected that the degree of parasite aggregation may change with age (Anderson & Gordon 1982; Pacala & Dobson 1988). Two of the predictions that have been most tested against field observations are those of a 'peak shift' (the age at which intensity reaches its peak tends to be younger the more intense the transmission in the community) and a decrease with age in the overdispersion of parasite counts among hosts (Woolhouse *et al.* 1991; Fulford *et al.* 1992, 1996; Michael & Bundy 1998). Null models that reproduce these patterns in the absence of density dependence have also been explored (Fulford *et al.* 1992; Woolhouse *et al.* 1994). In the rest of this section we examine age- and sex-related patterns of *O. volvulus* Mf prevalence, intensity and frequency distribution for the 25 North Cameroonian savanna villages presented in figure 3, grouped according to endemicity levels (see Boussinesq *et al.* (1997) for details of their geographical location along the Vina valley).

(a) *Levels of endemicity and intensity of transmission in the community*

For each village, the age- and sex-adjusted Mf prevalence and arithmetic mean intensity were calculated using the direct method (Kirkwood 1988). Visual inspection of infection profiles did not show evidence of rapid changes of infection status with host age of the type documented for other helminths (Anderson & May 1985*b*); host populations were therefore divided into broad age-bands to ensure reasonably large sample sizes. To ensure that once grouped into transmission categories, the sample size per sex- and age-class was at least 40 people, villages were classified into four endemicity ranks as follows: (I) mean intensity, $M \leqslant 10$ Mf mg^{-1} and prevalence, $p \leqslant 50\%$; (II) $10 < M \leqslant 35$ Mf mg^{-1}, $50\% < p \leqslant 75\%$; (III) $35 < M \leqslant 50$ Mf mg^{-1}, $75\% < p \leqslant 85\%$; and (IV) $M > 50$ Mf mg^{-1}, $p > 85\%$. This classification is somewhat arbitrary as it does not follow the criteria proposed by Prost *et al.* (1979) for hypo-, meso- and hyperendemicity in the OCP. However, it is adequate for the objectives of reflecting the intensity of transmission in the community as we shall now explain.

In absence of detailed entomological information for each locality, an approximation was obtained by comparison with the published data summarized in tables 3 and 4. Some of the villages included in this work are actually the same or in very close geographical proximity to those presented by Renz *et al.* (1987*b*) and Duke *et al.* (1975). Thus, the village of Bonandiga ($M = 62$ Mf mg^{-1}, $p = 93\%$) is the same as in Renz & Wenk (1987) with an ATP of about 1700 L3 per person per year (64 Mf mg^{-1}, 85%). The village of Koumbán ($M = 76$ Mf mg^{-1}, $p = 89\%$) is the same as in Duke *et al.* (1975) (ATP $\approx$ 3800, $M = 68$ Mf mg^{-1}, $p = 93\%$),

Table 5. *Observed* (p_{obs}) *and predicted* (p_{pred}) *microfilarial prevalence; mean number of adult female worms* (W_f) *mean number of palpable nodules per person* (PN) *and average contribution of an adult female worm to the mean number of Mf per skin snip for savanna villages in northern Cameroon, Bukina Faso and Côte d'Ivoire*

(Simuliid vectors belong to the *S. damnosum* complex as indicated in tables 3 and 4.)

	prevalence of Mf (%)			mean no. adult female worms per person		mean no. palpable nodules per person			average contribution of a female worm to Mf ss^{-1}	
locality	p_{obs} [a]	p^*_{pred} [b] for $\delta_{H\infty}=0$	p^*_{pred} [b] for $\delta_{H\infty}>0$	W^*_f [c] for $\delta_{H\infty}=0$	W^*_f [c] for $\delta_{H\infty}>0$	PN_{obs}	PN*[d] for $\delta_{H\infty}=0$	PN*[d] for $\delta_{H\infty}>0$	ss Mf worm^{-1} [e] for $\delta_{H\infty}=0$	ss Mf worm^{-1} [e] for $\delta_{H\infty}>0$
Tcholliré	49.5	52.6	46.4	5.4	4.3	—	0.2	0.1	5.8	5.5
Rey Manga	51.9	79.9	72.0	41.5	28.8	—	1.2	0.8	2.7	2.6
Nasso	54.8	84.7	77.4	57.3	39.0	—	1.7	1.1	2.6	2.5
Douffing	62.2	77.5	69.7	35.4	25.4	—	1.0	0.7	2.8	2.7
Larki	65.9	86.9	80.7	67.7	47.0	—	2.0	1.4	2.5	2.5
Péndié	70.3	88.2	84.7	75.8	55.8	—	2.2	1.6	2.4	2.6
Touboro	71.0	86.4	79.7	65.4	44.9	—	1.9	1.3	2.5	2.5
Gandi-2	71.8	87.5	82.2	71.5	50.8	—	2.1	1.5	2.4	2.5
Dangouadougou	73.0	88.9	90.3	80.0	77.1	—	2.4	2.3	2.4	2.7
Fétékro	76.0	89.2	95.9	82.3	122.9	—	2.4	3.6	2.4	2.9
Bonandiga	85.2	87.8	83.2	73.5	52.9	—	2.2	1.6	2.4	2.5
Ndiki	89.2	89.1	94.0	81.9	103.1	0.8	2.4	3.0	2.4	2.8
Mayo Galké	91.6	88.7	88.5	79.2	68.8	—	2.3	2.0	2.4	2.7
Koumbán	92.9	89.3	98.0	83.1	177.1	1.0	2.4	5.2	2.4	2.9
Mbai-Mboum	94.3	88.5	86.4	77.7	62.5	2.0	2.3	1.8	2.4	2.6
Bédara	98.0	89.3	98.0	83.1	175.0	2.6	2.4	5.1	2.4	2.9

[a] Overall Mf prevalence adjusted for age and sex and corrected for 24 h incubation of skin snips as indicated in tables 3 and 4.
[b] Prevalence of Mf expected according to equation (6) with parameter values as in figure 3 and mean Mf load as predicted by models in figure 4*b*,*c*.
[c] Since the predicted total number of worms is generally above ten, our assumption of $\phi = 1$ is justified (May 1977; Anderson & May 1985*a*).
[d] Each palpable nodule in West African savanna indicates, on average, a total of 34 live female worms in the body (Duke 1993).
[e] It has been considered that one skin snip weighs on average 2.84 mg according to Prost & Prod'hon (1978).

and the villages of Babidan and Koubao (respectively, 108 Mf mg^{-1}, 91%, and 122 Mf mg^{-1}, 94%) are very close to Bédara in Duke *et al.* (1975) (ATP $\approx$ 7000, 119 Mf mg^{-1}, 98%). These villages are all included in group IV. (Notice the similarity in intensity and prevalence between surveys carried out more than ten years apart, attesting for the strong stability and resilience of these parasite populations.) It is therefore reasonable to assume that for group I, transmission levels may be similar to those recorded in Tcholliré and Rey Manga (ATP between 20 and 50); for group II they could be similar to those reported for Douffing, Nonozé, Larki, and perhaps Ndiki ($50 < \text{ATP} < 500$); for group III, transmission intensity might be equivalent to that experienced in Gandi-2, Touboro, and Péndié (ATP between 500 and 1000), whereas for group IV ATP levels may well surpass 1000 L3 per person per year.

(b) *Prevalence and intensity profiles*

Figure 6 shows cross-sectional age-prevalence profiles for females (figure 6*a*) and males (figure 6*b*) for the four transmission ranks. In general, the proportion of people infected with *O. volvulus* Mf increases with age up to the 15–19 year age-class and tends to plateau thereafter with the exception of the females in category II, who show a monotonic increase with age. This trend of onchocercal infection to increase with age in the females is even more apparent in the intensity versus age-profiles, in marked contrast with the equivalent patterns for the males, who tend to reach a plateau from the 15–19 year age-group onwards (figure 7). There is no evidence of intensity markedly peaking and declining regardless of transmission category, neither is there a peak shift towards younger age-classes as observed in schistosome, hookworm and lymphatic filarial infections. A plot of the maximum Mf intensity against the age at which this maximum is reached for each separate village confirms that females tend to continue acquiring infections as age progresses whereas males tend to reach maximum Mf levels between 10 and 20 years of age regardless of the intensity of infection in the community (figure 8).

(c) *Parasite aggregation*

The negative binomial provided an adequate model for most of the Mf frequency distributions among hosts grouped by sex, age-group and transmission category. Mean intensity- and host age-related changes in the degree of parasite aggregation were measured both by the parameter k of the negative binomial (an inverse measure of overdispersion) and the variance over mean ratio (VMR), the latter correlating better with the maximum no. Mf mg^{-1} (tail end) of each distribution (figure 9*e*,*f*). Both indices showed a positive relationship with mean Mf load (figure 9*a*–*d*), but a less clear variation with age (figure 10*a*,*b*). Although k showed some increase with age, particularly up to the 15–19 year age-class, the data did not exhibit a systematic decrease in the degree of Mf aggregation for the older age-groups, this also being evident from inspection of the scatter plots depicted together with mean Mf burdens in figure 7.

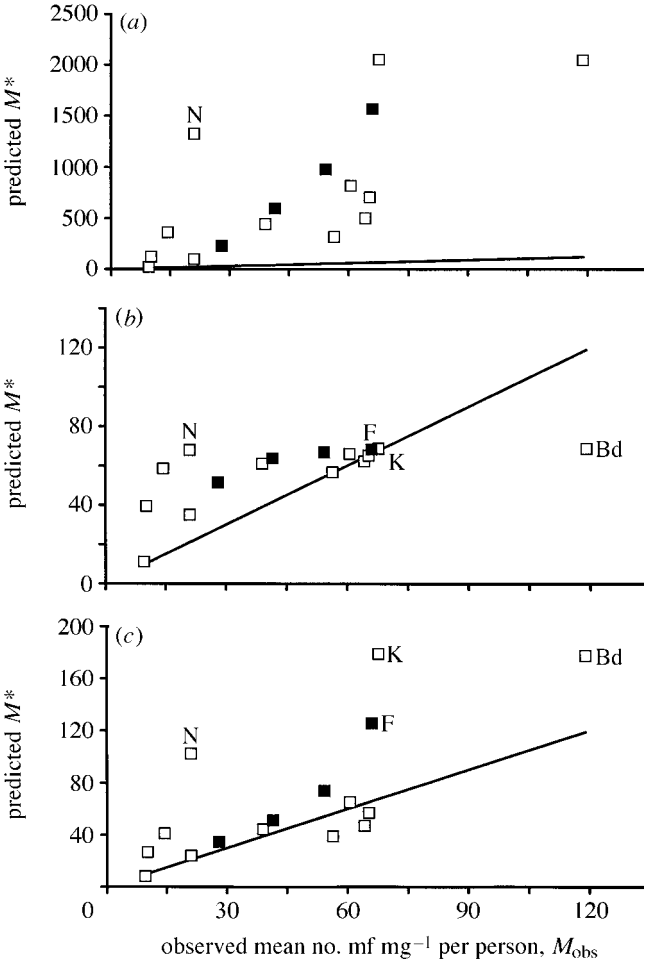

Figure 4. Model outputs (predicted equilibrium Mf burden per person, M^*) as compared with field observations (M_{obs}) for the following assumptions (solid line represents perfect agreement); (*a*) limitation of microfilarial establishment within the simuliid host (as in figure 2*a*), parasite-induced vector mortality (figure 2*b*), and no regulation within the human host ($\delta_H = \delta_{H_0}$); (*b*) limitation of Mf establishment within the fly (figure 2*a*) and of L3 establishment within humans (as in dotted line of figure 2*c*, $\delta_{H\infty} = 0$), plus excess mortality of infected vectors (figure 2*b*); (*c*) density-dependent limitation (figure 2*a*) and vector mortality (figure 2*b*) in the simuliid host, and partial decrease of L3 establishment within humans (as in solid line of figure 2*c*, $\delta_{H\infty} > 0$. Open markers for North Cameroonian localities; closed markers for those in Burkina Faso and Côte d'Ivoire. N, Ndiki; F, Fétékro; K, Koumbán; Bd, Bédara.

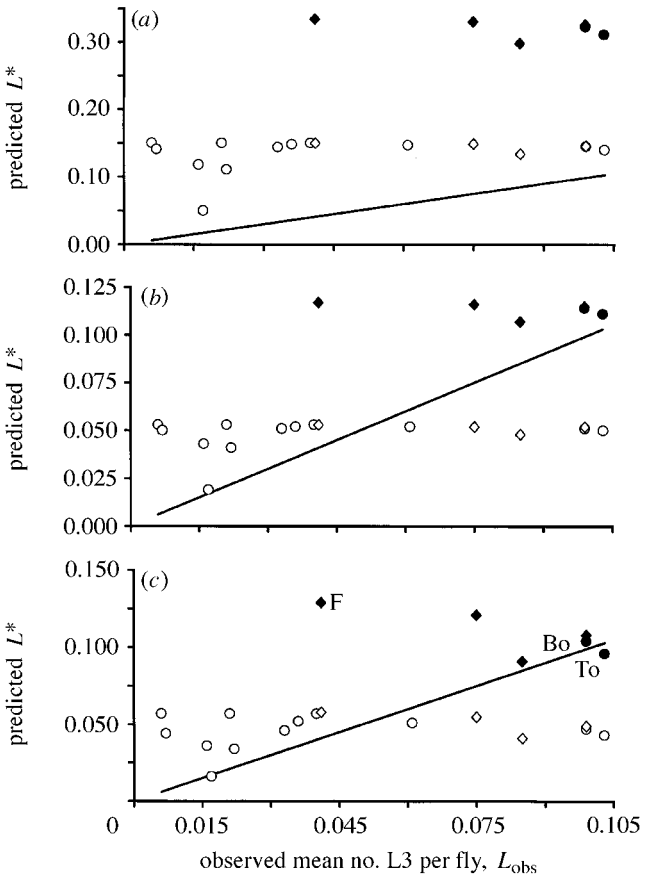

Figure 5. The predicted mean larval load per fly at equilibrium (L^*) versus field values (L_{obs}) for the following assumptions (solid line represents perfect agreement between model outputs and observations): (*a*) limitation of parasite establishment in the human host only (no regulation takes place in the fly); (*b*) and (*c*) as in figure 4*b*,*c*, respectively. Open markers assume that, *h*, the human-blood index is 0.3, whereas closed markers correspond to $h = 0.67$ (circles for north Cameroon and diamonds for B. Faso–C. Ivoire). F, Fétékro; Bo, Bonandiga; To, Touboro.

5. DISCUSSION

Despite its simplicity, model results highlight the relative contribution of processes regulating the abundance of *O. volvulus* populations operating within both human and vector hosts. In the absence of constraints to parasite population growth within humans, limitation and parasite-induced vector mortality seem insufficient to reproduce observed equilibrium worm burdens per person (figure 4*a*). On the other hand, the assumption of regulatory mechanisms operating within humans only (the host harbouring the longest-lived parasite stage) is not sufficient to yield values of the mean number of L3 per fly comparable to those recorded in the field (figure 5*a*). Best results are achieved when constraints are assumed to act against parasite establishment within both humans and flies, although mechanisms operating against incoming parasites within humans might be relatively weak (figures 4*c* and 5*c*). For the development of the OCP-derived simulation model ONCHOSIM, Plaisier *et al.* (1990) considered that the most important density-dependent mechanism was limitation of L3 output in savanna *S. damnosum*, with excess mortality of the blind as a minor process (Habbema *et al.* 1996). Our results suggest that parasite-induced vector mortality may also play an important role, and that additional mechanisms may be taking place in the definitive host. However, the model presented here ignores important complexities taken into account by ONCHOSIM, such as age-structure of host and parasite populations, age-dependent exposure to blackfly bites and heterogeneity between humans (Plaisier 1996).

Our estimates of R_0 and threshold biting rates (tables 3 and 4) are in very good agreement with those presented by Dietz (1982). The values of the basic reproductive ratio ranged from 1.5 (Tcholliré, with an ABR = 1000 bites per person per year) to 167 (Fétékro, ABR = 48 000 bites per person per year) and 265 (Koumbán, ABR = 177 000

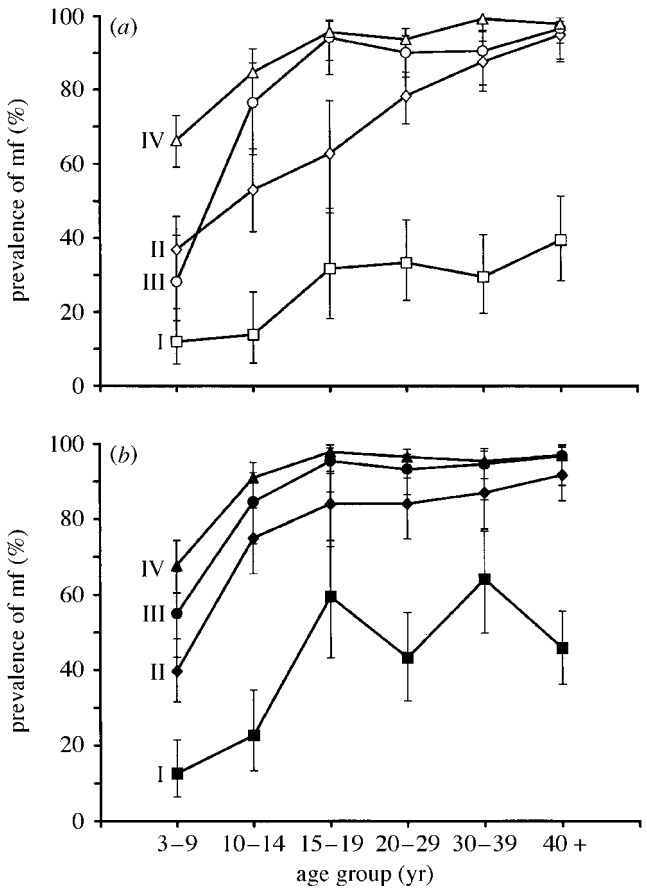

Figure 6. Age-profiles for the prevalence of skin microfilariae (%) in 25 North Cameroonian villages classified into four ranks (I–IV) according to their increasing endemicity level and transmission intensity (see text). Error bars are the exact confidence limits for the proportion of people infected in each age-class. (*a*) Open markers for females; (*b*) closed markers for males.

bites per person per year). At endemic equilibrium, however, effective reproductive ratio, R, must be equal to 1, density dependence curbing what, depending on local blackfly density, survival and anthropophily, among other conditions, may be an intrinsically high parasite reproductive potential. Everything else being equal, a biting rate of savanna *S. damnosum* of at least 700 bites per person per year is required for onchocerciasis to persist endemically when approximately one-third of the blood meals are taken from human hosts (a situation prevalent in northern Cameroon according to Renz (1987)). The higher anthropophily reported for more western locations (two-thirds of the blood meals are of human origin in Burkina Faso and Côte d'Ivoire, Toé *et al.* (1994)) results in a minimum vector density of about 300 bites per person per year.

These results contrast, however, with estimates of the threshold biting rate presented by ONCHOSIM, where TBR is calculated as follows (equation and parameter values from Habbema *et al.* (1996)): $1/(2\,a\,b\,cw\,Tl\,sr\,v)$, where a and b are parameters of the density dependence function regarding the parasite within the vector; cw is the maximum contribution to microfiladermia per fecund female worm at peak fecundity; Tl is the life expectancy of adult female parasites; sr is the proportion of L3 larvae maturing within the human host; and v is the probability of microfilarial establishment, survival and development within, and delivery by, the fly (including the fraction of blood meals taken on non-human hosts, z). With $a=1.2$; $b=0.0213$; $cw=7.6$ skin snip Mf per worm; $Tl=10$ years; $sr=0.0031$; $v=0.073$; and $z=0.04$, the threshold ABR would be equal to 1137 bites per person per year with $h=0.96$ $(1-z)$. As summarized in table 3, endemic parasite persistence has been reported for villages such as Tcholliré, with ABR values of 1000 and h of about 0.2 (Renz 1987). For Tcholliré, a village very close to the threshold biting rate and basic reproductive number, Mf prevalence is already sufficient to classify this locality as mesoendemic according to Prost *et al.* (1979). This fact confirms doubts expressed by other authors as to whether there is sustainable onchocerciasis transmission in hypoendemic localities (Tada *et al.* 1979).

It is interesting to notice that the proportion of infective larvae attaining maturity within the human host (parameter *sr*) in ONCHOSIM is taken to be equal to 0.0031 (Habbema *et al.* 1996), remarkably close to our δ_{H_∞} (0.0032), which prevails when ATP levels are high and community microfilarial loads become asymptotically proportional to the annual number of L3 larvae potentially received per person (i.e. when constraints against parasite establishment become less effective). The assumption embedded in ONCHOSIM of a lack of important regulatory processes in the human host may stem from its calibration with data deriving mainly from hyper- to holoendemic areas with high intensities of transmission (Plaisier 1996).

The predicted mean number of palpable nodules and adult female worms per person agrees well with the few observations available. Apart from the results presented in table 5, an extensive survey in Sudan–savanna locations of Cameroon showed that in a total of 11 villages, selected because of their degrees of transmission varying from low to intense, males and females had, respectively, mean numbers of 4.1 and 2.3 nodules per person (Anderson *et al.* 1974*b*). A nodulectomy trial in Burkina Faso revealed that in the village of Kourougbele, with a mean infection intensity of 25–38 Mf mg^{-1} (similar to that of Nasso), there was an average of four palpable nodules per person. The number of worms isolated by application of the collagenase technique to all excised onchocercomata, resulted in a mean of 37.4 females per person (Albiez 1983; Albiez *et al.* 1984). The correspondence between the microfilarial load in the skin and the estimated number of female parasites in the body is also strikingly similar to estimates derived from the more complex ONCHOSIM model. In order to maintain a community microfilarial load of 60 Mf ss^{-1} there would have to be 25–35 adult females per person (Alley 1992). Average skin densities of 30 and 71 Mf ss^{-1} would correspond to mean adult female burdens equal to 7.3 and 16.7, respectively (Remme *et al.* 1995).

Model results suggest that human host protection against reinfection may be rather incomplete, with parasite loads becoming proportional to the average force of infection as the intensity of transmission increases, and with it, overall host exposure to parasite antigens. Age-profiles of infection seem to confirm this expectation as mean Mf loads level off in both sexes for the lighter

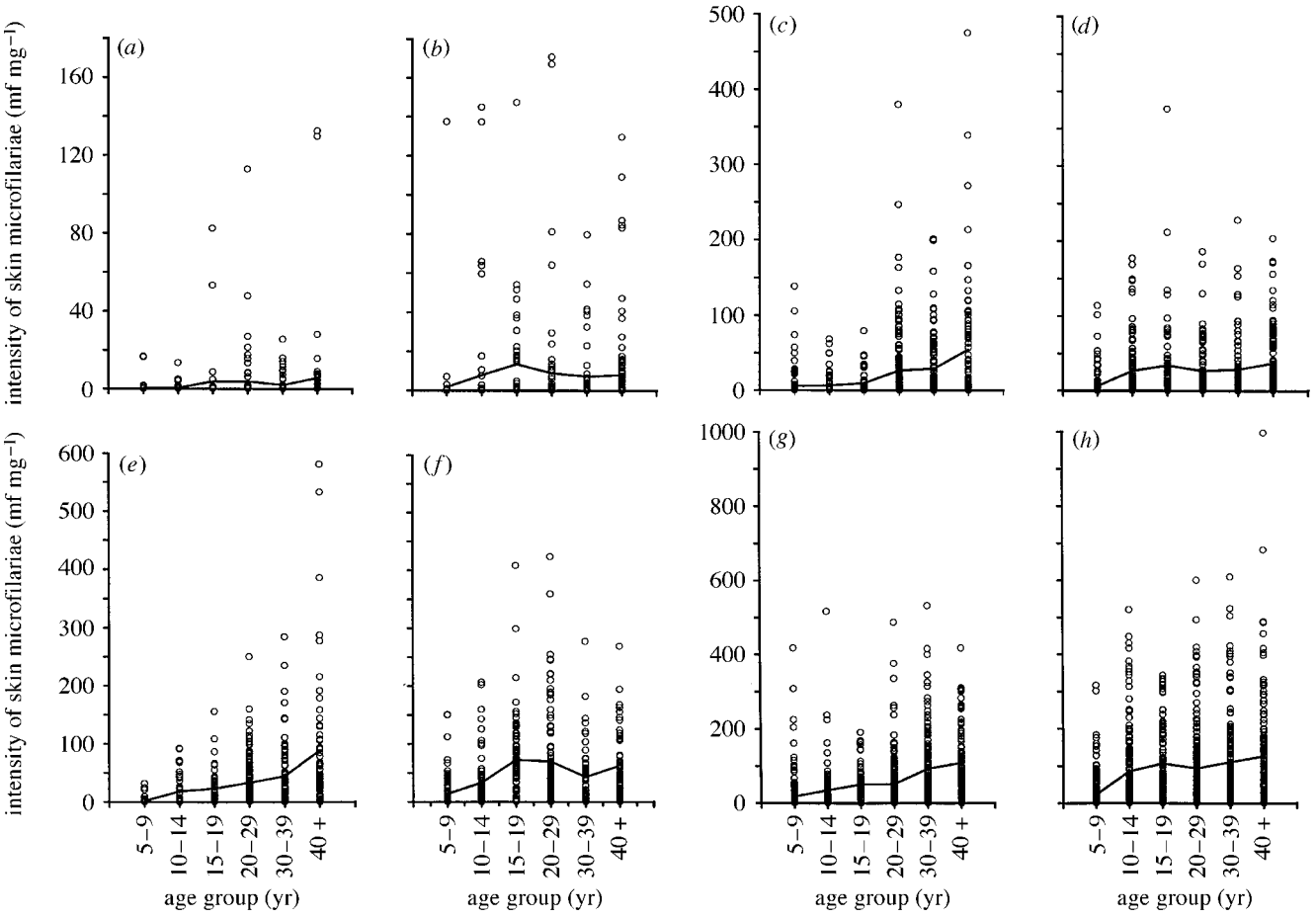

Figure 7. Age-profiles for the intensity of the skin microfilariae (Mf mg^{-1}) corresponding to transmission ranks I–IV. Open circles are the values for each individual whereas solid lines are the arithmetic means. Sample sizes are: (*a*) females I = 415 people ranging from 41 to 84 per age-band; (*b*) males I = 431 people (42–109 per age-band); (*c*) females II = 586 (43–147); (*d*) males II = 582 (63–141); (*e*) females III = 428 (51–129); (*f*) males III = 434 (56–104); (*g*) females IV = 781 (70–201); (*h*) males IV = 919 (97–204).

transmission rank I, do not decrease markedly after they have reached a maximum (males), or carry on increasing for the heavier transmission ranks II–IV (females). Additionally, there are no shifts of maximum Mf load towards younger ages in spite of increasing transmission intensity (figures 7 and 8). These age-related patterns of infection are very similar to those reported for neighbour savanna localities of northern Cameroon (Anderson *et al.* 1974*a*,*b*; Duke *et al.* 1975; Renz *et al.* 1987*b*), and more western countries (Thylefors *et al.* 1978; Kirkwood *et al.* 1983*a*). In all these surveys, the intensity of Mf (and of palpable nodules when recorded) tended to increase with age and entomological inoculation rate. The observation that in the females infection increases steadily and more gradually with age whereas, in the males it rapidly reaches a plateau from the 15–19 year age-group onwards, is also recorded by Anderson *et al.* (1974*b*), who favour the hypothesis of hormonal factors as determinants of differential immune status and susceptibility to parasite establishment and/or development (Alexander & Stimson 1988). However, Renz *et al.* (1987*a*) have shown that, in fact, boys are twice or thrice as much exposed as girls before the onset of puberty, whereas men and women may become more similarly exposed. In general, females only reach similar Mf loads to those of males in the oldest age-groups. In the same area of northern Cameroon, Anderson *et al.* (1974*b*) have reported that, similarly, the prevalence and mean number of palpable nodules increase monotonically with age in the females and only reach a plateau for those males aged 30–39 years onwards.

Pacala & Dobson (1988) have suggested that a test for density dependence in hostparasite interactions could be based on examination of VMR versus mean parasite load and of the negative binomial parameter k versus host age. Departures of the former from linearity or of the latter from constancy would be indicative of density-dependent mechanisms. However, these authors also state that a linear relationship between VMR and mean parasite burden would not exclude the possibility of the operation of regulatory constraints on the abundances of hosts and/or parasites. In our case, there is an increasing relationship between VMR and mean Mf load for both males and females (figure 9*c*,*d*) but k is also a positive function of the mean at the community level (figure 3) and for both sexes (with perhaps the exception of the male groups harbouring an average >50 Mf mg^{-1}; figure 9*a*,*b*). This apparent contradiction is resolved by the realization that VMR and k measure different properties of the parasite frequency distribution, the former being most sensitive to the presence of heavily infected hosts (tail ends) and the latter reflecting the proportion of hosts distributed around

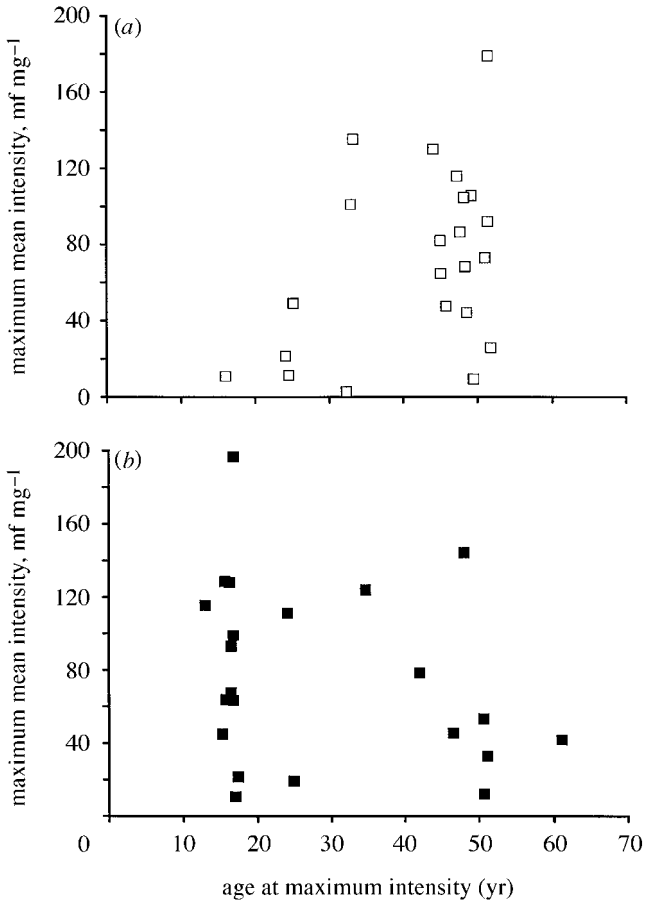

Figure 8. The maximum mean Mf load versus the mean age at which that maximum is reached for 23 villages of the data set; (*a*) open markers for females; (*b*) closed markers for males.

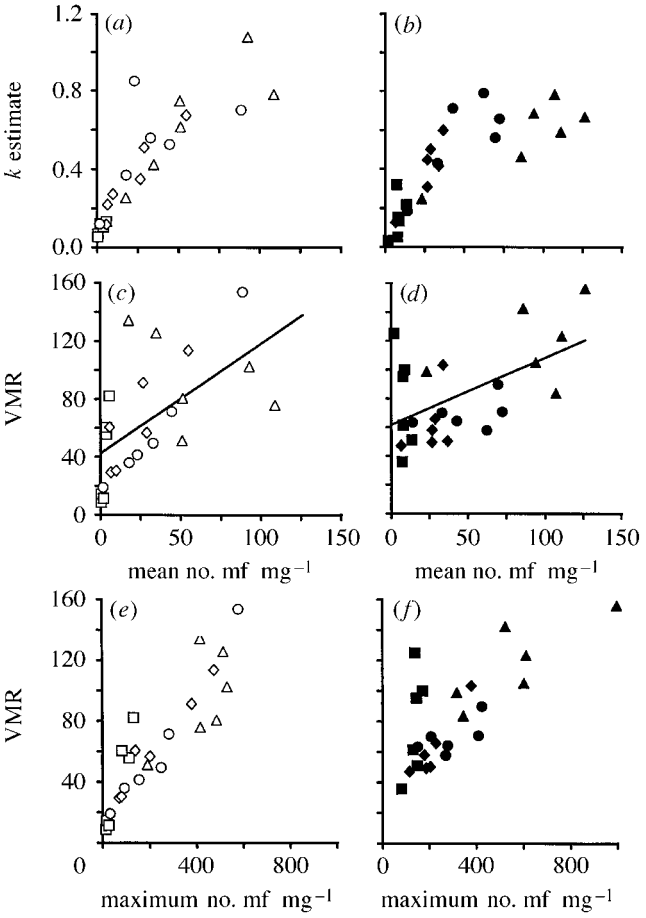

Figure 9. Indices of parasite aggregation used in this study versus the microfilarial load. (*a*, *b*) Negative binomial *k* estimate versus mean no. Mf mg^{-1} for females (open markers) and males (closed markers). Squares, diamonds, circles and triangles correspond, respectively, to transmission ranks I–IV as in figure 6. It can be seen that the relationship between *k* and mean Mf load is not linear as already established, at the community level, in figure 3. Spearman correlation coefficient for females, $r_S = 0.9254$ ($p < 0.0001$, $n = 24$); for males, $r_S = 0.8774$ ($p < 0.0001$, $n = 24$). (*c*, *d*) Variance over mean ratio (VMR) versus mean no. Mf mg^{-1} for, respectively, females (regression line: VMR = 42.21+0.76 *M*, $F_{1,22} = 12.06$, $p = 0.0022$; $r_S = 0.674$, $p < 0.001$), and males (VMR = 61.57+0.47 *M*, $F_{1,22} = 9.60$, $p = 0.0053$; $r_S = 0.433$, $p = 0.035$). (*e*, *f*) VMR versus the maximum no. Mf mg^{-1} in the corresponding frequency distribution for, respectively, females ($r_S = 0.899$, $p < 0.0001$, $n = 24$) and males ($r_S = 0.629$, $p = 0.001$, $n = 24$).

the mean (Scott 1987). The increase of *k* with age up to the 15–19 year age-band in both males and females may result from an increasing parasite acquisition such that the fractions of uninfected or lightly infected individuals become smaller. The tendency of *k* to increase with age is less marked in the 20+-year-olds (figure 10*a*). The presence of a few heavily infected hosts relative to the mean in nearly each age-, sex- and endemicity-group is reflected in the overall levels of dispersion measured by the VMR (figure 10*b*). As discussed by Anderson & Gordon (1982), the observed shapes of the age-profiles of infection intensity and aggregation are very sensitive to the relative magnitudes of the factors generating over- and under-dispersion. Extreme heterogeneity in exposure and/or susceptibility (determined by genetic or immunological factors) could override the effects of density-dependent mechanisms on these profiles.

The results of the model and the analyses of observed epidemiological patterns are consistent with emerging knowledge of onchocerciasis immunology. Recent (unpublished) work carried out in untreated hyper-endemic communities of Cameroon by Dr J. E. Bradley, indicates that cellular proliferation responses (those implicated in maintaining the infection-free status of putative immunes, Elson *et al.* (1995)) against onchocercal–filarial antigens derived from adult worms, Mf and L3, are dependent on both the intensity of microfiladermia and host age (the latter would encompass both immune response maturation and cumulative exposure to infective flies). In the 5–15-year-olds, increasing microfilarial load seems to skew the immune response towards a T_H2, antibody-dominated expression with predominance of immunoglobulin G (IgG) subclass (Gbakima *et al.* 1996). This, in virtue of the reciprocally inhibitory relationship between the T_H1–T_H2 subsets of T helper cells (Finkelman & Urban 1992), exerts a strong suppressive effect on cellular proliferation and production of gamma-interferon (IFN-γ) responses against adult worms. This is precisely the age-group in which the prevalence and intensity of infection invariably rise with age. In addition, at least 1% of less than one-year-old children living in meso- and hyperendemic onchocerciasis areas are carriers of Mf transmitted *in utero*

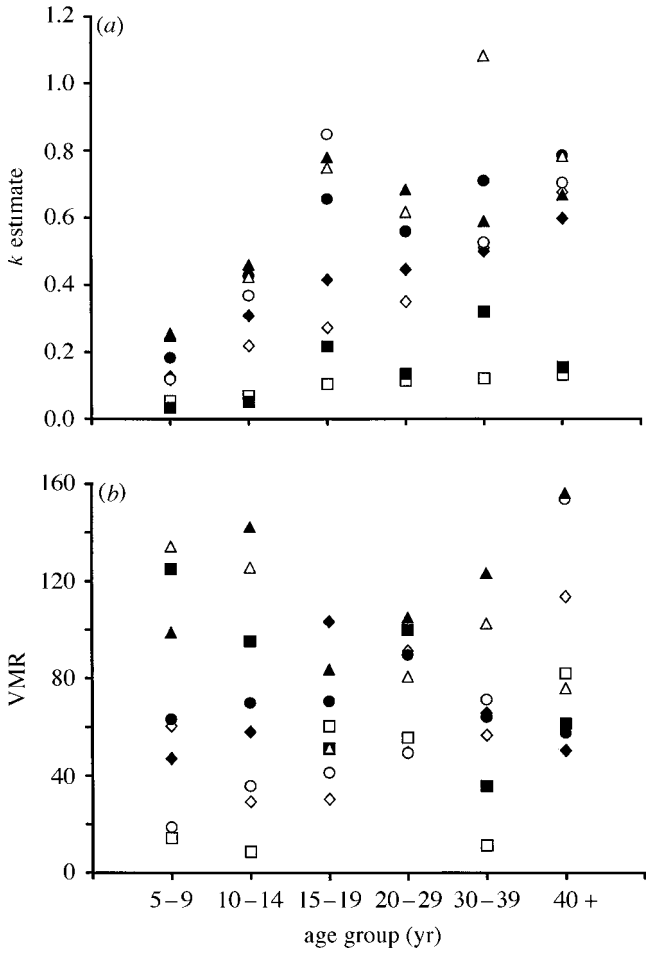

Figure 10. Indices of parasite aggregation used in this study versus age-group. (*a*, *b*) *k* estimate and VMR versus age-class for females (open markers) and males (closed markers); squares, diamonds, circles and triangles denote transmission ranks I–IV as in figure 6.

(Prost & Gorim de Ponsay 1979). This pre-natal exposure to *O. volvulus* antigens may render the child significantly more susceptible to infection after birth (Elson *et al*. 1996). In the 15–19-year-olds, adult worm- and Mf-stimulated proliferation and IFN-γ production peak and subsequently decline whereas interleukin-4 (IL-4) continues increasing, probably reflecting the shift from T_H1- to T_H2-type responses. The predominance of IgG4 antibodies during the course of onchocerciasis, as well as the presence of IgE and eosinophils are probably a result of this bias (Bradley *et al*. 1995; Stewart *et al*. 1995). Conversely, L3-stimulated proliferation and IFN-γ (but not IL-4), increase with age, suggesting a predominance of T_H1-responses in relation to infective larvae (the activation of this T-cell subpopulation is involved in delayed-type hypersensitivity reactions and macrophage-mediated parasite destruction, Finkelman *et al*. (1991); Mosmann & Moore 1991). Whereas cellular immunity against adult worms and Mf remains low in the 20+ year age-group (and levels of IgG4 high), proliferation against L3 continues rising with age (and exposure), only decreasing in the elderly. Females are more likely to belong to the putative immune group (perhaps their lower exposure results in a less unbalanced T_H1:T_H2 ratio), and even when infected exhibit lower levels of IgG isotypes (Elson *et al*. 1994).

These results support our hypothesis that, in onchocerciasis, regulation of parasite abundance within the human host is probably immunologically mediated, exposure-dependent and possibly more targeted against incoming infective larvae than against already established parasites (Maizels *et al*. 1993). However, immunity to reinfection might be acquired much more slowly as acquisition of adult worms continues into adulthood. In virtue of their early and intense exposure, boys may also mount an antibody-dependent response targeted against microfilarial survival and/or adult worm fecundity that could explain the saturation of their Mf loads whilst their nodule count continues increasing for a while. The analysis of the humoral immune response towards an *O. volvulus*-specific recombinant peptide, Ov103, known to be on the surface of Mf, has revealed a negative correlation with skin microfilarial load. This, together with the fact that this peptide is more frequently recognized by individuals with low skin loads, and the observation that antibodies against Ov103 can mediate microfilarial destruction *in vitro*, has suggested that these responses may play a role in the regulation of microfilarial burden *in vivo* (Gillespie *et al*. 1994). Clinical manifestations and in particular blindness, which are the result of inflammatory reactions with eosinophils and lymphocytes surrounding dead Mf, are more prevalent among males in these localities of Cameroon (Renz *et al*. 1987*a*,*b*). In this respect, the annual intensity of transmission and temporal dynamics of the host's exposure to ATP may play a decisive role (Schweitzer & Anderson 1991, 1992). The first years in human life are crucial to the acquisition of a worm burden that will probably remain untouched by protective immune responses, maximizing the chances of transmission to the vector, but which due to the eventual breakdown of tolerance will generate severe morbidity later in life. Ideally, the same cellular immunity studies should be conducted in villages with different endemicity levels and variable transmission regimes, as well as in communities treated with ivermectin, which, apart from killing Mf, has been shown to enhance cellular immunity (Schulz-Key *et al*. 1992; Soboslay *et al*. 1992).

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