Can ivermectin mass treatments eliminate onchocerciasis in Africa?

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Objective To elucidate the conditions in which mass treatment with ivermectin reduces the transmission of *Onchocerca volvulus* sufficiently to eliminate infection from an African community.

Methods ONCHOSIM, a microsimulation model for onchocerciasis transmission, was used to explore the implications of different treatment intervals, coverage levels and precontrol endemicities for the likelihood of elimination.

Findings Simulations suggested that control strategies based exclusively on ivermectin mass treatments could eliminate onchocerciasis. The duration of treatment required to eliminate infection depended heavily on the treatment programme and precontrol endemicity. In areas with medium to high levels of infection, annual mass treatments with 65% coverage for at least 25 years were necessary. Model predictions suggested that durations exceeding 35 years would be required if there were much heterogeneity in exposure to vector bites and, consequently, wide individual variation in microfilaria counts. If the treatment interval were reduced from 12 to 6 months the time for completion of the programme could be more than halved and elimination could be accomplished in areas of hyperendemicity, provided that the effects of each treatment would be the same as with annual treatments. However, it was doubtful whether high coverage levels could be sustained long enough to achieve worldwide eradication.

Conclusion Elimination of onchocerciasis from most endemic foci in Africa appears to be possible. However, the requirements in terms of duration, coverage, and frequency of treatment may be prohibitive in highly endemic areas.

Keywords Onchocerciasis/drug therapy; Ivermectin/therapeutic use/administration and dosage; Forecasting; Computer simulation; Africa (*source: MeSH, NLM*).

Mots clés Onchocercose/chimiothérapie; Ivermectine/usage thérapeutique/administration et posologie; Prévision; Simulation ordinateur; Afrique (*source: MeSH, INSERM*).

Palabras clave Oncocercosis/quimioterapia; Ivermectina/uso terapéutico/administración y dosificación; Predicción; Simulación por computador; África (*fuente: DeCS, BIREME*).

Voir page 389 le résumé en français. En la página 389 figura un resumen en español.

Introduction

Ivermectin (Mectizan) has contributed substantially towards the alleviation of suffering caused by onchocerciasis in 34 countries of Africa, the Eastern Mediterranean and Latin America (*1*). By reducing the microfilarial load in infected individuals it reduces transmission of the infection and prevents blindness and other serious consequences. The initial efforts of nongovernmental organizations and the Onchocerciasis Control Programme in West Africa to distribute ivermectin on a large scale were followed by the establishment of multinational, multiagency partnerships such as the Onchocerciasis Elimination Program for the Americas in 1991 and the African Programme for Onchocerciasis Control in 1995 (*1–3*). While the Onchocerciasis Control Programme used vector control as part of its strategy, the two latter bodies were exclusively concerned with supporting large-scale ivermectin treatment programmes based on community distribution. However, whereas the Onchocerciasis Elimination Program for the Americas aims at eliminating the parasite altogether from most affected areas in Latin America, the African Programme for Onchocerciasis Control seeks only to establish a sustainable community-directed drug distribution system in the countries concerned and thereby to eliminate serious onchocerciasis and, eventually, to have a telling impact on transmission.

In West Africa the Onchocerciasis Control Programme demonstrated that the prevalence and intensity of infection with *Onchocerca volvulus* could be reduced to insignificant levels through vector control (*4*). For economic reasons, however, it became apparent that neither vector control alone nor a combination of vector control and ivermectin treatment would provide a sustainable long-term solution for most areas of endemicity, where, consequently, reliance has to be placed solely on drug therapy for controlling or eliminating the disease. Although more effective alternatives to ivermectin alone, either by combining ivermectin with other drugs or macrofilaricides (*5*), hold promise, they may not become available in the near future. It was recently suggested that increasing the frequency of ivermectin administration from annually to six-monthly would increase the probability of eliminating the parasite in the long run (*6*), but this has been questioned for reasons of logistics and cost (*7, 8*). In fact, this is

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the strategy of the Onchocerciasis Elimination Program for the Americas, following the successful interruption of transmission by treatment programmes in isolated foci in Guatemala and Ecuador (9–12).

In Africa, several field studies have achieved significant reductions in the transmission of infection by repeated annual mass treatments with ivermectin (13, 14). Small-scale experiments by the Onchocerciasis Control Programme with six-monthly distribution in a small focus on the Gambia River in Senegal gave good results (B.A. Boatin, unpublished data, 2001), but it is difficult to generalize these findings to larger areas where the disease is hyperendemic. Long-term community trials are required in order to determine whether transmission can be stopped (13). Meanwhile, epidemiological modelling may suggest the potentials and pitfalls of different control strategies. A simulation study, using the microsimulation model ONCHOSIM for onchocerciasis transmission and control, predicted that programmes combining vector control and the mass distribution of ivermectin would lead to the elimination of the infection from a community much more quickly than vector control alone (15). However, this finding is not germane to today's control strategies because vector control will cease in 2002.

In the present study we model the epidemiological impact of community treatments with ivermectin alone. In order to make our results relevant to the African Programme for Onchocerciasis Control we consider areas of endemicity where there has never been any vector control. Using the ONCHOSIM model, we attempt to predict whether, and under what conditions, control strategies based on mass treatments with ivermectin may lead to the elimination of onchocerciasis. The factors investigated include the interval between treatments, coverage and the precontrol level of endemicity.

Methods

Research instrument

The ONCHOSIM epidemiological model describes the life history of the parasite in the human host and the fly vector *Simulium damnosum*, and simulates the effects of control efforts based on vector control and ivermectin therapy in a closed village community. We used this model to assess the relationship between the probability of elimination of *Onchocerca* infection and the duration and intensity of ivermectin-based control.

The ONCHOSIM model and its validation, mostly on the basis of field data from the West African savanna, in particular Asubende, Ghana (16), have been described elsewhere (17–19). Compliance, the probability of an individual being treated during a mass treatment round, was modelled by assigning to each person a random lifelong compliance factor: the higher this factor the more likely the individual is to comply during any given treatment round (17). A crucial assumption for the present study is that an application of the standard dose of approximately 150 µg/kg body weight immediately eliminates all microfilariae and that the adult female worms, after temporarily losing their fecundity, gradually resume the production of microfilariae over an average period of 11 months, reaching a new production level that is on average 35% lower than before treatment (20). Although this reduction was validated for annual treatments only, we assumed that each subsequent treatment, irrespective of the interval between treatments, would cause the same irreversible production loss and reinforce all previous production losses. We also assumed that no resistance to ivermectin would develop.

Procedures

The treatment programmes were characterized by the following variables: coverage, i.e. the percentage of persons treated in the community; the total number of treatments applied; and the intervals between successive treatments. The precontrol endemicity level in the simulated communities was varied by varying the annual biting rate, i.e. the average annual number of vector bites received by an adult, and the individual variation in this annual biting rate. In the model these two input variables together determine the endemicity level as quantified by the community microfilarial load, the geometric mean skin-snip microfilarial count (21) and other entomological transmission parameters, such as the annual transmission potential. A simulation run was thus fully determined by the five parameters listed in Table 1. Instead of using all possible combinations of these parameters, which would have led to an excessively large number of simulation runs, we randomly selected values from within the ranges indicated in Table 1. In this manner approximately 30 000 ONCHOSIM runs were performed, each with its unique set of values for the five variables. Each simulation run was programmed to continue for another 50 years after finishing the selected treatment programme in order to check whether the infection was eliminated (defined by community microfilarial load = 0).

In order to explore the extent to which our results were sensitive to the assumption of a 35% reduction in the production of microfilariae by adult worms, irrespective of the treatment interval, we also ran simulations with six-month treatment intervals and assumed a more pessimistic 20% per treatment reduction in this circumstance. The difference between these two values lies in the cumulative macrofilaricidal effect of treatment on the adult worm. At 20% this effect of six-monthly treatments is comparable to that obtained with annual treatment at 35%. Independently of this, six-monthly treatment still results in greater suppression of microfilariae as a

Table 1. **Ranges of values for quantification of variables selected for studying different ivermectin treatment programmes and levels of endemicity in communities**

Variable	Range
Treatment coverage of community[a]	25–85%
Total number of treatments applied	5–40
Interval between successive treatments	3–18 months
Annual biting rate[b]	10 000–30 000 vector bites/adult
Coefficient of variation for annual biting rate[c]	0.3–1

[a] % of total population treated.
[b] Higher annual biting rates, up to nearly 100 000, have been observed in some villages where the disease is hyperendemic. However, these values refer to maximum biting rates at selected catching points near blackfly breeding sites and are probably much higher than actual biting exposure of the population.
[c] The coefficient of variation is a measure of the variation in the annual biting rate between individuals.

result of the shorter treatment interval. This should result in approximately the same cumulative effects as annual treatment. These simulations were run for a coefficient of variation in the annual biting rate of 0.65 only. All the other parameters were varied as above.

Statistical analysis

As a result of the stochastic nature of ONCHOSIM, simulation runs with exactly the same input may produce different outcomes in terms of elimination or recrudescence. We therefore performed logistic regression analysis by means of SPSS version 8.0 in order to determine the relationship between the probability of elimination and the treatment and endemicity variables. By forward stepwise inclusion we first added simple linear and quadratic terms to the logistic regression equation. Terms were included in the equation by means of the score test ($P < 0.05$) and removed on the basis of the likelihood ratio test ($P > 0.1$). Simple interaction terms were then added by the same forward stepwise method. The resulting regression equation was used to calculate the probability of elimination for a given treatment strategy in specified conditions of endemicity.

Results

Fig. 1 represents a simulation based on a treatment programme of 10 annual dosages with a coverage of 65% in a hypothetical village with a precontrol community microfilarial load of 30 microfilariae per skin snip. After an initial decline of the community microfilarial load and the prevalence to low levels during the treatment programme (1990–2000), both eventually tended to return to their previous levels after treatment had ceased. The reduction in transmission that resulted from this treatment strategy was clearly insufficient to eliminate the infection.

It could be that a 10-year programme is too short to reduce transmission to a level at which the infection can no longer sustain itself in the community. The logistic regression equation fitted to the simulation results for the selected treatment strategy in this community predicts a probability of elimination of 5%, i.e. only 1 in 20 simulations would show elimination of infection. If the treatment programme were prolonged by increasing the number of treatments it would take approximately 27 years before the probability of elimination exceeded 99% (Fig. 2).

Below we adopt the 99% probability of elimination as the minimum requirement for a successful programme because the infection should be eliminated from all communities, i.e. villages, in a region if transmission is to be interrupted in the region.

Fig. 3 shows an example of how, on the assumption of yearly treatment intervals, the required duration of programmes varies with the community microfilarial load and the coverage level. For a coverage of 65% the middle line indicates the duration of treatment that would lead to a probability of elimination of 99%; elimination is almost certain at any point above this line while the risk of recrudescence increases below it. Clearly, in communities where the disease is hyperendemic, with a precontrol microfilarial load above 50 microfilariae per skin snip, a programme based on annual treatment and 65% coverage may have to be continued for more than 40 years in order to achieve elimination.

Fig. 1. **Output of a single ONCHOSIM simulation run, showing results of an ivermectin treatment programme of 10 annual dosages with a coverage of 65% in a hypothetical village with a precontrol community microfilarial load (CMFL) of 30 microfilariae per skin snip**
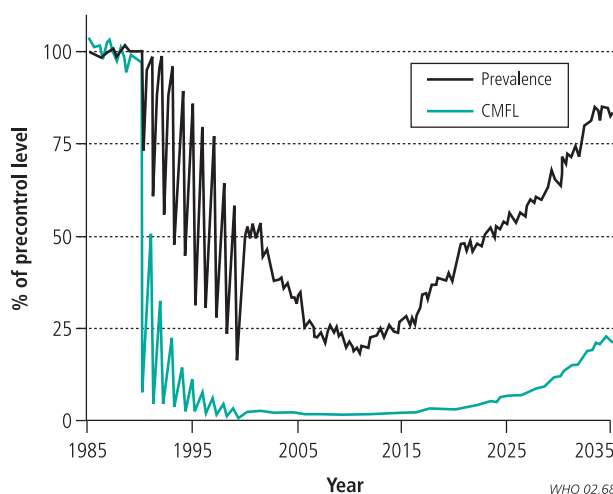

Fig. 2. **Effect of prolonging treatment programme by increasing number of annual treatments and holding coverage at 65%**
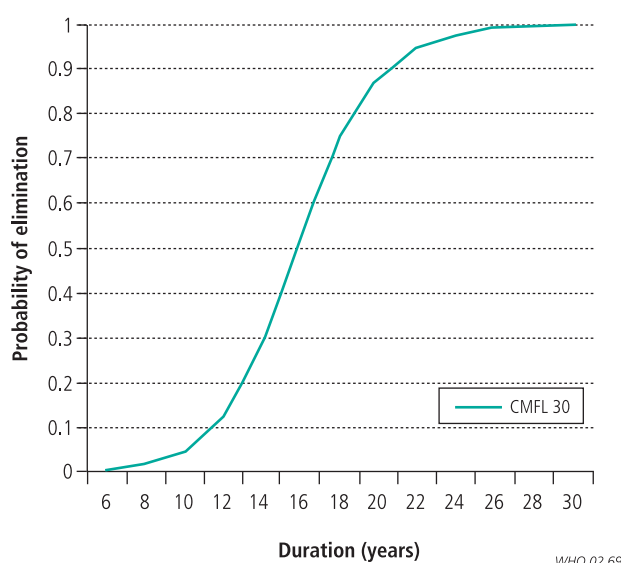

Fig. 3 also shows the substantial impact of the coverage level. For instance, if the community microfilarial load is 30 the treatment programme needs to be continued for approximately 18 years at 80% coverage or for 25 years at 65% coverage. In communities where the disease is hyperendemic, with a community microfilarial load of at least 60, only coverage levels exceeding 80% may lead to elimination. When coverage falls below 50%, even where endemicity is moderate, e.g. with a community microfilarial load of 20 or less, elimination may not be achieved within 30–40 years. As explained above, it was assumed that coverage was only partially random, with some individuals being consistently more likely to comply than others.

The way the treatment interval influences the duration of a programme is shown in Fig. 4. A comparison of Figs. 3 and 4

Fig. 3. **Variation of required duration of programmes for achieving 99% probability of elimination with community microfilarial load (CMFL) and coverage level, assuming annual treatment intervals and medium individual variation in biting rates**
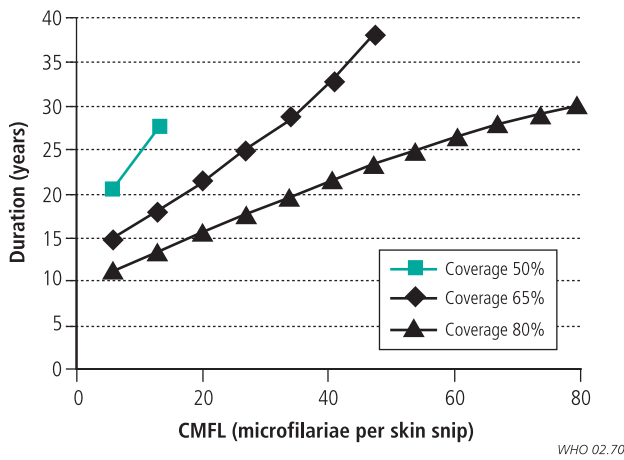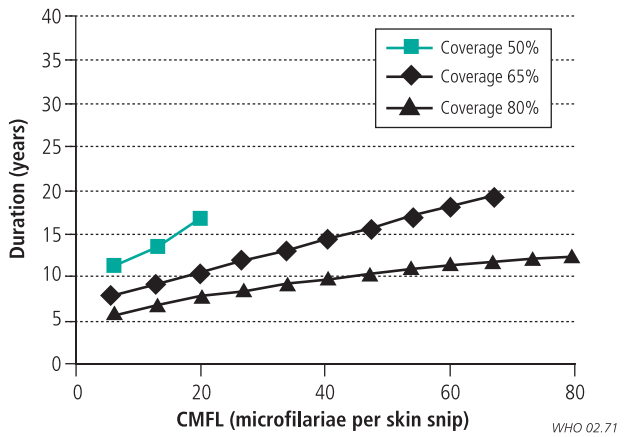

WHO 02.70

Fig. 4. **Required duration of programmes to achieve 99% probability of elimination when treatment interval reduced from 12 months to 6 months, assuming medium individual variation in biting rates**

WHO 02.71

Fig. 5. **Impact of level of individual variability (low-medium-high) on duration of treatment needed for 99% probability of elimination, assuming coverage of 65% and annual treatments**
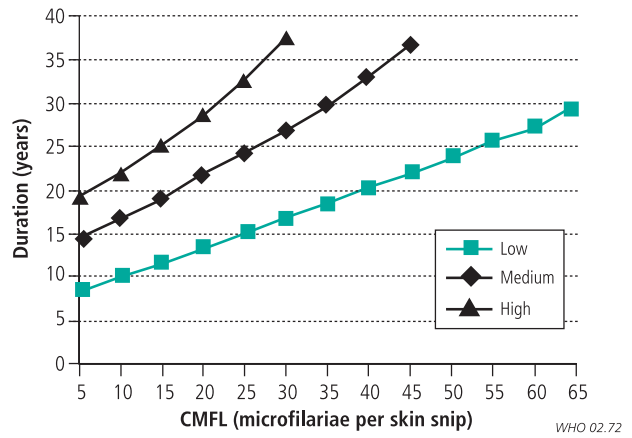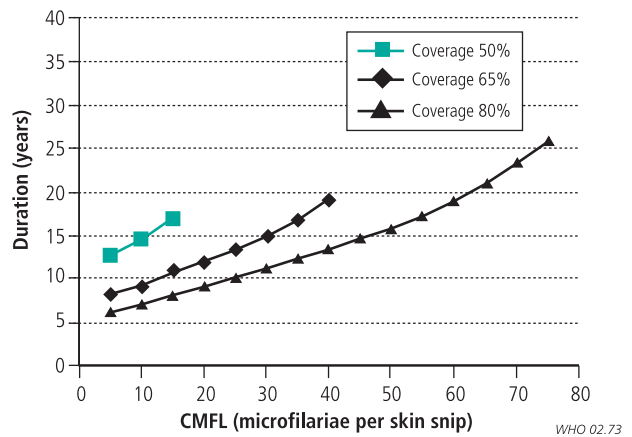

WHO 02.72

Fig. 6. **Effect of reducing treatment interval from 12 months to 6 months on required duration to achieve 99% probability of elimination, assuming macrofilaricidal effects of 20% per treatment**

WHO 02.73

demonstrates that if the treatment interval is reduced from 12 months to 6 months the required duration for achieving a probability of elimination of 99% is reduced by more than 50%. Furthermore, the elimination of infection is now also possible for areas of hyperendemicity provided that coverage levels of at least 65% can be maintained. Fig. 3 and Fig. 4 also show the effect of different precontrol community microfilarial loads on the required duration of treatment programmes. To adjust community microfilarial loads we varied the annual biting rate while keeping the individual variability in exposure to the biting rate always at an arbitrary intermediate level. However, as shown in Fig. 5, the level of individual variability also impacts on the duration of treatment needed for elimination. Generally, a high individual variability in exposure considerably increases the minimum duration of a treatment programme. Substantially different results were obtained when the pessimistic scenario of a 20% reduction in microfilariae production per treatment was assumed (Fig. 6). The number of treatments required in order to reach elimination, with the probability of elimination at 99%, then exceeded the number

for annual treatments by up to 50%. Moreover, the maximum community microfilarial load at which elimination remained possible was similar to that of the annual treatment scenario but with a 35% reduction in production levels.

Discussion

With 100% coverage, annual treatment with ivermectin would clearly lead to a complete interruption of transmission and the ultimate elimination of the parasite. As such coverage cannot be attained in practice the question arises as to whether lower coverage levels can tip the balance in favour of humans. The statistical analysis of simulations with the ONCHOSIM model shows that control strategies based on mass treatments with ivermectin can indeed lead to the elimination of onchocerciasis from communities where the disease is endemic, coverage levels of less than 100% are attained, and no form of vector control is practised. Our simulations suggest that, if annual treatments are given, a coverage of 65% is the minimum required for communities with low to medium-high community microfilarial loads, i.e. 5–30 microfilariae per skin snip, and that a coverage of 80% or more may often be necessary for

higher community microfilarial loads, i.e. 30–80 microfilariae per skin snip. The importance of coverage levels for the successful outcome of a treatment strategy has been recognized previously under field conditions. Several inexpensive, rapid and easy methods for its measurement have been developed, and one of them is currently in use (22, 23). We found that intervals of six months would require slightly less than half the time to reach elimination than yearly intervals. A treatment strategy based on six-monthly rather than annual intervals thus has two clear implications: the whole programme can achieve elimination at higher levels of community microfilarial load, and, where annual treatments would also accomplish elimination, six-monthly intervals would do so in less than half the time, i.e. with fewer treatment rounds. However, this strategy would fail if the population contained only two types of individuals, viz. perfect compliers, who would not contribute to transmission, and consistent non-compliers. Our conclusions therefore depend on the assumption that there are many individuals who sometimes comply and sometimes do not comply, e.g. because they are absent or pregnant at the time of the intervention. If this group were smaller than we assumed in our model the benefits of six-monthly treatments would be smaller than predicted. Also, the prospect of elimination by six-monthly treatments may be exaggerated as a result of our assumption that each treatment would result in a 35% reduction in microfilaria production, also when applied six-monthly. This assumption has not yet been validated for such intense treatment schemes. If it were not true, as in our pessimistic macrofilaricidal assumption of a constant 20% reduction in microfilaria production, our optimistic conclusions about the advantages of a six-monthly treatment scheme would be largely invalidated. Although elimination, when possible, would still be achieved in fewer years, the required number of treatments would exceed that under the annual scheme. This indicates that the macrofilaricidal effect is an important aspect of ivermectin treatment, supplementing its better-publicized microfilaricidal properties. Furthermore, shortening the treatment interval might have practical disadvantages, such as increased demands on drug supply, community participation, and so on. Strategies aimed at maintaining or increasing compliance and motivation at all levels, e.g. by using appropriate incentive schemes, may therefore be vital for the success of such high-frequency programmes.

Both the annual biting rate in a community and variation in exposure to biting among individuals strongly influence the duration of a treatment programme. In areas with medium-high to high levels of community microfilarial load, i.e. 30–80 microfilariae per skin snip, and an intermediate level of individual variation in the biting rate, annual treatments at a coverage level of 65% would have to be continued for at least 27 years in order to eliminate infection. Model predictions suggest that, in such areas, much longer durations, exceeding 38 years, would be required if there were a high level of individual variation in the biting rate and consequently in counts of microfilariae.

It should be borne in mind that the values of many parameters in the ONCHOSIM model, including the effects of ivermectin treatment, are based on field data from one focus of endemicity, viz. Asubende, Ghana, in the West African savanna, and that the transmission of onchocerciasis is simulated in villages of fewer than 400 inhabitants without migration of infected individuals and without reinvasion by infected flies (24). Our results are therefore only predictive for this type of setting. For an extensive account of the impact of these assumptions on our conclusions, reference should be made to an earlier study (15). For other areas in Africa, or other parts of the world, where different epidemiological, entomological and demographic conditions exist, the model should be requantified in accordance with local field data so that ONCHOSIM modelling studies can produce meaningful results. The effects of 10 years of ivermectin treatment in the Onchocerciasis Control Programme are now being analysed. It is intended to update model quantifications on the basis of the results of this analysis.

Our analyses suggest that the elimination of onchocerciasis by means of mass treatment programmes is feasible only where high treatment coverage can be maintained for the entire period of programme implementation, which is often very long. This requires, inter alia, an absence of prolonged civil unrest and a stable drug supply. Such foci should also be free from reinvasion by infective blackflies and should remain so. Comparatively low precontrol community microfilarial loads and a low individual variability in exposure to vectors are also necessary. These requirements indicate that, under field conditions, ivermectin mass treatment programmes by themselves would not always be able to eliminate onchocerciasis completely. In this connection it is of interest to note that Abiose et al. (7) concluded that a definite solution would be difficult with ivermectin alone. This suggests that six-monthly treatments could be considered for the elimination of the parasite from isolated foci where biting rates and other epidemiological factors were favourable. We therefore suggest that for most affected parts of Africa, in the absence of vector control, ivermectin treatment should primarily be considered as a measure for controlling morbidity by reducing transmission and microfilarial loads, for which purpose annual treatments would probably suffice (25, 26). Consequently, there seems to be no clear rationale for switching to more frequent treatments at present. Furthermore, more frequent treatments would require resources that might be better used for achieving high coverage rates. However, the impact of more frequent ivermectin administration on the development of drug resistance, and the response of the population to different treatment schedules, appear to be important subjects for research. Global eradication of the parasite by means of ivermectin alone does not appear to be feasible. This, together with the undesirability of permanent reliance on a single drug, suggests that priority should continue to be given to research into alternative drugs and safe, effective and affordable alternative elimination strategies, for example ones based on macrofilaricides (5, 27). ■

Conflicts of interest: none declared.

Résumé

Le traitement de masse par l'ivermectine peut-il éliminer l'onchocercose en Afrique ?

Objectif Déterminer les conditions dans lesquelles le traitement de masse par l'ivermectine réduit suffisamment la transmission d'*Onchocerca volvulus* pour éliminer l'infection dans une communauté d'Afrique.

Méthodes ONCHOSIM, un modèle de microsimulation de la transmission de l'onchocercose, a été utilisé pour explorer les répercussions de différents intervalles de traitement, taux de couverture et niveaux d'endémicité avant traitement sur la probabilité d'une élimination de l'infection.

Résultats Les simulations ont indiqué que des stratégies de lutte reposant exclusivement sur le traitement de masse par l'ivermectine pouvaient éliminer l'onchocercose. La durée de traitement nécessaire pour éliminer l'infection dépendait largement du programme appliqué et du niveau d'endémicité avant traitement. Dans les régions ayant un taux d'infection moyen à élevé, des traitements de masse annuels avec un taux de couverture de 65 % pendant 25 ans étaient nécessaires. D'après les prévisions du modèle, des traitements répétés pendant plus de 35 ans seraient nécessaires en cas d'hétérogénéité marquée de l'exposition de la population aux piqûres d'insectes vecteurs et donc de variation importante des numérations de microfilaires au niveau de l'individu. Si les intervalles de traitement étaient de 6 mois au lieu de 12, la durée totale du programme pourrait être divisée par deux au moins et l'élimination pourrait être réalisée dans des régions d'hyperendémicité, à condition que l'effet de chaque traitement soit le même qu'en cas de traitement annuel. Il était toutefois douteux qu'un taux élevé de couverture puisse être maintenu assez longtemps pour atteindre l'éradication mondiale.

Conclusion L'élimination de l'onchocercose dans la plupart des foyers d'endémie en Afrique semble possible. Toutefois, les exigences en termes de durée, de couverture et de fréquence du traitement peuvent être prohibitives dans les régions de forte endémicité.

Resumen

¿Es posible eliminar la oncocercosis en África mediante la administración masiva de ivermectina?

Objetivo Determinar las condiciones en que el tratamiento masivo con ivermectina reduciría la transmisión de *Onchocerca volvulus* en la medida suficiente para poder eliminar la infección en una comunidad de África.

Métodos Se utilizó un modelo de microsimulación de la transmisión de la oncocercosis (ONCHOSIM) para analizar el efecto de diferentes intervalos de tratamiento, niveles de cobertura y niveles de endemicidad preintervención en la probabilidad de eliminación.

Resultados Las simulaciones indican que las estrategias basadas exclusivamente en la administración masiva de ivermectina permitirían eliminar la oncocercosis. La duración del tratamiento requerido para eliminar la infección depende en gran medida del programa de tratamiento y de la endemicidad preintervención. En las zonas con niveles medios/altos de infección se necesitarían al menos 25 años de tratamiento anual masivo con una cobertura del 65%. Las predicciones del modelo muestran asimismo que en una situación de gran heterogeneidad en la exposición a las picaduras del vector, y grandes diferencias individuales por tanto en lo concerniente al recuento de microfilarias, el tratamiento debería prolongarse más de 35 años. Si el intervalo de tratamiento se redujera de 12 a 6 meses, la duración del programa podría reducirse a menos de la mitad y se podría lograr la eliminación en zonas de hiperendemicidad, siempre que cada tratamiento tuviera el mismo efecto que el tratamiento anual. Sin embargo, es dudoso que puedan mantenerse niveles altos de cobertura durante el tiempo suficiente para erradicar la enfermedad a escala mundial.

Conclusión La eliminación de la oncocercosis de los focos más endémicos de África parece un objetivo alcanzable. Ahora bien, las condiciones para ello en lo tocante a la duración, cobertura y frecuencia del tratamiento pueden ser prohibitivas en las zonas de alta endemicidad.

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