Required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in West Africa

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In the extension areas of the Onchocerciasis Control Programme in West Africa, aerial larviciding is supplemented with annual ivermectin treatment, mainly to achieve better control of morbidity. The purpose of this study is to determine whether and to what extent the addition of annual ivermectin treatment permits earlier cessation of vector control than originally recommended. The effectiveness of combined ivermectin distribution and vector control was assessed using an epidemiological model. Model predictions suggest that, dependent on the pre-control endemicity of the area and the proportion of persons treated during each ivermectin round, large-scale annual treatment permits a considerable reduction in the duration of vector control. Taking into account uncertainty about the efficacy of ivermectin, our results indicate that, provided treatment coverage is at least 65% and there is no importation of infection from elsewhere, 12 years of combined control will be sufficient to reduce the risk of recrudescence to below 1% in even the most afflicted areas.

Introduction

When the Onchocerciasis Control Programme in West Africa (OCP) started its activities in 1975, the only reliable strategy for controlling river blindness was larviciding of the rivers where the vector, *Simulium damnosum*, breeds. This technique enables the interruption of transmission of *Onchocerca volvulus* until the parasite reservoir in the human host is reduced to levels that will not lead to recrudescence after the cessation of larviciding and return of the flies. On the basis of model projections it was estimated that 14 years of vector control would be sufficient to achieve this objective, provided there was no importation of new infection (through humans or flies) (*1*).

The registration of ivermectin for human use in 1987 represented a breakthrough in the control possibilities for the disease. Treatment with ivermectin causes a drastic decline in microfilariae (mf) densities and has a significant impact on the development of ocular pathology (*2–4*). Furthermore, ivermectin has few side-effects and is proven to be suitable for large-scale application (*5*, *6*). The availability of ivermectin made possible a reorientation of the OCP and a review of its original plans. The expected primary role of the drug was the control of morbidity in extension areas and in those parts of the original area where vector control was unsuccessful or where vector reinvasion was reported (*7*). It was, however, equally important to determine to what extent mass ivermectin treatment, either on its own or in combination with vector control, could contribute to control of mf transmission. Although community treatment trials suggested a noticeable impact on transmission (*8–10*), the remaining level of transmission was too high to justify the total substitution of mass chemotherapy for vector control. This was confirmed by preliminary model predictions showing that annual ivermectin treatment alone was not expected to eradicate the parasite from an endemic area within a period of 25 years (*11*, *12*).

The present article reports an estimate of the required duration of a strategy based on the combi-

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nation of vector control and annual ivermectin treatment. This strategy is currently applied in extension areas of the OCP. In these areas, vector control was initiated during 1988–90, while routine ivermectin treatment started in 1990 (*10*, *13*). An important question is whether and to what extent the addition of ivermectin to larviciding allows for a reduction in the minimum duration of vector control of 14 years for the prevention of recrudescence (*1*, *14*). Such a shortening would imply significant savings in effort and money. In addressing this question, we utilize recent findings on the effect of ivermectin on the viability of adult worms (*15*). Assessment of the potential effects of various strategies is based on model predictions.

Materials and methods

In this study, the effectiveness of a strategy — a certain combination of vector control and annual ivermectin treatment — is represented as the risk of recrudescence of infection after strategy cessation. Calculation of this risk is based on the stochastic microsimulation model ONCHOSIM and the statistical analysis of results. A complete description of this model and its validation have been reported elsewhere (*16–18*).

Basic assumptions

Vector control operations are assumed to be 100% effective, i.e. to reduce the biting rate to zero. In agreement with empirical observations, flies immediately recolonize their former breeding sites after the cessation of larviciding (*8*). It is, therefore, assumed that the post-control biting rate is equal to the pre-control level. On the basis of analysis of longitudinal data from a community trial of annual ivermectin treatment in Asubende (Ghana) (*15*, *19*), the following assumptions with respect to the effect of an ivermectin treatment given at a standard dose of approximately 150μg/kg body weight are made: all mf are eliminated, after a temporary loss of fertility, mf production of female worms increases for 10–11 months, and mf production reaches a new equilibrium level 35% lower than before treatment (95% confidence interval (CI): 25–40%). Both the recovery period (mean, 10–11 months) and the irreversible fertility reduction (mean, 35%) vary between treatments (coefficient of variation (CV) = 0.54). The irreversible fertility reduction has an exponential effect, i.e. after n treatments the average female worm produces mf at $100 \times (0.65'')\%$ of the rate before treatment (e.g. 12% after five treatments). We test the implications of a lower drug efficacy by assuming a 25% irreversible fertility reduction per treatment (the lower bound of the CI). It is further assumed that 3% of treatments fail totally as a result of malabsorption (diarrhoea and/or vomiting) (*6*). The treatment coverage (proportion of the census population in a village receiving the drug) is also a variable in the analysis reported here. We take account of age- and sex-differences in coverage (in part due to temporary exclusion criteria (*19*)), individual variation in willingness to comply with treatment, and those permanently excluded from treatment as a result of chronic illness. An explanation of how these individual factors yield mean population coverage is provided in the Annex.

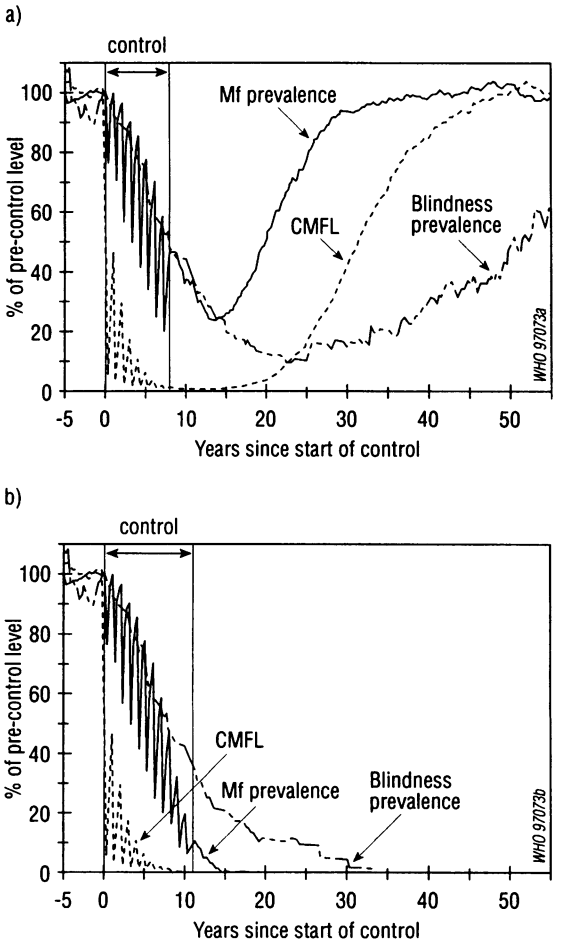
On the basis of these assumptions, ONCHOSIM has been used to simulate various strategies in human populations of around 300 (representative village size). Two model villages are considered: one with a high and the other with a medium pre-control mf-endemicity level. The levels chosen are similar to those used in Tiercoura and Folonzo (in Burkina Faso), as discussed previously (*1*, *17*), which had pre-control community microfilarial loads (CMFL, the geometric-mean mf load in adults) of 70 and 30mf per skin-snip, respectively. For these villages, denoted in this article as HIGH and MED, respectively, observations of pre-control biting rates are lacking. Using observations from the Pru river, close to the highly endemic Asubende region in Ghana (*8*, *19*), the annual biting rate in the absence of vector control in HIGH was estimated to be 27000 bites per person per year (for adult men) and in MED, 16000. Maximum exposure to bites is reached at the age of 15 years. Women are, on average, 30% less exposed than men. The CV of bites/person within a given age and sex group is estimated to be 0.39 for HIGH and 0.54 for MED. Since the biting rate in a village is a risk factor for recrudescence (*1*), we also model a Tiercoura-like village with an exposure (bites/person) CV of 0.58.

Simulation of control strategies

A control strategy is described by the number of years of vector control (v), the number of annual ivermectin treatments (i), and the treatment coverage (c, assumed to be constant during the whole duration of the strategy). A number of combinations of v (range: 0–15 years), i (range: 0–25), and c (range: 45–75%) are simulated. The result of each simulation is represented as recrudescence (value = 1) or no recrudescence (value = 0). We posit that recrudescence has occurred when, 50 years after strategy cessation, the CMFL is higher than 10mf/skin-snip (*1*). As the model is stochastic, a given control strategy for one simulation can result in

recrudescence and for another not. It is assumed that importation of infection from elsewhere (by humans or flies) does not occur. Thus, recrudescence is exclusively dependent on local transmission. An example of a control strategy followed by recrudescence (failure) is shown in Fig. 1(a), while an example of a successful control strategy is shown in Fig. 1(b). Both results are derived from a single simulation, and the possibility of dissimilar results from repeated simulations of identical strategies cannot be excluded.

Fig. 1. **Simulated microfilaria (mf) prevalence, community mf load (CMFL), and blindness prevalence, as a percentage of pre-control levels, in a high-endemicity village during and after combined vector control and annual ivermectin treatment (coverage, 65%).** a) Recrudescence after 8 years of combined control; b) No recrudescence after 11 years of combined control.



Statistical analysis of simulation results

As a result of variability in simulation outcomes, statistical analysis is required to relate recrudescence risk to strategy characteristics. Since recrudescence is a binary (0/1) variable, risk estimates were obtained by means of logistic regression using SPSS software. In their most complete form, regression equations included the independent variables v and ic, their square and cubic forms (e.g. v^2, ic^3), as well as linear, square, and cubic combinations (e.g. v^3i^2c). The variables i and c always appear as a combination because $i = 0$ implies the absence of ivermectin treatment regardless of the value of c, and vice versa. Regression coefficients were first estimated with only the linear and square terms; insignificant terms were removed from the equations (likelihood-ratio test, $P > 0.1$), and possibly significant cubic terms were added ($P < 0.05$). The Wald criterion (*20*) was used to select the terms eligible for inclusion or exclusion. Regression equations were derived for each of the model villages and for each assumption of drug efficacy. The resulting equations, each based on 3000 to 6000 simulations, enable a one-step calculation of the risk of recrudescence for a given v, i, and c. The reverse (i.e. given i and c, to determine how long the control strategy must last to reduce the risk to 0.01) is determined numerically. For several control strategies, goodness-of-fit of the equation was tested by comparing the risks predicted by the regression model with those obtained by simulating the same strategy 100 times and calculating the proportion of recrudescence. In all cases both estimates were in close agreement.

Results

Fig. 2 shows how the risk of recrudescence depends on combinations of annual ivermectin treatment and vector control in village HIGH. It is assumed that average treatment coverage is 65% and that both control methods start in the same year. The curves represent isorisk lines, and connect those strategies resulting in equal recrudescence risks (0.01, 0.1, 0.5, and 0.99). Below or to the left of each isorisk line (less vector control and fewer annual treatments, respectively) risk is higher than on the line; above or to the right, it is lower. In the absence of ivermectin treatment (points on the ordinate), approximately 13 years of vector control are required to reduce the recrudescence risk to 0.01. If larviciding is combined with annual ivermectin treatment throughout the control period, a total duration of 11 years is sufficient to achieve the same result (intersection point of isorisk and dashed line). The isorisk lines shown in Fig. 2 diverge with an increasing number of annual

Fig. 2. **Isorisk lines (representing equal probabilities (*P*) of recrudescence) for different combinations of vector control and annual ivermectin treatment (coverage, 65%) in a high-endemicity village.** Dashed line represents equal numbers of years of vector control and ivermectin treatments.

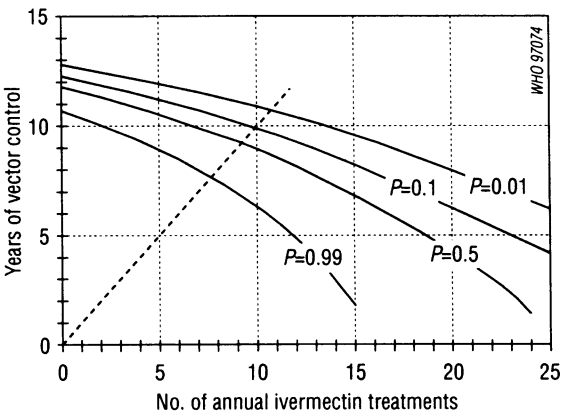
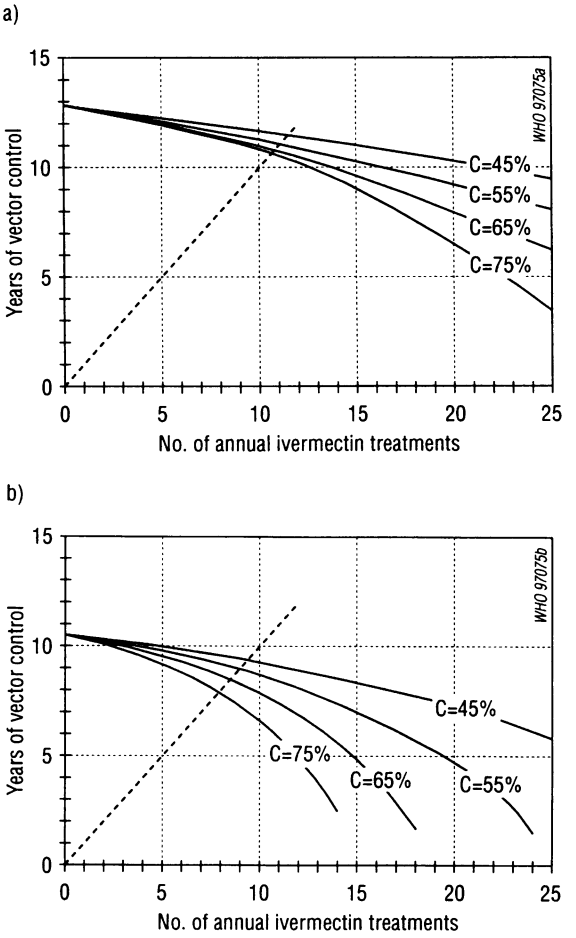


Fig. 3. **Isorisk lines (P = 0.01) for different combinations of vector control and annual ivermectin treatment, at different coverage levels (C) of ivermectin treatment.** Dashed line represents equal numbers of years of vector control and ivermectin treatments. (a) High-endemicity village; (b) Medium-endemicity village.



ivermectin treatments. In the absence of ivermectin treatment, the risk of recrudescence changes from 0 to 1 when the duration of vector control is shortened from 13 to 10.5 years. With 11 ivermectin treatments, the same range of risk occurs over a much wider range of duration of vector control: 11–6 years. If ivermectin treatment is continued for 25 years, even in the absence of vector control recrudescence risk is reduced to 0.5. However, 6 years of larviciding are still required to reduce the risk to below 0.01. The reason for this divergence is that ivermectin treatment involves more random factors, with respect to both the participation of persons (coverage and/or compliance) and the effect of treatment. As the number of treatments increases, so does the cumulative effect of these chance factors, leading to greater variability in the calculation of recrudescence risks.

The effect of alternative treatment coverage levels for village HIGH is shown in Fig. 3(a). Isorisk lines (0.01) are shown for varying coverage levels. Especially for longer periods of treatment, the effect of treatment coverage is considerable. Higher coverage levels allow greater reductions in the duration of vector control. For example, if annual treatment continues for 10 years with 45% coverage, the control strategy can be shortened by only slightly more than 1 year compared with a strategy without ivermectin treatment. When coverage is 75%, savings of almost 2 years can be achieved. Fig. 3(b), representing the same parameters for village MED, demonstrates that the effectiveness of control strategies is highly dependent on pre-control endemicity. A period of 20 years of only annual ivermectin treatment (coverage, 65%) is sufficient to achieve a recrudescence risk <0.01; in village HIGH a supplement of at least 8 years of vector control would be required to achieve the same risk. Shorter periods of ivermectin treatment permit shorter durations of vector control in MED than in HIGH.

Simulation results for a village with a pre-control endemicity level like that of HIGH, but with more individual variation in biting rates (greater exposure heterogeneity) indicate that reductions in

larviciding are only slightly lower than for more homogeneous-exposure high-endemicity villages. For example, with 10 annual treatments (coverage, 65%) in the standard HIGH village the duration of vector control can be reduced by 22 months, while in a heterogeneous HIGH village the corresponding reduction is 19 months. However, in a heterogeneous-exposure HIGH village, at least 14 years of vector control only would be required (standard HIGH, 13 years).

Considerably lower savings are calculated with the assumption that ivermectin treatment is less efficacious (25% reduction in fertility instead of 35%). In this case, 10 years of treatment (coverage, 65%) allow for only a 15-month reduction in vector control.

Under all assumptions, the savings increase exponentially with additional years of ivermectin treatment, as is apparent from the concave shape of the curves in Fig. 2 and Fig. 3. For example, 10 treatments (coverage, 65%) in village HIGH result in a saving of 22 months (Fig. 2). By adding five treatments the saving increases another 16 months. Another five treatments increase the possible reductions in vector control by 20 more months.

Table 1 shows savings under the assumption that vector control and annual ivermectin treatment always have the same starting moment and same duration (i.e. 10.5 years of vector control means 11 ivermectin treatments). The general guideline is that if ivermectin treatment is given annually to 65% of the population, the total duration of vector control can be 1.5–2 years less than in the absence of treatment.

Table 1: **Reduction in number of months of vector control as a result of annual ivermectin treatments**[a]

Pre-control endemicity level	Duration of vector control alone (months)	Reduction (months) at ivermectin coverage of:			
		45%	55%	65%	75%
High[b]	154	16	20	24	26
Medium[c]	126	14	18	24	31
High[d]	162	15	20	23	25
High[e]	154	13	16	18	20

[a] Synchronous start and finish of vector control and ivermectin treatment. Risk of recrudescence at finish <1%.
[b] Community microfilarial load = 70 per skin-snip; biting rate = 27 000 per adult man per year; biting-rate coefficient of variation = 0.39.
[c] Community microfilarial load = 30 per skin-snip; biting rate = 16 000 per adult man per year; biting-rate coefficient of variation = 0.54.
[d] Biting-rate coefficient of variation = 0.58.
[e] Assumed 25% reduction in fertility of adult female worms due to ivermectin (not 35%).

Discussion

The model presented in this article reflects the expected effects of the current practice of OCP in its extension areas. The primary aim of adding ivermectin treatment to larviciding activities was to prevent morbidity during the early years of vector control, when the intensity of infection is still so high that new cases of blindness or severe ocular lesions cannot be excluded. Ivermectin has proved to be an efficacious drug for the treatment and prevention of ocular lesions of onchocerciasis (*3*, *4*). However, as such combined control continues, a question of major operational importance is to what extent the reduction of the community mf load as a consequence of annual ivermectin treatment allows for an earlier cessation of vector control. On the basis of the results obtained with the ONCHOSIM model, we conclude that where vector control is accompanied by annual ivermectin treatment, the required duration of control can be reduced by 1 year (coverage, ca. 45%) to 2 years (coverage, ca. 65%) compared with strategies relying on vector control alone (see Table 1). Given the original guideline of 14 years of vector control alone (*1*), this implies that when at least 65% coverage can be assured and when there is no importation of infection from elsewhere, 12 years of combined control will be sufficient to prevent recrudescence, even in areas of very high endemicity such as our model village HIGH.

The effectiveness of the combination of strategies is highly dependent on treatment coverage, an important determinant of which is the efforts of the control programme to reach as many persons as possible with treatment. There are, however, exogenous factors that relate to a person's ability or willingness to comply with treatment. Pregnant women, women during the first week of lactation, and children below 5 years of age should be excluded from treatment (*6*), and these exclusion criteria should be taken into account by considering an age/sex-specific compliance profile (see Annex). Though these exclusions limit the effectiveness of any one treatment round, in the long-term the impact will be moderate as children below 5 years of age harbour low numbers of worms, and pregnant or breast-feeding women will only miss one round (9 months + 1 week is <1 year). More important are persons permanently excluded because of chronic diseases (e.g. epilepsy), or who have a limited ability or willingness to participate. In the terms of the model, the latter group has a low compliance index (see Annex). As there will be persons with a considerable mf load among those with a low compliance index (even after a period of control), and as they will have a relatively high contribution to transmission when vector control

ceases, it is advisable not only to attempt to reach a high level of coverage (65%–75%, (*21*)), but also to trace people who systematically miss treatments.

All the results so far discussed are based on the assumption that larviciding and ivermectin treatment start in the same year. However, in some parts of the extension areas large-scale ivermectin treatment started with a delay of 2 years. Therefore, for the village HIGH we calculated recrudescence risks for various time lags before the introduction of treatment. A time lag of up to 4 years — more than in any of the areas — results in no observable difference compared with a synchronous start, in the sense that the 0.01 isorisk lines are virtually contiguous. However, such time lags result in longer total durations of control: with a guideline of 12 years of combined control, a time lag of 2 years implies a total duration of 14 years.

In a previous study (*1*) we showed how uncertainty concerning model parameters is reflected in the outcome of the recrudescence analysis. The guideline of 14 years' minimal duration of only vector control in an area without importation of infection is largely based on "unfavourable" assumptions about the parasite life span, the efficiency of the *Simulium* vector in transmitting the parasite at low mf loads, and the heterogeneity of exposure to fly bites. The present study is mainly concerned with the potential savings in vector control efforts by the addition of ivermectin treatment. Most of the uncertainty about these estimates is related to the efficacy of the drug. We have previously found that with a schedule of annual administration, each ivermectin treatment causes an irreversible reduction of ca. 35% in the fertility of female parasites (*17*). However, the 95% confidence interval for this estimate is 25–40%. In Table 1 it is seen that with a 25% fertility reduction, savings are only 1.5 years with a treatment coverage of 65%. However, both this estimate and the 14-year recommendation of the original guideline are based on unfavourable assumptions on model parameters. In such a "worst-case" projection there is no need to revise the recommendation of 12 years of combined control (although $14 - 1.5 > 12$).

The conclusions presented here are also determined by making the following assumptions about the effectiveness of vector control and the circumstances in the areas where it is carried out: prior to control there was a stable endemic situation; and the pre- and post-control biting rates are equal. It is possible, however, that observed pre-control endemicity (CMFL) underestimates the true endemicity, for example because of the Sahelian droughts of 1968–74 preceding the start of the OCP (*22*). Furthermore, we assumed that there is no transmission throughout the whole period of vector control and that there is no immigration of infected flies and infected persons. It is clear that in many places these conditions are not met. Reinvasion of infected flies has been reported frequently (*23*, *24*). Though importation of infection by human migration is not yet an important problem (*22*), computer simulations have demonstrated that a few infected migrants settling in a small village considerably raise the risk of recrudescence. It is therefore clear that the recommendation presented here can be applied only after critical review. A thorough study of local circumstances and the history of vector control (especially control failures) should be included in decision-making.

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Résumé

Durée des traitements annuels par l'ivermectine et de la lutte antivectorielle dans le cadre du Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest

Au moment du lancement du Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest (OCP) en 1975, la seule stratégie fiable de lutte contre la cécité des rivières consistait à traiter par des produits larvicides les rivières abritant les gîtes larvaires du vecteur de la maladie, *Simulium damnosum*. Il était alors estimé, d'après des modèles prédictifs, que la lutte antivectorielle devrait être poursuivie pendant au moins 14 ans pour empêcher la recrudescence de l'infection et de la maladie après l'arrêt des opérations.

L'homologation de l'ivermectine en 1987 a amélioré de façon décisive les moyens de lutte contre la maladie. Le traitement par cette substance entraîne une baisse immédiate du nombre de microfilaires (Mf) et une réduction durable de la fécondité des vers femelles adultes. Depuis 1990, l'épandage aérien de larvicides est complété par des traitements annuels par l'ivermectine dans

les zones d'extension de l'OCP, afin principalement d'obtenir une réduction de la morbidité. La présente étude a pour but de déterminer si et dans quelle mesure l'addition d'un traitement par l'ivermectine à l'épandage de larvicides permet d'avancer l'arrêt des opérations par rapport au calendrier recommandé.

L'évaluation de l'efficacité de l'utilisation combinée de la distribution d'ivermectine et de la lutte antivectorielle s'appuie sur les prévisions du modèle épidémiologique ONCHOSIM. Un grand nombre de stratégies de lutte ont été simulées, chacune étant caractérisée par la durée de la lutte antivectorielle, le nombre de traitements annuels par l'ivermectine et le pourcentage de la population traité lors de chaque passage. On a considéré deux niveaux d'endémicité définis par le taux de Mf avant traitement et deux hypothèses d'efficacité de l'ivermectine. L'efficacité d'une stratégie est exprimée par le risque de recrudescence de l'infection après l'arrêt des opérations, calculé à partir des simulations obtenues avec le modèle ONCHOSIM et de l'analyse statistique des résultats.

Les prévisions du modèle laissent à penser que le traitement annuel à grande échelle par l'ivermectine permet effectivement d'envisager une réduction considérable de la durée de la lutte antivectorielle. Alors qu'avec la lutte antivectorielle seule il faudrait au moins 13 ans pour empêcher la recrudescence (risque $< 0{,}01\%$) dans un village de forte endémicité (charge microfilarienne (Mf) dans la communauté $\approx$ 70 Mf/biopsie cutanée), l'association de la lutte antivectorielle et d'un traitement annuel par l'ivermectine (taux de couverture $\approx 65\%$) permettrait d'arrêter la lutte au bout de 11 ans. Dans une zone d'endémicité moyenne (charge microfilarienne dans la communauté $\approx$ 30 Mf/biopsie cutanée), une stratégie associée permettrait d'arrêter la lutte au bout de 9 ans.

Compte tenu de l'incertitude quant à l'efficacité de l'ivermectine, on peut conclure que, à condition que le taux de couverture soit d'au moins 65%, une stratégie associant la lutte antivectorielle et le traitement annuel par l'ivermectine permettrait d'abaisser au bout de 12 ans le risque de recrudescence à moins de 1%, même dans les zones les plus touchées. Cette recommandation ne pourrait toutefois être appliquée sans danger que dans les régions où la lutte antivectorielle est très efficace et où il n'y a pas d'importation de l'infection par l'homme ou par les mouches. Toute décision rationnelle quant à la durée minimale d'application des stratégies de lutte associées doit s'appuyer sur une étude attentive des conditions locales.

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Annex

Calculation of individual treatment probability

An ivermectin mass treatment round, w, is primarily described by its coverage, C_w. However, calculating coverage is complicated by several standard exclusion criteria for treatment. Moreover, compliance with treatment differs from person to person. Exclusion criteria are either permanent (chronic illness) or temporary (children below 5 years of age as well as pregnant and some breast-feeding women). We can define the population eligible for treatment as the total population minus the fraction permanently excluded, f (equal to, say, 0.05). Coverage of the eligible population, C'_w, is then:

$$C'_w = C_w/(1 - f) \quad (1)$$

Temporary contraindications and other age- and sex-related determinants of compliance can be described as relative compliance, $c_r(k, s)$, which is a function of age group, k, and sex, s (male = 1, female = 2). On the basis of the data from the OCP, the following values of c_r are used:

Age group (k, in years)	0–4	5–9	10–14	15–19	20–29	30–49	≥50
$c_r(k, 1)$	0.00	0.75	0.80	0.80	0.70	0.75	0.80
$c_r(k, 2)$	0.00	0.75	0.70	0.74	0.65	0.70	0.75

Only the ratio between the values of $c_r(k, s)$ for the different groups is relevant. The coverage, $c(k, s, w)$ in each of the age and sex groups at treatment round w is calculated as:

$$c(k, s, w) = \frac{c_r(k, s) \times N(w)}{\sum_{s=1}^{2} \sum_{k=1}^{n_a} c_r(k, s) \times N(k, s, w)} \times C'_w \quad (2)$$

where

$N(k, s, w)$ = the number of individuals eligible for treatment in age group k and sex s at treatment round w, and

$N(w)$ = the total number of eligible individuals at treatment round w, and

n_a = the number of age groups.

The probability of participation in treatment round w for an eligible person i of age group k and sex s is given by:

$$P_{iw} = co_i^{\,j(w)} \quad (3)$$

where $j(w) = (1 - c(k, s, w))/c(k, s, w)$, and co_i = the personal compliance index. This is modelled as a lifelong constant for each individual and is randomly generated from a uniform distribution on the interval [0, 1].

Note: for all k, s the average value of $P_{i,w} = c(k, s, w)$.