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Control of onchocerciasis in Africa: Threshold shifts, breakpoints and rules for elimination

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ABSTRACT

Control of onchocerciasis in Africa is currently based on annual community-directed treatment with ivermectin (CDTI) which has been assumed to be not efficient enough to bring about elimination. However, elimination has recently been reported to have been achieved by CDTI alone in villages of Senegal and Mali, reviving debate on the eradicability of onchocerciasis in Africa. We investigate the eradicability of onchocerciasis by examining threshold shifts and breakpoints predicted by a stochastic transmission model that has been fitted extensively to data. We show that elimination based on CDTI relies on shifting the threshold biting rate to a level that is higher than the annual biting rate. Breakpoints become relevant in the context of when to stop CDTI. In order for the model to predict a good chance for CDTI to eliminate onchocerciasis, facilitating factors such as the macrofilaricidal effect of ivermectin must be assumed. A chart predicting the minimum efficacy of CDTI required for elimination, dependent on the annual biting rate, is provided. Generalisable recommendations into strategies for the elimination of onchocerciasis are derived, particularly referring to the roles of vectors, the residual infection rate under control, and a low-spreader problem originating from patients with low parasite burdens.

1. Introduction

Control of onchocerciasis in Africa is currently based on annual community-directed treatment with ivermectin (CDTI) under the administration of the African Programme for Onchocerciasis Control (APOC). It has been assumed that CDTI is not efficient enough to bring about elimination in Africa, but may be used to control onchocerciasis as a public health problem (Dadzie et al., 2003). Recently, however, elimination by CDTI alone has been reported in villages of Senegal and Mali (Diawara et al., 2009), reviving the hope that onchocerciasis can be eliminated in Africa. This effort receives support from the Onchocerciasis Elimination Program for the Americas (OEPA), that has successfully eliminated onchocerciasis in many sites (Richards et al., 2001; Sauerbrey, 2008). More efficient vectors and different ecological conditions, however, make it difficult to reproduce these successes under African conditions (Thylefors and Alleman, 2006).

Studies with the simulation program ONCHOSIM suggested that onchocerciasis can be eliminated under high ivermectin coverage and when pre-control endemicity is not too high, but parameters such as the duration of the program and heterogeneities in compliance seem to be of utmost importance (Winnen et al., 2002). In particular, the question whether semi-annual treatment intervals (as performed by OEPA), as opposed to annual treatment, are sufficient to achieve elimination is still under discussion (Abiose et al., 2000; Richards et al., 2000; Cupp et al., 2010). ONCHOSIM can provide answers about treatment options under specific conditions but, being an individual-based simulation program, it is difficult to generalise results from ONCHOSIM to other situations. Simple models, on the other hand, may provide general guidelines but these results are often too simple to support practical decision-making during a control program. An overview of the available onchocerciasis models is provided in Basáñez and Ricardez-Esquinca (2001).

The intention of this work is to investigate the eradicability of onchocerciasis in Africa by examining a mathematical model which is sufficiently complex and realistic to represent the characteristics of onchocerciasis transmission and control, providing generalisable recommendations about the efficient design of control or elimination strategies. As a sequel to a methodological paper which focused on the development and calibration of this model (Duerr and Eichner, 2010), this paper specifically studies the role of breakpoints and transmission thresholds (Duerr et al., 2005). Breakpoints are parasite burdens below which an endemic state is not possible. The ultimate goal of any intervention based on parasite control is to eliminate the infection by lowering parasite burdens below a breakpoint (in contrast to vector control which aims for lowering the number of vectors beyond a critical number of vectors).

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One factor that complicates such an analysis is that breakpoints must primarily refer to the longest-living parasite stage in the parasite's life-cycle, whereas interventions can be targeted against short-living stages. In onchocerciasis, breakpoints should thus be expressed in terms of adult female *Onchocerca volvulus* (with a life-expectancy between 9 to 14 years (Plaisier et al., 1991)) whereas CDTI is targeted against the microfilariae (MF, with a life-expectancy of approximately 1 year). Breakpoints for the average MF density (MF per mg skin snip) can theoretically be calculated, but they are of limited use for a control program in practise: using CDTI, elimination would require that the MF density be held constantly under the MF breakpoint for a period of 9–14 years - the life span of the adult female *O. volvulus*. Such a long-term guarantee cannot be realistically given by any control program. A further complication is that mechanisms of density-dependent regulation within the parasite–host–vector relationship can compromise intervention efforts to such an extent that the MF density in a population will not approach a breakpoint, but remain endemic even at very low MF densities. The classical concept of thresholds for vector abundance can partially compensate for these complications.

Fig. 1 illustrates and summarises threshold concepts and the terminology used in this paper. In onchocerciasis, vector abundance is quantified by the annual biting rate (ABR), the average number of bites taken by *Simulium* flies on one human host per year. The threshold biting rate (TBR) is the critical ABR, i.e. the average number of bites per human host per year, below which endemic onchocerciasis is not possible. Persistence graphs as shown in Fig. 1 allow for a quantitative visualisation of both threshold concepts, the TBR as the vector-related threshold defining elimination criteria during the control program, and the breakpoints as parasite-related thresholds defining when control can be stopped, as follows.

The 'zone of endemic transmission' represents average parasite burdens that can be found as endemic states. This zone would result as the trace of the pre-control equilibrium curve when shifted to the right, as is the case under CDTI. The 'zone of non-endemic transmission' can only harbour transient parasite burdens; it is divided by the breakpoint curve into an over- and an under-critical part. The 'zone of over-critical transmission' is located above the breakpoint curve. A parasite population in this zone will relapse when the intervention is stopped and will stabilise at the pre-control endemicity. The 'zone of under-critical transmission' is located below the breakpoint curve. A parasite population in this zone will die out without further interventions, i.e. stopping the intervention at this stage would result in elimination.

CDTI cannot reduce the average number of adult female parasites below a breakpoint; as a persistence shifting intervention (Duerr et al., 2005) it can only shift the TBR to higher values. The shifting process occurs in a time-dependent fashion depending on the survival curve of adult female parasites. As explained in Fig. 2 the concept of breakpoints helps to elucidate when an intervention program can be stopped. In Fig. 2 CDTI is assumed with an efficacy that shifts the TBR from 700 to 2,300 bites per person per year after several years of CDTI. Intervention outcomes are compared for two villages, L and M, which differ in their local ABR (village L, 'low', with 2,000 and village M, 'moderate', with 6,000 bites per person per year). In the absence of intervention the TBR lies at 700 bites per person per year, and villages L and M have on average approximately four and seven adult female *O. volvulus* per host, respectively (Fig. 2A). After 5 years of CDTI the TBR is shifted to approximately 1,500 bites per person per year, and parasite burdens in villages L and M have reduced to approximately two and four adult female *O. volvulus* per host, respectively (Fig. 2B). After 10 years of CDTI the TBR has reached its maximum shift at approximately 2,300 bites per person per year (Fig. 2C). This is not sufficient to exceed the ABR of village M, where the endemicity stabilises at approximately three adult female *O. volvulus* on average. In village L, however, the TBR exceeds the local ABR and an endemic state is no longer possible. The average parasite burden of approximately 0.7 adult female *O. volvulus* per host in village L represents a transient state on the way to elimination. Stopping the intervention at this stage, however, would still provoke a relapse into pre-control endemicity during the following years because the average parasite burden is still above the breakpoint of the pre-control persistence curve. After 15 years of CDTI the situation is unchanged for village M which has stabilised at its control-specific endemicity, but the average parasite burden in village L is still declining on the way to the infection-free state (Fig. 2D). Stopping the intervention in village L at this time would be safe because the parasite burden is lower than the breakpoint of the pre-control persistence curve.

In this investigation we explore the eradicability of onchocerciasis first by persistence graphs that show predictions of the prevalence and the density of parasites dependent on the ABR. CDTI-induced shifts of the TBR will be derived and used to predict inversely the minimum efficacy of CDTI dependent on the ABR. The results point to possible risk factors for successful control and they can finally be summarised as rules for elimination strategies.

2. Materials and methods

2.1. Modelling approach

The current investigation is based on a previously published methodology (Duerr and Eichner, 2010). In that paper, we developed a stochastic model to maximise congruence between model

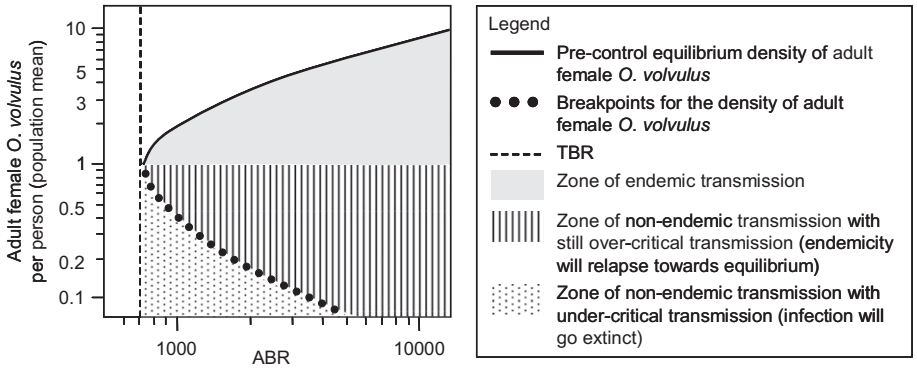

Fig. 1. Terminology used in this paper. Zones of endemicity according to the average number of adult female *Onchocerca volvulus* per host and dependent on the annual biting rate (ABR). Infection cannot persist in a community if the ABR is below the threshold biting rate (TBR; dashed, vertical line). The solid and the dotted curves represent equilibrium and breakpoint parasite densities under pre-control conditions. Community-directed treatment with ivermectin (CDTI) shifts these two curves to the right (see Fig. 2).

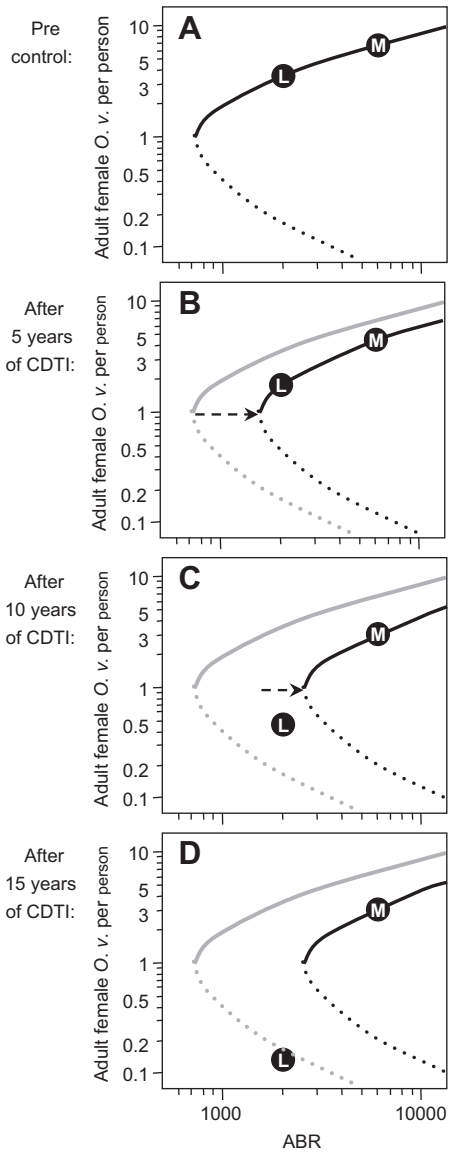

Fig. 2. Persistence shift caused by community-directed treatment with ivermectin (CDTI) at four time points during the course of a control program. In each graph the average number of adult female *Onchocerca volvulus* (*O. v.*) per host is shown dependent on the annual biting rate (ABR). Intervention outcomes are compared for two villages L and M which differ in their local ABR (village L, 'Low', with 2,000 and village M, 'Moderate', with 6,000 bites per person per year). CDTI is assumed with an efficacy that shifts the threshold biting rate (TBR) from 700 to 2,300 bites per person per year after several years of CDTI. Continuous curves represent the equilibrium parasite burdens and dotted curves represent ABR-specific breakpoints. Absolute values on the log-axes illustrate the order of magnitude rather qualitatively. The pre-control curve is shown in B–D in grey for comparison.

output and onchocerciasis data (prevalence and intensity of adult female parasites and MF, vector-related measures such as the number of L3s per fly, ABR, the annual transmission potential (ATP), etc.). Throughout this paper the term 'density' refers to parasite numbers per host; e.g. the density of adult female parasites means the average number of adult female *O. volvulus* per person, and MF density means the average number of MF per mg skin snip. The model has not been calibrated to the community microfilaria load, CMFL, which is usually estimated from adults 20 years of age or over.

The model considers processes of density-dependent regulation which can be classified as limitation and facilitation processes, as reviewed earlier (Duerr et al., 2005). The majority of density-dependent influences originate from limitation processes, which counteract efforts to eliminate the infection. In onchocerciasis, these limitation processes are: (i) the annual infection rate, which depends on the ATP, (ii) the production of MF as a function of the burden of adult female parasites in a host, (iii) MF uptake by flies, dependent on the MF density in human hosts, (iv) fly mortality, which depends on the number of MF ingested by a fly during a blood meal, and (v) larval development within the fly, which is influenced by the number of MF ingested by a fly during a blood meal. In contrast, there is only one 'standard' facilitation process, namely the mating probability of parasites (May, 1977; May and Woolhouse, 1993). The considerations of other facilitation processes, which support efforts to eliminate the infection, will be discussed later.

Modelling the eradicability of onchocerciasis by CDTI requires the quantification of the effects of this type of intervention. As a microfilaricide, ivermectin reduces MF density in the human host. Epidemiologically relevant is the average reduction of the MF density in the population, which depends on many variables including the percentage of the population reached by the control program, the number of treatment rounds per year and the intra-host efficacy of ivermectin. It is beyond the scope of this investigation to describe results dependent on these variables separately. Instead, we combine these variables into a common measure, called 'efficacy of CDTI'. It represents the reduction in the average MF density in the population achieved by CDTI. For example, an efficacy of CDTI of 80% would reduce the average MF density in the population from 10 to two MF per mg skin snip.

2.2. Calculating breakpoints

A breakpoint is defined as an ABR-specific parasite burden below which an endemic state is not possible because the parasite population will die out without any further control effort. In mathematical terms, it is an unstable equilibrium state which separates the two stable equilibriums of the endemic state and the infection-free state. Breakpoints actually should be quantified multi-dimensionally, considering all relevant variables such as adult worm density, MF density, ABR, ATP, etc. For the purpose of applicability we reduced this system to the most influential variable, the density of adult female *O. volvulus*. Fig. 3 shows the role of breakpoints under CDTI. Breakpoints can be numerically determined by varying the initial values between the ABR-specific equilibrium parasite burden and the infection-free state (zero). Here, we vary the average number of adult female *O. volvulus* per person, because breakpoints should refer to the longest-living parasite stage (see Section 1).

As the infection process of the stochastic model also considers the number of developing L4s, the variation in initial values refers not only to the initial value for the expected number of adult female *O. volvulus* per person ($\overline{W}_{ini}$), but also involves a corresponding initial value for the expected number of L4s per person ($\overline{L}_{ini}$). In the equilibrium state, the relationship between $\overline{W}_{ini}$ and $\overline{L}_{ini}$ is determined by the life expectancies of adult female *O. volvulus* $1/\sigma_W = 10$ years and L4s $1/\sigma_L = 1$ year. The initial value for the number of L4s per person is then $\overline{L}_{ini} = \overline{W}_{ini} \cdot \sigma_W/\sigma_L$.

In addition to varying the expected values of $\overline{W}_{ini}$ and $\overline{L}_{ini}$, an iterative search of breakpoints requires assumptions on the initial distributions of adult female parasites, $P(W)$, and of L4s, $P(L)$. We make use of the fact that the prevalence of parasites increases with the density of parasites. The model reflects this property using the following two correlations that can be found independently of the efficacy of control: (i) the relationship between prevalence and density of adult female parasites can be described by $P(W) = aW^b/(1+aW^b)$ with parameters $a = 1.5622$ and $b = 1.2417$, and (ii) the relationship between prevalence of adult female parasites and prevalence of L4s can be described by

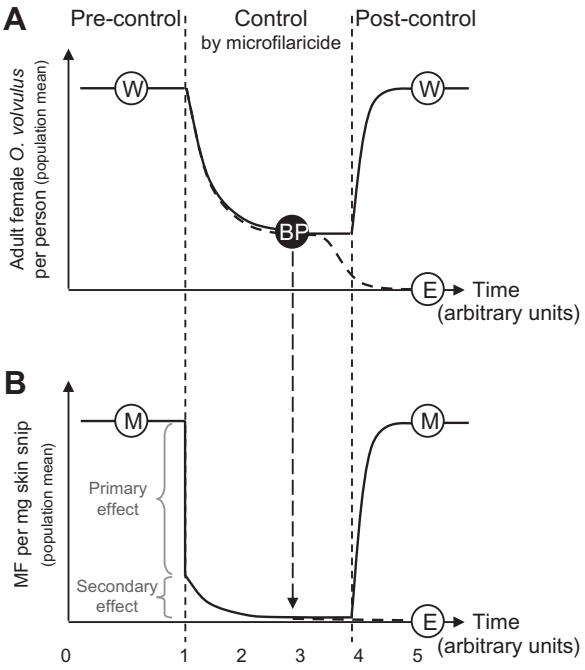

Fig. 3. Qualitative illustration of the role of breakpoints and the longitudinal changes in the average densities of adult female *Onchocerca volvulus* (A) and microfilariae (MF per mg skin snip, (B)) in the human population. The graph is specific for a certain annual biting rate (ABR), and proportions in time and parasite burdens will change as the ABR changes. In circles: W, endemic equilibrium density of adult female parasites per host; M, endemic equilibrium MF density; BP, breakpoint; E, Elimination. Time 0–1: endemic state as found under pre-control conditions. Time = 1: onset of control: treating the population with a microfilaricide will quickly reduce the average MF density in the population ('primary effect' of approximately 80% in (B)), but not so the adult female parasite population (A). Time = 2: the further reduction in MF densities follows the reductions in the adult female parasite population under a control-reduced infection rate ('secondary effect'). Ongoing infection is possible because the parasite is not eliminated. Time = 3: if long-term control by a microfilaricide is capable of bringing the adult female parasite burden below its ABR-specific breakpoint, elimination will follow (dashed line). If the breakpoint cannot be reached, parasite burdens will remain endemic at a new, control-specific equilibrium (solid line). Time 4–5: if control is stopped when the breakpoint has not been reached, parasite burdens in the population will return to their pre-control equilibrium values.

$P(W) = P(V)^{c(1-P(V)d)}$ with parameters $c = 0.587$ and $d = 0.2206$. With these relationships, any initial value for $\overline{W}_{ini}$, which is proposed by the algorithm searching for breakpoints, can be complemented with initial values for $\overline{L}_{ini}$, $P(W)$ and $P(L)$.

3. Results

3.1. Prevalence and density of adult female parasites

Fig. 4 shows densities and prevalences of adult female *O. volvulus* and MF predicted for different efficacies of CDTI. According to Fig. 4A and B the zone of non-endemic transmission spans an average burden of adult female parasites of less than 0.8 adult female parasites per person, which is equivalent to a prevalence of less than 53% of humans with adult female parasites. As suggested previously (Duerr et al., 2005), CDTI can only shift the persistence graph to the right, but not suppress the average burden or prevalence of adult female parasites below a breakpoint; it cannot even make the current parasite burden fall in the zone of non-endemic transmission (Fig. 4A and B). If a control program detects 'endemicity' in the zone of non-endemic transmission, this cannot be an endemic state but must be (apart from the possibility of random fluctuations) a transient state on the way towards elimination. In such a case CDTI is likely to have been effective enough to shift the TBR above the ABR.

As the ABR increases, the breakpoints for the density of adult female *O. volvulus* quickly reach values of less than 0.1 adult female *O. volvulus* per person and are then practically zero (Fig. 4A). Due to these low values, which cannot be resolved diagnostically, the density of adult female *O. volvulus* is not an appropriate indicator for a control program to monitor intervention success. In contrast, Fig. 4B shows that the prevalence of adult female *O. volvulus* is a better indicator for a control program because the zone of non-endemic transmission starts – independently of the ABR – at a prevalence of 53% (proportion of the population harbouring at least one adult female *O. volvulus*). A prevalence of less than 53% of carriers of adult female *O. volvulus* under control indicates that (apart from random fluctuations, see above) the control program is in principal capable of shifting the TBR over the ABR and thus is in principal capable of achieving elimination.

3.2. Prevalence and density of MF

Under pre-control conditions, the average MF density in the population is predicted to be between 0.8 MF per mg skin snip in the vicinity of the TBR to approximately 60 MF per mg skin snip when the ABR exceeds values of 100,000 bites per person per year (Fig. 4C). Even under very efficient control, providing an ivermectin-related reduction of the MF density in the population by 95%, an equilibrium endemicity with very low MF densities in the population is possible (e.g. under an efficacy of CDTI of 95%, the MF density in the population is predicted to be between 0.01 MF per mg skin snip in the vicinity of the TBR to approximately 1 MF per mg skin snip when the ABR exceeds 100,000 bites per person per year, Fig. 4C). Clearly, average MF densities lower than 0.1 MF per mg skin snip are diagnostically difficult to detect, implying that infection may remain endemic even under efficient control at levels which diagnostically would be declared to be zero.

These considerations also apply for MF prevalence (Fig. 4D). Under pre-control conditions, the MF prevalence is predicted between 9% in the vicinity of the TBR and 90% when the ABR exceeds 100,000 bites per person per year. Reducing MF burdens by 95%, the endemic prevalence of MF ranges from 0.5% in the vicinity of the TBR to approximately 50% when the ABR exceeds values of 100,000 bites per person per year (Fig. 4D).

3.3. Endemic versus non-endemic transmission

The borderlines between the endemic and the non-endemic states are represented in Fig. 4 as dashed lines, and it is important not only to consider the levels of these borderlines, but also to consider their orientation. For MF they proceed downwards, implying that infection can remain endemic at lower levels when the ABR increases. The practical relevance for control based on CDTI is that elimination thresholds for the density or the prevalence of MF cannot be given independently of the ABR; threshold levels for the density or the prevalence of MF decrease with increases in the ABR.

As a hypothetical example to illustrate this, consider two villages, both of which show an average MF density of 0.2 MF per mg skin snip after several years of CDTI, during which they have been exposed to different ABRs, say of 1,000 and 3,000 bites per person and year, respectively. In village 1 (circle 1 in Fig. 4C) a MF density of 0.2 MF per mg skin snip would represent a transient MF density which is located in the zone of non-endemic transmission (CDTI must have been sufficiently efficient to shift the TBR past the ABR of 1,000; the observed MF density is just a 'snapshot-density' on the way to elimination). In village 2 (circle 2 in Fig. 4C) the same MF density would have stabilised at this point which represents an endemic state (CDTI has not been efficient enough to shift the TBR over the ABR of 3,000).

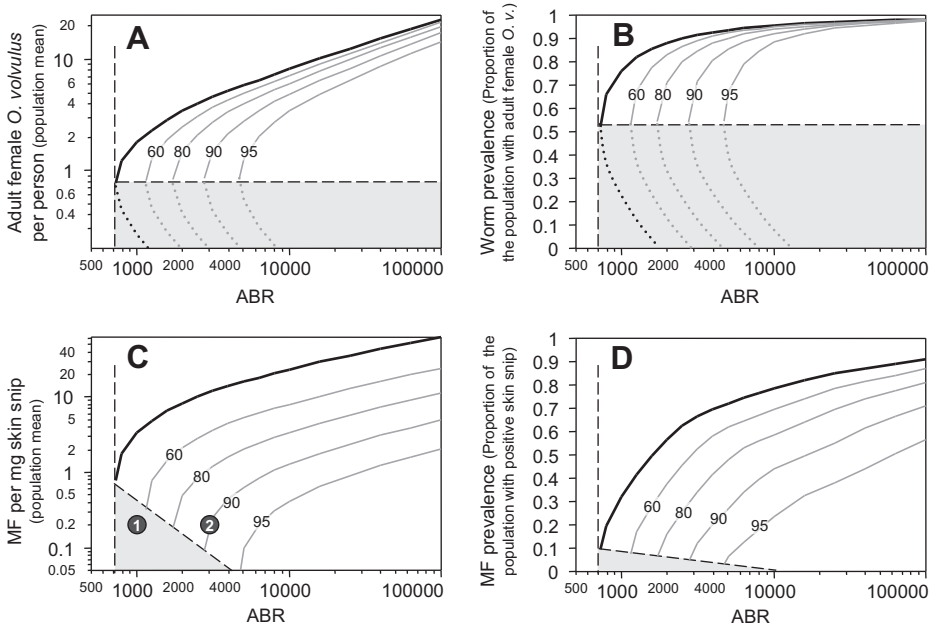

Fig. 4. Density and prevalence (solid curves) of adult female *Onchocerca volvulus* (*O. v.*) and microfilariae (MF) predicted for different efficacies of community-directed treatment with ivermectin (CDTI) on the population MF density (MF per mg skin snip). The highest, black curve in each graph represents the pre-control endemicity dependent on the annual biting rate (ABR). The other four curves assume that CDTI reduces the average MF density in the population by 60%, 80%, 90% and 95%. Breakpoints are predicted for adult female *O. volvulus* only (dotted curves in A and B). Grey shaded areas in each graph represent the zone of non-endemic transmission. The pre-control threshold biting rate (TBR) lies at 730 bites per person per year (vertical dashed line). For MF densities in C and D, the borderline between the zone of endemic and non-endemic transmission (dashed line) decreases with both the ABR and the efficacy of control, leading to very low values for MF endemicity that are difficult to detect. In contrast, for the adult parasite burden shown in A and B the borderline between the zone of endemic and non-endemic transmission are located at higher endemicity and proceed horizontally, indicating that the status of the elimination program may be monitored independently of the ABR or the efficacy of control. The two filled circles (1 and 2) in C represent two villages to illustrate non-endemic versus endemic transmission (see Section 3.3). Breakpoints for the density and prevalence of MF are not shown because they can be misleading (see Section 1).

For higher ABRs it may be likely that one might assume elimination due to not clinically detecting MF whilst the MF still exist in a controlled low-density, but endemic state. Monitoring the prevalence of adult female parasites instead can overcome this difficulty, because the borderline between endemic and non-endemic transmission proceeds horizontally (Fig. 4A and B) and thus threshold conditions can be expressed for adult female parasites independent of the ABR and the efficacy of CDTI. For these reasons, monitoring the prevalence of adult female parasite burdens is superior to monitoring the prevalence of positive skin snips. As a rule of thumb, the model predicts that a CDTI program moves towards elimination if the prevalence of carriers with adult female *O. volvulus* can be suppressed for a sufficient number of years below 50% (this estimate may be influenced by demography and birth rates).

3.4. Threshold shifts by CDTI

Controlling onchocerciasis by means of a microfilaricide is quantitatively identical to a control regimen in which the reproductive capacity of the parasite is reduced. As shown in Fig. 4, this shifts the persistence graph, and thus the TBR, to the right. These threshold shifts become relevant when ivermectin treatment achieves an average MF reduction in the population of over 80%, and becomes substantial when the MF reduction exceeds 90% (Fig. 5). TBR shifts may provide an option for eliminating the infection by additional vector control which may lead to elimination even when conducted at a low level.

The results can be summarised into three steps that are necessary to eliminate onchocerciasis by means of CDTI: (i) achieve an efficacy of CDTI that shifts the TBR to the right of the ABR (or reduce the ABR by supplementary vector control below the CDTI-shifted TBR), then (ii) maintain this level of CDTI over a period which covers the life span of adult female *O. volvulus*; and (iii) CDTI can be stopped, when the average parasite burden is lower than the ABR-specific breakpoint of the pre-control curve (not the shifted persistence curve which holds under CDTI).

3.5. Risk factor infection rate

The results suggest that control based on CDTI alone will – under feasible treatment coverage – not be capable of eliminating

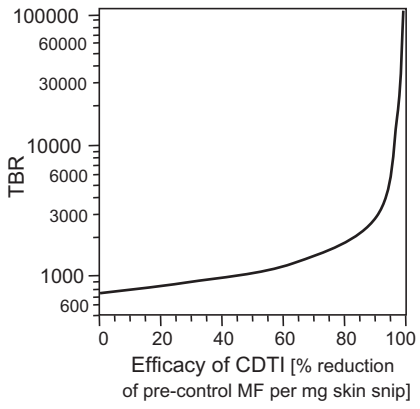

Fig. 5. Predicted values for the threshold biting rate (TBR) as a function of the efficacy of community-directed treatment with ivermectin (CDTI). Efficacy is represented on the horizontal axis by the percentage reduction of the average pre-control microfilaria density (MF per mg skin snip) in the human population. The TBR does not increase substantially if the MF density in the population is reduced by 80% or less. Considerable threshold shifts seem to be possible only for very high reductions in the MF density (which may be unrealistic for feasible coverages of a programme based on CDTI).

onchocerciasis when the annual biting rate exceeds values of 5,000 or 10,000 bites per person per year. The reason for this pessimistic prediction can be found in the dominance of limitation processes (see Section 4 and Supplementary Fig. S1) which lead to high infection rates even when the CDTI-induced MF reduction is substantial. Fig. 6 illustrates this by showing the infection rate under control as a percentage of the corresponding pre-control level. For a given ABR, a considerable reduction in the infection rate by CDTI occurs only when the ABR approaches the TBR. The graph shows that infection rates as high as 25–50% of the pre-control level can be expected in villages where the ABR under control is just slightly above the (shifted) TBR. Consequently, considerable endemicity can prevail in villages where minor efforts in additional vector control would be able to push the CDTI-based program towards the target of elimination.

4. Discussion

The model yields pessimistic predictions for the prospects of eliminating onchocerciasis in Africa by a strategy that is based solely on community-directed treatment with ivermectin (CDTI). The reports from Senegal and Mali have shown on the other hand that onchocerciasis can be eliminated (Diawara et al., 2009). Such deviations between theory and practise will not be viewed as contradictions here, but as a function of the endemicity. This allows for generalisations and conclusions about the control of onchocerciasis in Africa.

(i) The role of the ABR: control programs – even when based on CDTI alone – must take into account the region-specific abundance of vectors, as the influence of the ABR on intervention success can be as strong as, for instance, the influence of the percentage of the population covered under CDTI.
(ii) The role of CDTI-induced threshold shifts: control based on CDTI elevates the TBR. This may provide an option for eliminating the infection by limited vector control, depending on the ABR.
(iii) Impact of a macrofilaricidal effect of ivermectin: a reduced life expectancy of adult female *O. volvulus* under ivermectin treatment facilitates successful control, but this auxiliary effect becomes increasingly negligible when ABRs exceed 10,000 bites per person per year.

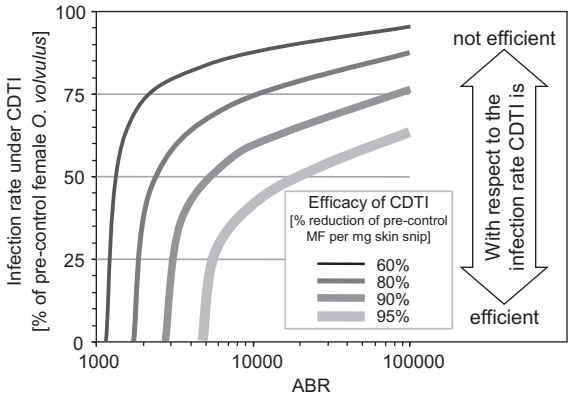

Fig. 6. Infection rate with adult female *Onchocerca volvulus* under different schemes of community-directed treatment with ivermectin (CDTI) and dependent on the annual biting rate (ABR). Curves represent proportions of corresponding pre-control levels. 'Efficacy of CDTI' means the percentage reduction of the average microfilaria density (MF per mg skin snip) in the human population. The threshold biting rate (TBR) for each curve is located where the curve meets the zero infection rate.

(iv) The role of the infection rate: the long-term efficacy of control based on CDTI is determined by the adult worm infection rate under CDTI. Diagnostics for determining the infection rate should be improved.
(v) The role of breakpoints: CDTI, which primarily suppresses the average MF density in the population, cannot suppress the endemicity below a breakpoint for the average density of adult female parasites in the population. The role of breakpoints restricts us to endgame scenarios.
(vi) The role of low-spreaders: many patients with low parasite burdens compromise successful control more acutely than few patients with high parasite burdens. Diagnostic tools that detect the prevalence of adult parasites should be improved and extended.

The role of the ABR: The endemicity of infection increases with the ABR and thus efforts of control must increase with the ABR to achieve comparable levels of intervention success (Fig. 4). A simple comparison may illustrate this: assume a community of 1,000 citizens which, after years of successful control, harbours only one microfilariae-positive individual. Then, it makes a difference whether 10 or 1,000 flies per year (ABR = 10 or 1,000 bites per person per year) will feed on this patient and will transmit the infection to the remaining, non-infected part of the population. For a control program based on CDTI this means that the efficacy required for elimination must increase with the ABR. This relationship has also been expressed previously in terms of other variables. For example, Winnen et al. (2002) showed that the duration of treatment required to eliminate infection depends on the pre-control endemicity which is a correlate for the ABR.

The role of CDTI-induced threshold shifts: As shown in Fig. 2, elimination under CDTI is not primarily caused by having reached an ABR-specific breakpoint but by the fact that control must have shifted the persistence graph far enough to the right so that the TBR exceeded the ABR over several years. CDTI alone cannot lower the average burden of adult female parasites into the zone of non-endemic transmission as the residual infection rate can still remain significant under control (Fig. 6). For these reasons elimination strategies must be focused on increasing the efficacy of CDTI so that the TBR can be shifted above the ABR (Fig. 5). Currently, the most promising option for maximising effects by CDTI seems to be treating the population at semi-annual intervals (Cupp et al., 2010). This, however, may reach the boundaries of feasibility in Africa. If improving coverage or increasing the number of treatment rounds per year cannot improve the efficacy of CDTI by the required amount, lowering the ABR is the only option, e.g. by additional vector control which can lower the ABR towards the CDTI-elevated TBR. It should be noted that a macrofilaricidal effect may support elimination strategies, as described below.

An elimination strategy that has been successful in one village may not produce the same success in villages with higher ABRs. It is misleading to state that elimination can be expected below a certain MF endemicity as the critical endemicity depends on the ABR (Fig. 4). As shown in Fig. 5, the TBR asymptotically approaches infinite values as the efficacy of CDTI increases. It is easy to appreciate a gain in efficacy, but the term "infinity" deserves attention here. For a control program based on CDTI it means that any gain in efficacy (for instance by increasing coverage) can cause an over-proportional shift in the TBR. Although the prediction in Fig. 5 suggests that this becomes relevant only for efficacies exceeding 80% or 90%, it is worth emphasising that any increase in the efficacy of CDTI results in an over-proportional effect on the TBR. Efficacies of 80% or 90% are ambitious but the message is: 'a further step of one percent is a step towards infinity'.

Impact of a microfilaricidal effect of ivermectin: A macrofilaricidal effect of ivermectin reduces the life expectancy for adult

female *O. volvulus* under ivermectin treatment. Although this effect could not be demonstrated during the early years of ivermectin treatment (Albiez et al., 1988; Duke et al., 1991; Awadzi et al., 1999), it was proposed later in a long-term study (Duke, 2005) and after merging the results of several trials with multiple treatments per year (Cupp and Cupp, 2005). As these studies do not quantify the average reduction of the life expectancy of adult female *O. volvulus*, we investigated the effect via sensitivity analyses of life expectancies for adult female *O. volvulus* between 3 and 10 years under ivermectin treatment (10 years represents 'no macrofilaricidal effect' as this value is assumed in the model for the natural life expectancy of adult female *O. volvulus*). The term 'macrofilaricidal' is used in the following in a broader sense as other side-effects of ivermectin can similarly affect the transmission dynamics, e.g. an ivermectin-associated degeneration of the adult worm population or inhibitory effects on reproduction, embryogenesis or on insemination by male worms, etc. (see, for instance Albiez et al., 1988; Chavasse et al., 1992; Duke et al., 1992; Klager et al., 1993).

As shown in Fig. 5, increasing the efficacy of CDTI leads to a better than linear increase in the TBR. Interchanging the axes of this graph (plotting the inverse function), and replacing the TBR by the ABR, provides a graph which is relevant in practical terms as shown in Fig. 7: it shows by what proportion CDTI must decrease the average MF density in the population, dependent on the ABR, in order to eliminate the infection in the population. As one would expect, the minimum efficacy of CDTI required for elimination increases with the ABR. A macrofilaricidal effect supports control efforts by lowering this minimum efficacy. Substantial advantages from a macrofilaricidal effect can, however, only be expected for ABRs of about 10,000 bites per person per year or less. For ABRs exceeding 10,000 bites per person per year the beneficial impact of a macrofilaricidal effect diminishes substantially. As mentioned above, these predictions are more pessimistic than the results of simulations with ONCHOSIM (Alley et al., 2001) which considers fewer limitation processes than the model used for investigations here.

The role of the infection rate: Fig. 6 shows that for higher ABRs, and even under efficient CDTI, the rate of the infection quickly approaches values not far from the pre-control level. The reasons are illustrated in Supplementary Fig. S1. This figure makes it intuitively clear that the number of limitation processes which are located between the stage where intervention is performed and the stage where infection of humans takes place is critical. Disadvantageous for CDTI is that its efficacy becomes down-regulated by every limitation process which occurs between the stage of intervention (microfilaricide, Supplementary Fig. S1E) and the stage of infection of humans with L3s (Supplementary Fig. S1D). The limitation processes involving vectors (Supplementary Fig. S1A and B) compromise the impact of CDTI, and make vectors overly influential.

Fig. 6 reflects ABR-related issues as found previously: a substantial reduction of the infection rate under control is expected only when the ABR is in the vicinity of the TBR. As a rule of thumb, Fig. 6 may be interpreted dually: that the prevalence will exceed 50% of its pre-control level when the long-term ABR in a village is two or three times higher than the (shifted) TBR under CDTI. The practical relevance for a control program is that the (invisible) TBR cannot be far from the ABR when infection levels under control are less than 50% of the pre-control level. In these cases even minor vector control might push the infection towards elimination. It is important to note that this would require only a partial vector control and not an almost perfect one as in the era of the Onchocerciasis Control Programme (OCP).

The idea that the infection rate under control can be used as a measure of how close the program is to achieving elimination may require more empirical support. Monitoring the infection levels in children would then become a highly relevant tool for monitoring the efficacy of CDTI, and improving methods for the detection of adult parasites should again receive a higher research priority.

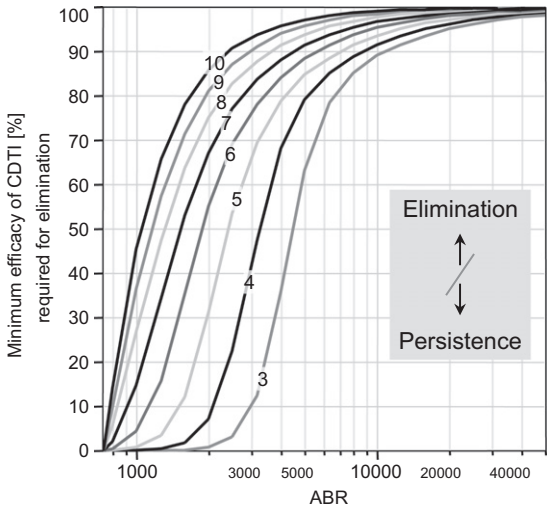

Fig. 7. Efficacy of community-directed treatment with ivermectin (CDTI) required for elimination of onchocerciasis, dependent on the annual biting rate (ABR) and for different life expectancies of adult female *Onchocerca volvulus*. The 'efficacy of CDTI' on the vertical axis represents the average reduction of the microfilaria density (MF per mg skin snip) in the population, and is a net measure comprising the contributions of variables such as coverage, number of treatment rounds per year and the intra-host efficacy of ivermectin. The curves represent minimum efficacies required for elimination of the infection given life expectancies of adult female *O. volvulus* ranging from 3 to 10 years (the curve for 10 years represents 'no macrofilaricidal effect' and is identical with the inverse of the curve shown in Fig. 5). A CDTI-related reduction of the life expectancy of adult female *O. volvulus* (e.g. via a macrofilaricidal effect of ivermectin) would reduce the minimum efficacy of CDTI required for elimination. For a given ABR, efficacies above the curve lead to elimination.

The role of breakpoints: As shown in Fig. 2, breakpoints become crucial when a decision must be made about when CDTI control can be stopped. Control can be stopped when the average burden of adult female parasites is below a breakpoint. This requires that CDTI has shifted the TBR above the ABR for a period of time that corresponds to the life span of adult female *O. volvulus:* between 9 and 14 years (possibly less, if there is a macrofilaricidal effect). As shown in Fig. 4, the breakpoint curves quickly drop off to values which are practically zero, or which cannot be detected, as the ABR increases. This leads to a pessimistic view about the possibility of elimination of onchocerciasis. Steeply decreasing breakpoint curves span a wide belt of parasite burdens which allow for non-endemic transmission. In these zones of over-critical transmission (cf. Fig. 1, the region between the breakpoint curves and the endemic equilibrium curves) elimination may occur thanks to random extinction of the parasite, perhaps due to an extended dry period or other ecological changes, but it cannot be expected. The results presented here suggest that elimination of onchocerciasis by means of CDTI is almost impossible when ABRs exceed the order of 10,000 bites per person per year. In such cases reducing the ABR (or more generally, reducing exposure) is the only option for strategies which aim for elimination.

The role of low-spreaders: A surprising result of our model is that unstable transmission is predicted to occur even with high values for the density and prevalence of adult female *O. volvulus* (about 0.8 adult female *O. volvulus* per person on average and a prevalence of 53%; see Fig. 4A and B). In a village with 100 citizens these values would imply a parasite distribution of approximately

80 adult female worms distributed among 53 infected persons. The distribution of the parasites among the population can make the infection-associated mortality of flies relevant, in particular if limitation processes control the MF uptake of vectors, as is the case for most African vectors. We discuss the following two scenarios.

Scenario A (lumped infection): If the 80 adult female worms are distributed among 20 patients, then the average parasite burden among the population is not changed, but the prevalence is decreased to 20%. In this case there is an average density of four adult female worms per patient and consequently we expect a higher MF density in these patients. If flies feed on patients with higher MF density, they will more likely die due to extra infection-associated mortality. This fact, together with the fact that fewer flies will take blood meals, will lead to a decrease in the overall intensity of transmission.

Scenario B (dispersed infection): If, on the other hand, the 80 adult female worms are distributed among 80 patients, this does not alter the average parasite burden among the population, but increases the prevalence to 80%. In this case, we expect an average density of one adult female worm per patient and consequently a lower MF density in these patients. In this scenario, more flies will be able to feed on infected hosts and their individual risk of dying due to the extra infection-associated mortality is lower. Taken together these two effects would increase the overall intensity of transmission.

So our model suggests that a super-spreader problem (which has been described for other, mostly directly transmitted, diseases) does not exist for onchocerciasis, but the opposite problem can occur: transmission and persistence of onchocerciasis may be maintained by many hosts with low MF densities which are efficiently transformed via the vector into a low infection rate. It also confirms the general assumption that heterogeneities between parasites, vectors or hosts promote the persistence of the parasite (Anderson and May, 1991), and is in line with concerns that hypoendemic areas might act as reservoirs of infection (Katabarwa et al., 2010).

Scenarios A and B are simplified in the sense that factors such as mating probability have been neglected. Under dispersed infection, for instance, mating probability will lower the elevated intensity of transmission when the parasite burden in patients is very low. Thus, the abovementioned effects will not be linear, but will show a unimodal relationship, the investigation of which is beyond the scope of this paper. The two scenarios show furthermore that breakpoints require a multi-dimensional description of endemicity, which is neglected here for the purpose of applicability (see Section 2).

Uncertainties: Usually clinical studies focus on collecting field data where endemicity is high and action is needed. This means that model calibrations can rarely consider low-endemicity data and thus rely on extrapolation near the state of non-endemicity (elimination). Predicting elimination, however, relies on properly calibrated models, and their predictive capacity is weak when the distance between observed endemic states and the extrapolated state of non-endemicity is large. Although the model has been extensively fitted to pre-control onchocerciasis data originating from extended regions in West and Central Africa (Duerr and Eichner, 2010), deviations between predictions and observations can result from such extrapolations into regions of non-endemicity. Weaknesses in the data could arise from variables such as ABR values, MF densities or adult worm burdens, all of which can be affected by sampling errors, bias or different evaluation methods (e.g. MF counts can depend on the incubation method and ABR estimates can be biased by zoophily of vectors, etc.).

The current model was designed to maximise the correlation between model output and onchocerciasis data for the equilibrium prevalence and intensity of different parasite stages, with special consideration given to density-dependent processes. Supplementary Fig. S1 illustrates that the eradicability of a parasitic disease depends on the number and the degree of density-dependent processes, which we classify into limitation and facilitation processes. In general it can be shown that facilitation processes 'facilitate' the eradicability of a parasite, whereas limitation processes 'limit' the prospects of success (Duerr et al., 2005). Thus, predictions will be too pessimistic if a model over-estimates limitation, and they will be too optimistic if the model over-estimates facilitation. The pessimistic predictions presented here can mostly be attributed to the large number of limitation processes in the model. On the other hand, the model output matches available onchocerciasis data quite well (Duerr and Eichner, 2010).

As the mating probability is the only facilitation process in the current model, predictions presented here will be overly pessimistic if there are other facilitation processes with significant influence. Candidates for such facilitation processes are a macrofilaricidal effect of ivermectin on adult female *O. volvulus* (Duke, 2005) and parasite-induced immunosuppression (Duerr et al., 2003) in combination with ivermectin-facilitated immunity (Schulz-Key et al., 1992; Soboslay et al., 1994).

Generalisations and recommendations: Beyond the quantitative uncertainties in a model-based prediction of thresholds and breakpoints, the following conclusions and rules can be derived in general:

Rule 1: Elimination of onchocerciasis by CDTI depends on the persistence-shifting property of CDTI. Future investigations into threshold conditions should address the shift of the TBR caused by CDTI. (The concept of breakpoints is still relevant, but is difficult to put into the context of a control program, because threshold conditions depend on the ABR.)

Rule 2: The TBR increases over time by sustained CDTI. Elimination is possible if CDTI shifts the TBR above the actual ABR. Thus, the baseline ABR determines whether elimination can be achieved or not. Even if CDTI with a given efficacy has achieved elimination in a region with low ABR, the same efficacy can fail to eliminate onchocerciasis in regions with a higher ABR.

Rule 3: TBR shifts caused by CDTI make vector control measures more likely to succeed compared with OCP efforts without CDTI. Partial and even minor vector control may lead to elimination if CDTI alone has not achieved elimination.

Rule 4: CDTI can only under-proportionally reduce the infection rate when limitation processes are involved. A low level infection rate compromises any elimination strategy because newly acquired adult female worms live for years and thus will delay elimination for years.

Rule 5: Improvements in diagnostic tests for the prevalence of adult female parasites and diagnostic measures for the infection rate (especially in children) would be useful as the prevalence of adult parasites seems to be the best measure of the status of a control program.

Rule 6: At the current stage of investigation under-running a 50% prevalence of carriers with adult female worms seems to be the best indicator that a CDTI program is potentially capable of achieving elimination (compare Fig. 4: MF endemicity is not an appropriate indicator as it may reside below a detection due to microfilaricidal treatment).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpara.2010.12.009.

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