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Determinants of the eradicability of filarial infections: a conceptual approach

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Lymphatic filariasis and onchocerciasis are subject to major intervention programs by the WHO. The Onchocerciasis Control Programme in West Africa was launched 30 years ago and has led to considerable insights into the control of this infection. The Global Alliance to Eliminate Lymphatic Filariasis is a relatively recent control program with ambitious targets concerning its efficacy and its schedule. These expectations, however, are based on certain assumptions about the density-dependent processes of limitation and facilitation which determine eradicability: the levels of transmission thresholds and breakpoints. Here, we review these processes operating in filarial infections and show their impact on the persistence of the parasite, as well as pointing out those issues where more information is required to develop sound predictions about the eradicability of these infections.

Introduction

Among the parasitic diseases that result from an infection with filarial nematodes, onchocerciasis and lymphatic filariasis are the two most prevalent diseases, with ~17 million and ~120 million people being infected, respectively [1,2]. Because both diseases can substantially impair the individual (pathology, increased mortality) as well as the population (socioeconomic development), they are subject to major intervention programs by the WHO. The Onchocerciasis Control Programme (OCP), initiated in 1974 in seven West African countries and performed over an extended area until the end of 2002, was based on vector control by aerial application of larvicides. Its successor program, the African Programme for Onchocerciasis Control, relies mainly on mass drug administration of the microfilaricide ivermectin. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched in 1998 and is based on mass drug administration of various microfilaricides [3]. The Glossary provides definitions of the terms eradication, elimination and control [4,5].

A fund of practical experience in attempting to eliminate a filarial disease is available from the control of onchocerciasis [6], but questions remain. The OCP achieved elimination in several West African foci [7] but large-scale elimination seems hardly possible [8,9]. Recently observed cases of recrudescence [10] give cause for concern that the capacity of the parasite to reinvade its host or the frequency of reintroductions is higher than assumed. This might result from underestimating the effects of mechanisms which stabilize the persistence of the parasite in the host population [11]. Besides heterogeneities (e.g. heterogeneity in exposure), regulatory processes in the host–parasite relationship are a main determinant of the persistence (and, consequently, of the eradicability) of a parasite [12]. Figure 1 shows density-dependent processes at three stages in the filarial life cycle. These processes are illustrated specifically for onchocerciasis because the regulatory processes in the human host are able to be investigated owing to the accessibility of the adult worm burden, which up to now is almost impossible to investigate in lymphatic filariasis.

The eradicability of lymphatic filariasis was suggested more than ten years ago [13] but it is a multifaceted procedure because intervention programs in some places have achieved elimination very easily, whereas others have not been successful, in spite of a long-term operation [14,15]. The first well-documented elimination of lymphatic filariasis occurred on some of the Melanesian islands, where Anopheles-transmitted *Wuchereria bancrofti* infection disappeared accidentally as a side effect of a malaria control campaign based on DDT house spraying [16]. A second example was reported from villages of a Chinese province where mass drug administration of diethylcarbamazine eliminated Anopheles-transmitted *Brugia malayi* infection [17]. Both examples contrast with experiences in those Melanesian islands where Aedes-transmitted *W. bancrofti* infection could not be eliminated, in spite of 50 years of diethylcarbamazine distribution [15].

Apparently, successful control of lymphatic filariasis is closely associated with the local parasite–vector combination. As long as 30 years ago, it was suggested that density-dependent processes can differ profoundly between vectors and that this might be the reason for such inconsistent patterns in the success of control programs [18]. Density-dependent processes can be divided into facilitation and limitation processes (see Glossary), regardless of whether they operate in the vector or in the host. Their effects can most appropriately be explained

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Glossary

ABR: Annual biting rate (number of vectors that take a blood meal on one human host per year).
ATP: Annual transmission potential [average number of infectious larvae (L3) transmitted to one human host per year].
Breakpoint: A parasite number or density below which infection cannot persist. Breakpoints can be determined for each parasite stage and also for the ATP; they represent ABR-specific, unstable equilibria, resulting from facilitation processes. Breakpoints guarantee the existence of a stable zero equilibrium, which is a prerequisite of stable elimination (if there are no breakpoints and the ABR exceeds the TBR, the zero equilibrium is unstable; that is, the reintroduction of few infections can lead in the endemic state).
Control: Reduction of the incidence of infection to a certain level where the disease is no longer considered to be a public health problem [4,5].[4][5]
Density-dependent processes: Regulatory processes in the vector–parasite–host relationship which depend in a nonlinear way on the parasite density – that is, the number of parasites per host (see also Facilitation and Limitation).
Elimination: Local reduction to zero of the incidence of infection; because infection can be imported from other areas that are still endemic, permanent intervention is required [4,5] to maintain elimination as a stable state of the trivial equilibrium.[4][5]
Equilibrium: A parasite density (here: adult parasites per host, microfilariae per mg skin snip, L3 per fly or ATP) which is sufficiently constant over a long period of time. The equilibrium solution of a mathematical model results from setting the derivatives equal to zero, such that there is no longer a change in the variables. The term 'trivial equilibrium' describes the zero equilibrium which is stable in the case of facilitation and unstable in the case of limitation (provided ABR>TBR; below the TBR the trivial equilibrium is stable). Positive unstable equilibria are synonyms for breakpoints.
Eradication: Global reduction to zero of the incidence of infection; once achieved, further interventions are not necessary [4,5] (Eradicability is a term often used in a broader sense, without discriminating between the local and the global aspect).[4][5]
Facilitation: A positive feedback process in which a parasite (at any stage) promotes the success of parasites at the same or another stage, regarding survival, development, reproductivity, etc. Because any population is limited in space, reproductivity, etc., a facilitation process must be associated with at least one 'stronger' limitation process. For sufficiently high ABRs, a data-based comparison between a facilitated and a nonregulated relationship implies an intersection between both relationships at an unstable equilibrium (breakpoint) (the stable equilibrium must originate from the associated limitation process which leads to a second intersection). The facilitated relationship falls short of the nonregulated relationship before the breakpoint (it is 'underefficient'), shifting the transmission threshold towards a higher value. Because of the induction of breakpoints and the 'underefficacy' at low parasite densities, facilitation processes can positively influence ('facilitate') the eradicability of an infection.
Limitation: A negative feedback process in which a parasite (at any stage) compromises the success of parasites at the same or another stage, regarding survival, development, reproductivity, etc. Because any population is limited in space, reproductivity, etc., limitation must be the rule. However, it is possible that the limited part of the process is not yet, or might not be, observable. For sufficiently high ABRs, a data-based comparison between a limited and a nonregulated relationship implies an intersection between both relationships at the common, stable equilibrium value. The limiting relationship exceeds the nonregulated relationship before the stable equilibrium (it is 'overefficient'). Because of 'overefficacy' at low parasite densities, limitation processes decrease transmission thresholds and breakpoints and thereby negatively influence ('limit') the eradicability of an infection.
Superinfection: In the context of filarial diseases, this term is used for describing the process of infection with a new parasite while being already infected with one or more parasites of the same species.
TBR: Threshold biting rate (an ABR below which the infection cannot persist). A more general term is transmission threshold.
Transmission threshold: A vector density below which infection cannot persist (see also TBR).

with respect to eradicability because facilitation processes will 'facilitate' the eradicability of a parasite, whereas limitation processes will 'limit' the prospects of such a success. The interaction between both types of density dependence determines the existence and levels of breakpoints and transmission thresholds, which are defined as follows:

'Transmission thresholds' refer to a vector density below which the infection cannot persist. If there are too few vectors, an adult parasite will die before any of its offspring are transmitted, and, consequently, the infection does not get transmitted. The validity of this concept, which applies to all vector-borne infections, was demonstrated by Ross [19], who investigated the transmission dynamics of malaria. A key variable is the rate at which vectors feed on human hosts per unit of time, the annual biting rate (ABR). The threshold below which the infection cannot persist, the threshold biting rate (TBR), is a measure of the persistence of the parasite population [20]. The values of the TBR vary considerably between parasite subspecies [21–24] and depend on the density-dependent processes operating in vectors and hosts and on the heterogeneity in contact rates between vectors and hosts.

'Breakpoints' refer to a parasite density below which the infection cannot persist. The reasons for the existence of breakpoints are best explained by the mating process, first described mathematically for schistosomiasis [25]: as transmission depends on sexual reproduction of the parasite, an individual must harbor at least one female and one male parasite to contribute to the transmission of the infection. Averaged over the population, however, breakpoints do not necessarily remain at two parasites per host and can still be relevant for control measures if falling short of one parasite per host. The mating process transforms the process of microfilariae (Mf) production by adult female worms into a facilitation process because mating (and hence reproduction) becomes increasingly facilitated at high parasite burdens. Breakpoints in the transmission of filarial infections have undergone only rudimentary investigation but have been suggested to be relevant for the elimination of lymphatic filariasis (see 'Density-dependent processes in vectors', below).

Thresholds and breakpoints form the important points in a persistence graph; this is explained in Figure 2. Such a graph shows how equilibrium parasite burdens, transmission thresholds and breakpoints depend on the number of vector–host contacts and thereby enables the eradicability of an infection to be assessed. The persistence graph is derived from ABR-specific equilibrium solutions of mathematical models, of which a basic one, used in the present manuscript, is described in Box 1.

Density-dependent processes in vectors

Before going into details of facilitation and limitation, it will be helpful to consider the case of nonregulated transmission by vectors. In this case, a constant percentage of Mf ingested by the vector during a blood meal develops to the infective stage and, hence, the number of infectious larvae (L3) per fly increases linearly with the Mf density in the skin of infected hosts. Limitation and facilitation in vectors cause deviations from this linear relationship, as shown in Figure 1c.

Limitation is associated with the fact that no population (e.g. the number of parasites per fly) can increase indefinitely. In vectors, this means that the relationship between Mf intake and L3 output is only initially linear and approaches a constant value with increasing Mf intake. This relationship can be found in vectors of both lymphatic filariasis and onchocerciasis [18,26–28]. In the

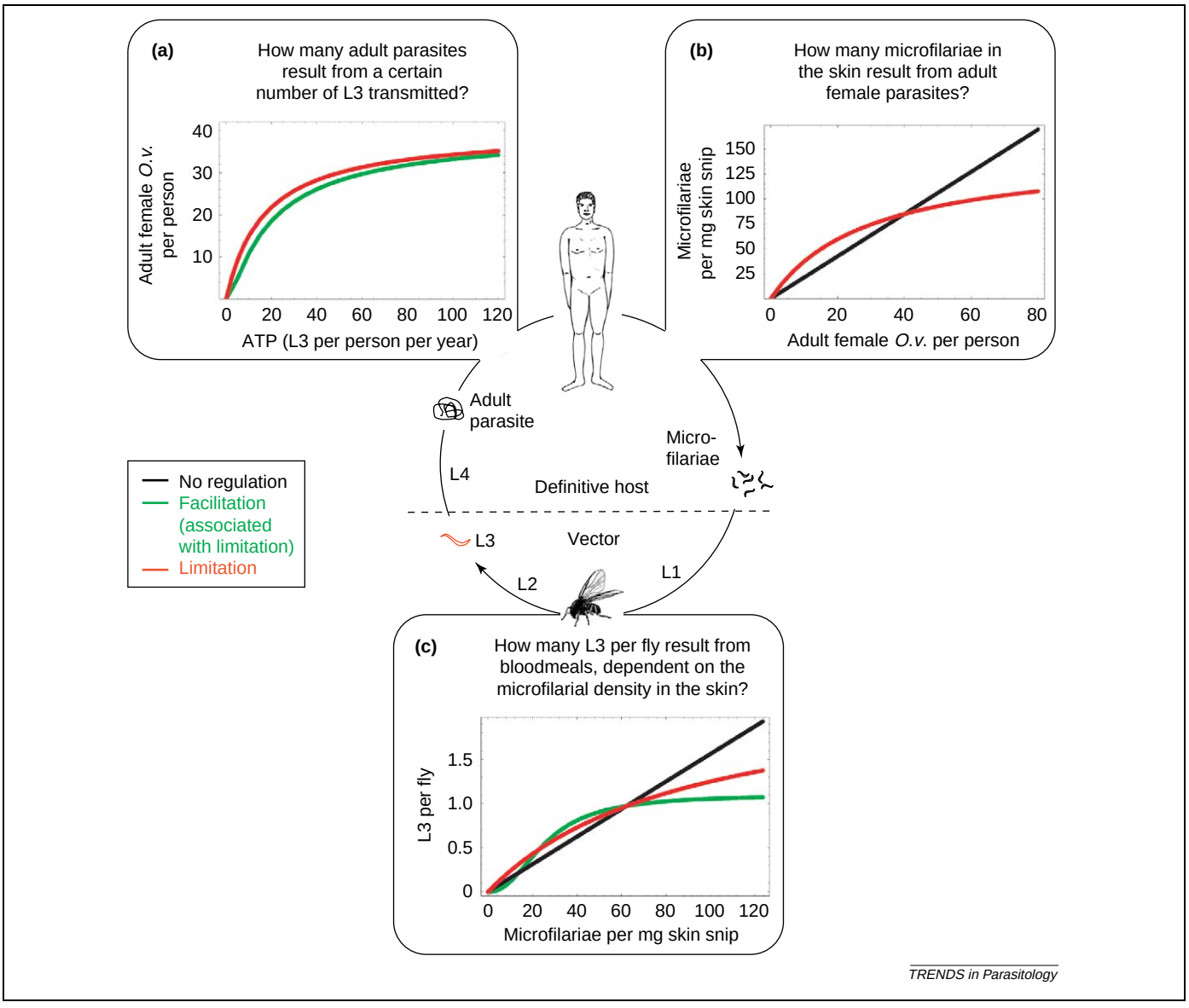

Figure 1. Density-dependent processes in filarial infections. Parasite life cycle of a filarial infection, using the example of *Onchocerca volvulus*, and three stages for which density-dependent processes have been suggested. **(a)** Limitation [owing to protective immunity against infectious larvae (L3)] in the establishment of adult parasites is suggested by the observation that, in hyperendemic transmission, the rate of establishment of adult parasites is independent of, rather than proportional to, the annual transmission potential (ATP) [40]. The saturating relationship becomes sigmoid if facilitation (owing to parasite-induced immunosuppression) in the establishment of adult parasites is assumed. (A nonregulated relationship is not represented in (a) because a parasite life cycle must include at least one limitation process to guarantee a stable equilibrium; throughout, this 'default' process is assumed to be represented by limitation with respect to the ATP. Both curves in (a) result from the equilibrium solution of Equation I in Box 1 with respect to w, the burden of adult female *O.v.*; that is, $dw/dt=0$.). **(b)** Limitation in the microfilarial density [39] can result from either a reduction in the life expectancy of microfilariae (Mf) (as a consequence of protective immunity) or from density-dependent Mf production (crowding effects which reduce the fecundity of adult female parasites [54]). **(c)** Both types of density dependence and nonregulation have been demonstrated in vectors and strongly depend on whether or not the vectors (i) have a cibarial armature and/or (ii) form a peritrophic membrane (for an overview on lymphatic filariasis and onchocerciasis, see references [15] and [28], respectively). Limitation prevails in most vectors; that is, the probability of successful development into an L3 decreases if many Mf are ingested during the blood meal.

simplest case, limitation in vectors results from an excess mortality, caused by ingestion of too many Mf. If the survival of vectors is profoundly affected, it might even be possible that the average number of L3 per fly decreases at high Mf densities [21]. Compared with the nonregulated (linear) case, transmission in the case of limitation can be more efficient at low Mf densities, and maximum transmission is guaranteed over a wide range of high Mf densities (this occurs as a result of the fact that both relationships must intersect to explain an identical equilibrium, implying that the limited process is 'over-efficient' before, and 'under-efficient' after, this intersection). Limitation processes counteract the eradicability of an infection by shifting transmission thresholds towards lower values, which require higher control efforts to be achieved.

Facilitation has been observed in anopheline mosquitoes [18,27,29] and in Simulium species transmitting Amazonian onchocerciasis [28]. These vectors possess a cibarial armature, a tooth-like chitin structure which lacerates ingested Mf. At low Mf densities, this cibarial armature substantially reduces the proportion of surviving Mf and, as a result, transmission is inefficient and transmission thresholds are shifted towards higher values, which can more easily be achieved by control measures. At high Mf densities, however, the cibarial

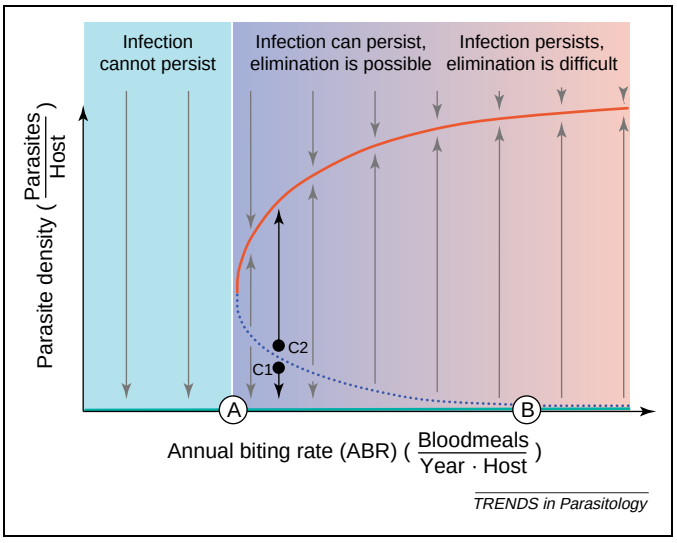

Figure 2. Persistence curve for filarial infections. Persistence curves show equilibrium parasite densities, dependent on the number of vector–host contacts [annual biting rate (ABR)]. The red curve shows the stable, positive equilibria: provided that there are sufficient vector–host contacts and parasites, the average parasite density in human hosts is represented by this curve. The green line shows the stable, trivial equilibria (parasite density = 0): transmission of the infection is not possible because of too few vector–host contacts or too few parasites. The blue-dotted curve, resulting from breakpoint-inducing facilitation processes, represents the unstable equilibria (breakpoints): if the parasite density falls short of a breakpoint, the system will tend towards the trivial equilibrium and the infection will become extinct without further efforts (successful intervention, C1). If the parasite density exceeds a breakpoint, the system will return to the stable, positive equilibrium and the infection will continue to persist (untimely cancelled intervention, C2). The vertical arrows represent the dynamic behavior of the system: starting from any point on a line, an arrow points to the equilibrium parasite density at which the undisturbed system will stabilize. In the green section of the graph, the infection cannot persist because the critical transmission threshold [threshold biting rate (TBR), point A] is not reached. In the blue section of the graph, the infection can be eliminated by reducing the parasite density below the ABR-specific breakpoint. Point B indicates an ABR at which facilitation-induced breakpoints disappear so that the stable zero equilibria (green line) exist only because of the mating process. Breakpoints can be so close to the zero equilibrium that they are hardly relevant for elimination (represented by the smooth transition from the blue into the red sections of the graph).

armature might be inefficient because it is masked by a few Mf promoting the survival of the others (the observation of this process had led to the introduction of the term 'facilitation'). Because limitation must occur at higher Mf densities, the facilitation curve in Figure 1c becomes sigmoid (for simplicity, the term 'facilitation' is used in the following as a short form for 'initial facilitation with associated limitation').

The eradicability of filarial infections that are subject to facilitation processes profits, not only from threshold shifts but also from the fact that facilitation leads to unstable transmission [18,30], synonymous with the existence of breakpoints. Although the mathematical approach, and to some extent also the data investigation involved in this approach, have been criticized [31], it seems to be a rule that facilitation processes shift the persistence graph to the right – that is, they increase transmission thresholds and introduce breakpoints into the transmission of an infection. The question then remains as to whether or not a certain facilitation process is practically relevant for an intervention program [29,32,33]. Detailed information about the degree of limitation and facilitation remains an absolute requirement for the precise determination of the location of breakpoints.

Density-dependent processes in the human host

The processes in the vectors are not the only factors that determine the eradicability of a filarial infection; the processes that operate in the human host are likewise important. In onchocerciasis, these can be investigated more easily owing to the availability of nodulectomy data. Unlike adult parasites in lymphatic filariasis, which are difficult to localize and cannot be removed from the host tissue, adult *Onchocerca volvulus* aggregate in subdermal nodules (onchocercomata), some of which can be palpated and surgically excised, providing quantitative measures for the parasite population, the endemicity and the intensity of infection [34,35]. Although only a fraction of parasites is accessible by nodulectomy [36,37], the true parasite burden can be deduced [38] and used to investigate feedback mechanisms [39], which can operate in many stages of the intrahost life cycle of the parasite.

The first immunological mystery occurs as early as the stage of parasite acquisition: of several thousands of L3 to which a human host is annually exposed (annual transmission potential, ATP), only a few manage to develop into an adult parasite. Surprisingly, the number of successfully maturing L3 seems to be almost constant in hyperendemic transmission – that is, high ATPs do not necessarily mean high numbers of maturing L3s [40]. This is confirmed by infection experiments in jirds, which have shown that only at low doses does a proportionality occur between the dose of infection and the number of established parasites; higher infection doses do not increase considerably the number of successfully establishing L3s [41]. Although studies in the *Brugia* mouse model have provided further insights into the immunological role of L3s [42], little is known as to how the sum of the various immunological processes will influence intervention campaigns. We still do not understand the mechanism by which a human body is protected against infection by the presence of thousands of L3 but the process responsible is certainly highly limited with respect to the ATP and thus compromises efforts to eliminate the parasite.

Parasite acquisition not only depends on the vector-related force of infection but has also been suggested to depend on the parasite density in the human host [40]. Density-dependent parasite establishment could be a consequence of parasite-induced immunosuppression, which seems to be a mechanism involved in most filarial infections [43–45] and might even be involved in most nematode infections [46]. Immunosuppression is assumed not only to promote parasite persistence within the host [47] but also to increase the susceptibility of the host to superinfection. This is a facilitation process, in that parasites that have already established themselves in the host increase the rate at which further parasites are acquired. This means that an already established parasite reduces the period of time until an infection with the next parasite can occur (a process which necessarily needs to be associated with a limitation process) [40]. Facilitated infection rates introduce breakpoints into the transmission of an infection [48], also known from ecology as the Allee effect [49]. As in the example of facilitation in the vectors, this process helps to eradicate the infection:

Box 1. Basic model for the transmission of a filarial infection

To provide a comprehensible modeling framework, the transmission cycle of a filarial infection is described deterministically, neglecting the age structure of the human population. Parameter values are adapted to West African savannah onchocerciasis, for which regulatory processes are better investigated. The changes in the burdens of adult female parasites, w, and microfilariae, m, with time t are given by Equation I and Equation II:

$$\frac{dw}{dt} = \lambda(w, ATP) - (\sigma_w + \sigma_h)w \qquad \text{[Eqn I]}$$

$$\frac{dm}{dt} = \varphi(w)\beta(w) - (\sigma_m + \sigma_h)m \qquad \text{[Eqn II]}$$

where ATP=annual transmission potential; λ=parasite establishment rate (PER; i.e. number of adult female parasites establishing per host per year); $1/\sigma_w$=ten years: life expectancy of adult female parasites [37,55]; $1/\sigma_h$=50 years: life expectancy of humans, ϕ= mating probability, for promiscuous parasites given by $\phi(w)=1-(1+w/k)^{-(k+1)}$ [56,57], whereby the sum of male and female worms is assumed to be geometrically distributed, hence $k\approx 1$ [38]; β=rate at which microfilariae (Mf) per mg skin snip result from the number of adult female *O. volvulus* per year. $1/\sigma_m$=1 year: life expectancy of Mf [37]. The coexistence of immunosuppression and protective immunity in human hosts is assumed to operate on the PER, implemented as (Equation III):

$$\lambda(w, ATP) = \lambda_0 f_F(w) f_L(ATP) \qquad \text{[Eqn III]}$$

Where λ_0=1 per year: number of adult female parasites establishing in a noninfected host per year; $f_F(w)=(1+csw)/(1+sw)$: Facilitated parasite establishment due to parasite-induced immunosuppression with parameters λ_0 c=5.75 per year: number of adult female parasites establishing in a heavily infected host per year; s=0.1: slope by which λ_0 c is achieved (modified from [40]); $f_L(ATP)=(\alpha\ ATP)/(1+\alpha\ ATP)$: Limited parasite establishment due to protective immunity against infectious larvae (L3) with parameter α=0.06 (hypothetical value, chosen to provide a baseline threshold biting rate (TBR) comparable to existing, deterministic onchocerciasis models [21,23]). Limitation for Mf is implemented as (Equation IV)

$$\beta(w) = \frac{bw\sigma_m}{1 + rw} \qquad \text{[Eqn IV]}$$

b=5 Mf per mg skin snip are contributed per adult female worm in hosts with low parasite burdens; r=0.034: slope by which the asymptote $b\sigma_m/r$=147 Mf per skin snip is achieved (modified from [39]).

Survival of flies – with respect to the time-dependent processes – is assumed to be negligibly small so that it does not need to be implemented dynamically. Limitation in the number of L3 developing from Mf ingested during a blood meal is adopted from [23] (Equation V):

$$l(m) = \frac{a_1 m}{1 + a_2 m} \qquad \text{[Eqn V]}$$

with a_1=0.021 and a_2=0.0088. According to precontrol data from the Onchocerciasis Control Programme, the ATP increases linearly with the annual biting rate (ABR) at slope ε=0.02, thus (Equation VI)

$$ATP = \varepsilon ABR \frac{l}{l*} \qquad \text{[Eqn VI]}$$

Numerical solutions of the model have been evaluated with initial values of $w(0)=w_0$ and $m(0)=0.1\ w_0$. If w_0 leads to the trivial equilibrium of $w=0$, then, either the TBR has not been achieved or a breakpoint has been under-run. If w_0 leads to an equilibrium of $w>0$, then an endemic state is possible and a stable equilibrium has been reached. For all combinations of processes, the equilibrium solutions ($t\rightarrow\infty$) for high ABRs are: $w^*=40$ adult female parasites per human host, $m^*=75$ Mf per mg skin snip, $l^*=1$ infectious larva per fly. Parameter values for nonregulated relationships are chosen such that the equilibria are identical to the corresponding regulated relationship.

during a control campaign, the reducing parasite density results in an increasing immunological host competence, which, in turn, helps to reduce the parasite burden. A consequence of this positive feedback is that the infection will cease if parasite density drops below a certain breakpoint. If two or more facilitation processes are combined, transmission thresholds and breakpoints can be shifted towards values that are highly relevant for intervention programs.

Benefits resulting from facilitation processes can be balanced or even overridden by coexisting limitation processes. In onchocerciasis, the investigation of nodulectomy data clarified the relationship between the burden of adult parasites and the microfilarial density in the skin [39]. Whereas the Mf density increases almost proportionally with the burden of adult *O. volvulus* of the forest strain (linear relationship), the relationship in savannah onchocerciasis is nonlinear, showing considerable limitation. From this standpoint, elimination of savannah onchocerciasis is more difficult to achieve than that of forest onchocerciasis. Figure 3 illustrates these effects by summarizing how limitation and facilitation processes in vectors and human hosts modify the eradicability of a filarial infection, using the example of onchocerciasis.

Sources of uncertainty

Apart from differences in the persistence patterns between the specific parasite–vector–host combinations, there are sources of uncertainty which similarly affect all subtypes of these infections. This can be shown by the examples of two sensitivity analyses, one referring to a parameter in the transmission cycle and the other referring to interventions by microfilaricides.

One of the least understood processes in the transmission cycle of filarial infections is the relationship between the ATP and the parasite establishment rate (i.e. the number of adult parasites annually establishing in a host per year). Whereas the ATP usually ranges from dozens up to several thousands of L3 per host per year, the parasite establishment rate usually amounts to a few parasites per host per year, in onchocerciasis hardly exceeding values over five per year, even at high ATPs [40]. Limited parasite establishment, which has also been investigated with respect to the microfilarial density [50], is in the present model linked to the ATP by parameter α (Equation III in Box 1). Other models usually implement this functionality by the 'probability that an infectious larva develops into an adult parasite'. A sensitivity analysis can illustrate the uncertainty arising from variations in this parameter. Considering a persistence profile as shown in Figure 3d, and varying α in the range 0.02–0.10 (this might represent the precision by which the parameter can be estimated from the best dataset currently available), the transmission threshold ranges from 400 to 2000 bites per person per year, and breakpoints shift accordingly. Transmission thresholds and

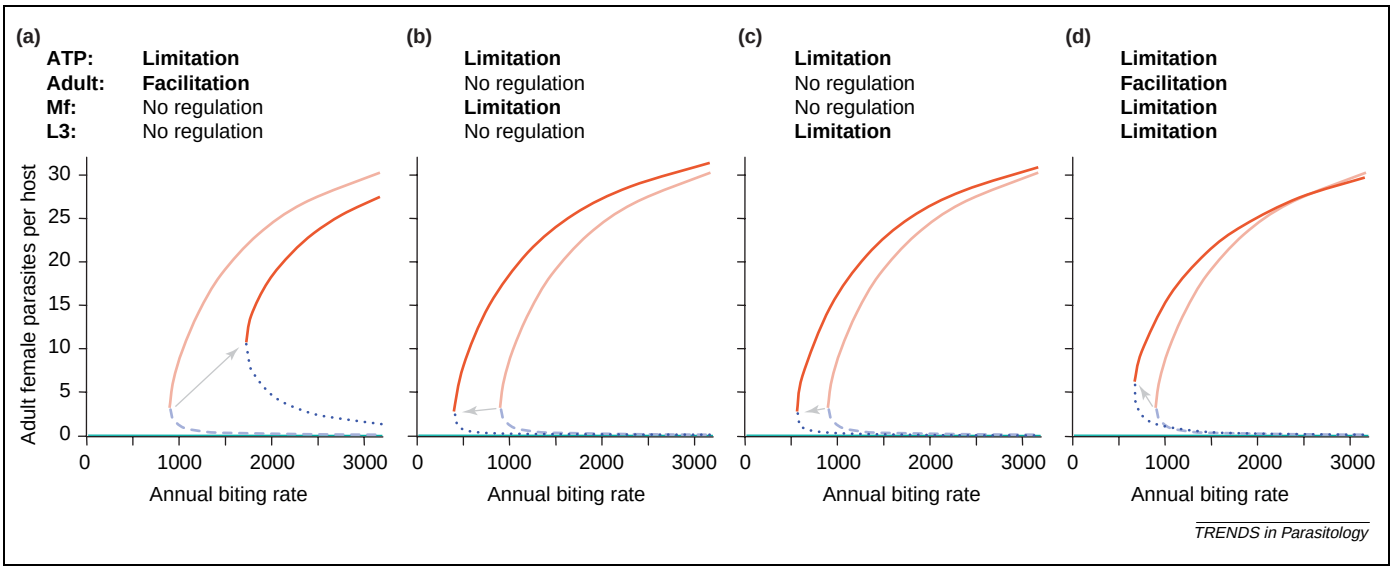

Figure 3. Density-dependent processes modifying eradicability. Persistence graphs resulting from density-dependent processes, operating at different stages of the parasitic life cycle. The pale-colored curve in each graph represents the persistence pattern that results if there is no density dependence [all processes are nonregulated except for the limited relationship between parasite establishment and annual transmission potential (ATP), Equation III in Box 1]. The threshold biting rate (TBR) lies at ~900 bites per person per year (bpy), and breakpoints result only from the mating process. Parameter values refer to West African savannah onchocerciasis, as outlined in Box 1. Adult: Number of adult female parasites establishing per year in a host (Equation III in Box 1). Mf: Microfilarial density in the skin dependent on the number of adult female parasites in the human host (Equation IV in Box 1). L3: Number of L3 developing in a fly from microfilariae (Mf) ingested during preceding blood meals (Equation V in Box 1). **(a)** Persistence graph resulting from facilitated parasite establishment: the transmission threshold increases to a TBR of ~1700 bpy, and breakpoints are shifted considerably towards higher parasite burdens, indicating facilitated eradicability. **(b)** Limitation in the Mf density complicates control measures because the transmission threshold decreases to a TBR of ~400 bpy and, accordingly, the breakpoints are shifted towards lower parasite burdens. **(c)** Limitation in flies also worsens the prospects of elimination by decreasing the transmission threshold to a TBR of ~500 bpy. **(d)** Persistence graph under the assumption that the density-dependent processes in (a), (b) and (c) operate simultaneously. In this example, the parameter values chosen for the three processes yield a TBR that is still more pessimistic compared with the case of nonregulation in all three processes – that is, the effects of the two limitation processes outbalance the facilitation process.

breakpoints appear to be strongly influenced by a parameter which cannot precisely be determined, challenging our ambitions to predict the eradicability of the infection.

In the second example, we consider an intervention based on a microfilaricide (e.g. ivermectin) which reduces the Mf density, without affecting the number of adult worms in the beginning of the control. In onchocerciasis, a beneficial, density-dependent side effect could result from ivermectin-facilitated immunity [51]; that is, the therapy improves the immunological competence of hosts, which, in turn, helps to control the microfilaremia in the course of therapy. The microfilaricidal effect mimics a reduction in the reproductivity of adult female parasites and shifts the persistence graph to the right. By contrast, vector control is not a 'persistence-shifting' intervention because it does not primarily alter the regulatory processes within parasites, vectors or hosts. Dependent on slightly different assumptions concerning the density-dependent efficacy of the microfilaricide, the three scenarios shown in Figure 4 produce transmission thresholds of 18 000, 11 000 and 8000 bites per person per year, and the location of breakpoints can differ substantially if compared at identical ABRs. This shows that the decisive factor in the eradicability of a filarial infection with a microfilaricide is not its efficacy in the heavily infected population (in the early stages of control) but its efficacy in the almost 'cured' population (with low Mf densities after a certain time of control). It does not appear to be possible to predict the long-term effects of an intervention based on microfilaricides without first having clarified the density-dependent effects associated with their administration.

Eradicability and predictability

Variations in the density-dependent processes between vectors, parasites and hosts can lead to profoundly different persistence patterns (see above). The eradicability of a filarial infection will depend on the opposing processes of facilitation and limitation. Predictions of the success of intervention programs will be overoptimistic if the degree of facilitation is overestimated or if the degree of limitation is underestimated, and overpessimistic if the degree of facilitation is underestimated or the degree of limitation overestimated. Sensitivity analyses have established that, for example, the relationship between the ATP and the establishment of adult parasites or density-dependent side effects of microfilaricides are sources of uncertainty that can seriously affect the eradicability of an infection.

Mathematical models and computer simulations have been employed in planning control strategies and evaluating the intervention success of onchocerciasis and lymphatic filariasis, and criticisms about their applicability and predictive capacity have been raised. As such models will always translate our input (e.g. regulatory processes) into some output (e.g. a prediction of intervention success at a certain time), their predictive capacity directly reflects our level of knowledge. If our knowledge is poor, a mathematical model will poorly reproduce reality – this is actually a useful implication because it can verify whether our knowledge about the infection is sufficiently complete. It is impossible to build mathematical models that, at the same time, maximize realism, generality and precision [52]. The deterministic model presented here is developed for the purpose of generality, enabling a

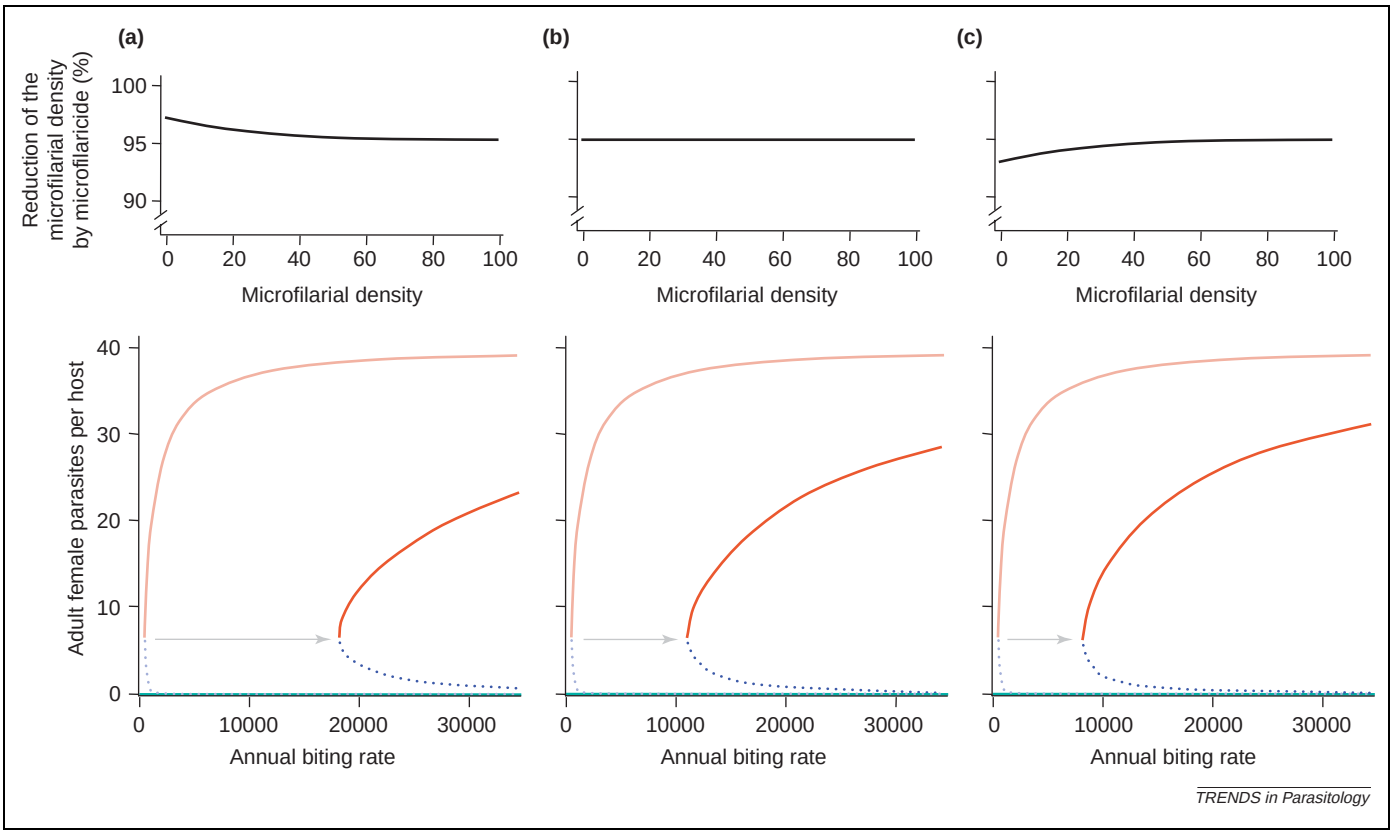

Figure 4. Persistence-shifting intervention and uncertainties. The eradicability of a filarial infection can also be affected by the density-dependent side effects of certain interventions (see 'Sources of uncertainty'). The figure shows how the persistence graph (lower graphs, colors as in Figure 1) is altered by administration of a microfilaricide. The pale-colored curve in each graph represents the persistence pattern without intervention (density-dependent processes as in Figure 3d). The full-colored curves represent the persistence patterns resulting from a microfilaricide-based intervention, whereby density-dependent characteristics of the microfilaricidal effect are shown in the upper graphs. In the three scenarios, the microfilaricide reduces the microfilariae (Mf) density by 95% at the population level but can deviate from this in a density-dependent manner by 2%. **(a)** An effect which might result from ivermectin-facilitated immunity. As a result of this mechanism, the reduction in the Mf density improves in (a) from 95% to 97% during the course of therapy (from right to left in the upper graph). The corresponding persistence graph shows that under this assumption, the threshold biting rate (TBR) increases from ~900 to ~18 000 bites per person per year, suggesting that elimination might be easily achieved. Compared with the TBR of ~11 000 in the case of no density dependence [scenario **(b)**, 95% reduction independent of the Mf density], a mechanism such as ivermectin-facilitated immunity can considerably increase the prospects of elimination. In scenario **(c)**, chosen with respect to symmetry to (a), the reduction in the Mf density declines from 95% to 93% during the course of therapy (from right to left in the upper graph), which shifts the TBR to ~8000 bites per person per year. The examples show that a slight variation in the density-dependent side effects of an intervention can considerably alter the prospects of elimination.

comparative analysis with the intention of maximizing the understanding how these processes affect the eradicability of a filarial infection. Models which maximize realism and precision must consider, for example, demographic and stochastic aspects, the age structure of the population, heterogeneities among parasites and hosts and the epidemiological significance of zoophily of vectors and animal reservoirs. Heterogeneities, for instance, are expected to make predictions more pessimistic with respect to control because they can aid stabilizing the persistence of the infection [11].

Although logistic successes (availability of microfilaricides and broad participation of countries) at the beginning of the GPELF have been noted [53], it is not yet clear if mass drug administration of microfilaricides can efficiently perturb the stabilizing processes within the host–parasite relationship. The patchy distribution of different vector–parasite combinations makes it difficult to address the eradicability of lymphatic filariasis as a whole. Instead, we should refer to the elimination of the infection in its specific context of parasite strain, vector and density-dependent processes operating in both vectors and hosts. Precise predictions of the prospects for success of the GPELF would profit from improving methods such as ultrasound techniques that enable the quantification of the adult parasite burden to investigate the regulatory processes in the human host.

The experiences gained during the OCP have shown that certain risk factors can challenge the large-scale and long-term success of interventions. For example, infections that are imported by flies migrating from endemic into controlled regions will be overly compromising if we ignore important limitation processes that increase the capacity of the parasite to reinvade the population and persist at low transmission intensities. However, if we neglect important facilitation processes, which promote eradicability, then we will miss opportunities in those stages of an intervention campaign when the elimination of the parasite is within reach. The latter might be especially relevant for the Onchocerciasis Elimination Programme of the Americas, which has yielded promising results [8]. Density-dependent processes determine eradicability, and their identification should be an integral part in our strategies to eliminate or eradicate a parasite.

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American Society of Tropical Medicine and Hygiene 2004 Young Investigator Award Competition Results

Winners

Kim-Sung Lee – Universiti Malaysia Sarawak Faculty of Medicine & Health Sciences
'Human infections with *Plasmodium knowlesi* in Malaysian Borneo'

Laurin Kasehagen – Case Western Reserve University
'*Plasmodium vivax* susceptibility in Duffy-negative heterozygotes in Papua New Guinea'

Kimberly Keene – Colorado State University
'RNA interference as an innate immune response to arboviral infection in the mosquitoes *Anopheles gambiae* and *Aedes aegypti*'

Nilda Rodriguez – University of Iowa
'A novel program of macrophage gene expression induced by phagocytosis of *Leishmania chagasi*'

Honorable Mention

Alisa Alker – University of North Carolina Chapel Hill
'Association between mutations in DHFR and DHPS and clinical outcome of malaria in children treated with sulfadoxine-pyrimethamine in the Democratic Republic of the Congo'

Jennifer Anderson – Johns Hopkins University School of Public Health
'Antigenic Profile of nymphal Dermacentor variabilis salivary gland proteins fed on a sylvatic host, *Peromyscus leucopus*: construction and analysis of a *D. variabilis* specific salivary gland library'

Renee Larocque – Montreal General Hospital / McGill University
'Randomized controlled trial of mebendazole plus iron supplementation versus placebo plus iron supplementation during pregnancy'

Charlotte Lanteri – University of North Carolina Chapel Hill
'Uptake of the Trypanocidal Agent DB75 by *Trypanosoma brucei brucei*'

Awards were presented at the 53rd ASTMH annual meeting In Miami, Florida, USA, in November 2004.

Cash prizes for the ASTMH YIAC Winners (US$1000) and Honorable Mention finalists (US$250) are made in honor of William Petri, Sr. *Trends in Parasitology* congratulates these young investigators through a one-year complementary subscription to the journal.

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