TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (1997) 91, 82–86

Onchocerca volvulus: striking decrease in transmission in the Vina valley (Cameroon) after eight annual large scale ivermectin treatments

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Abstract

The impact of repeated ivermectin treatments on the transmission of *Onchocerca volvulus* was evaluated in the Vina valley, northern Cameroon, by comparing the prevalence and intensity of infection observed in untreated 5–7 years old children living in the treated communities before and after 7–8 successive annual rounds of ivermectin treatment of the general population of those communities. The villages studied were Ngoumi and Babidan, where the initial community microfilarial loads (CMFL) were 83·7 and 216·4 microfilariae per skin snip, respectively. In 1995, after 8 annual treatments, the prevalence and intensity in Ngoumi had decreased by more than 90%, compared with the pretreatment values, and the prevalence continued to decrease between 1992 and 1995. In Babidan, after 7 annual treatments, the prevalence and intensity had also decreased significantly, but less than in Ngoumi. The study demonstrated that repeated treatments brought about a notable reduction in the transmission of *O. volvulus* in the Vina valley, despite unfavourable factors such as mean drug coverages below 60% and the good vectorial competence of *Simulium damnosum s.s.* and *S. sirbanum*.

Keywords: onchocerciasis, *Onchocerca volvulus*, ivermectin, transmission, Cameroon

Introduction

Since 1990, large scale ivermectin distribution programmes have been developed in most of the countries where onchocerciasis is endemic. The success of these programmes prompted the World Bank and the World Health Organization to implement an ambitious African Programme for Onchocerciasis Control (APOC), whose objectives are particularly to co-ordinate and reinforce all the ivermectin distribution activities in the African countries outside the Onchocerciasis Control Programme (OCP) area (REMME, 1995). The duration and cost of APOC, and the distribution strategies to be recommended, depend largely on the impact of repeated ivermectin treatments on the transmission of the disease. The expected impact has been evaluated using the ONCHOSIM model developed during the OCP (PLAISIER *et al.*, 1990), and mathematical simulations using various hypotheses have shown that ivermectin could interrupt transmission in hyperendemic areas only if annual distributions were repeated for at least 20 years, with drug coverage greater than 65% (MOLYNEUX, 1995; WHO, 1995). These predictions should be compared with observed data in order to refine progressively the model, which will be mainly devoted, as part of APOC, to defining the most efficient ivermectin distribution strategies.

The impact of ivermectin distributions on the transmission of *Onchocerca volvulus* can be evaluated by following the prevalence and intensity of infection in cross-sections of people who never received the drug, but live in treated communities. This method was first used in Liberia by TAYLOR *et al.* (1990), and then on several occasions in the OCP area (WHO, 1995) and in Cameroon (BOUSSINESQ *et al.*, 1995). The latter study demonstrated that 5 successive ivermectin distributions brought about a marked decrease in the prevalence and intensity of infection in untreated children. The present study was intended to evaluate the additional impact after 3 subsequent treatment rounds.

Patients and Methods

Study area

The Vina valley lies in a Sudan-savannah area of northern Cameroon, and extends about 250 km from west to east (Figure). The valley is limited on the north and south by 2 ranges of mountains rising to 1920 m, and extends on the east to Chad and the Central African Republic (CAR). The population of about 20000 lives in 63 communities. The major occupations are subsistence agricultural farming and cultivation of cotton. The villages lie almost exclusively on a road that runs almost parallel to the course of the Vina river. No marked migration occurred in these villages during the study. This was due to the facts that the nearest important town that might attract the young population, Ngaoundere, is more than 250 km away and the cotton development project in the Vina valley guarantees a regular income for the population. In this area, onchocerciasis is hyperendemic in many villages, and causes severe ocular complications (ANDERSON *et al.*, 1974; PROD'HON *et al.*, 1991). Cytotaxonomic studies have shown that the main vectors of the disease are *Simulium damnosum s.s.* and *S. sirbanum* (see TRAORE-LAMIZANA & LEMASSON, 1987). No vector control has ever been undertaken in the Vina valley.

Pretreatment parasitological examinations were carried out in 31 villages in order to evaluate the initial levels of endemicity of onchocerciasis in the valley. This survey was performed in 3 phases, between 1987 and 1989.

The impact of 5 successive treatments (1987–1991) on the transmission of onchocerciasis was evaluated first in 1992 by examining children who had never taken ivermectin, but lived in all the 5 villages located immediately west of the town of Touboro, and whose general population had been treated annually since 1987. These localities, which are contiguous, were Bonandika, Man Rigara, Voye, Mbailara and Ngoumi (BOUSSINESQ *et al.*, 1995).

The present study was designed to evaluate the impact of ivermectin after 3 additional treatments, and was performed in 2 villages. Ngoumi (7°46'N, 15°11'E), which had been already examined in 1992, was selected again in 1995 for 2 reasons. First, it is representative of the villages treated since 1987, and second, one objective of the present study was to compare data collected in 1992 and 1995, in order to evaluate whether a further decrease in transmission occurred after the 3 treatments given in 1992, 1993 and 1994. The second village, Babidan (7°47'N, 15°33'E), was first treated in 1988 and then annually thereafter. It was selected in 1995 because of the parasitological results of the pretreatment survey, which showed its initial level of endemicity for onchocerciasis to be considerable. The total populations recorded in Ngoumi and Babidan during the nationwide census of 1987 were 1735 and 392, respectively.

Pretreatment parasitological examinations

Pretreatment parasitological examinations were per-

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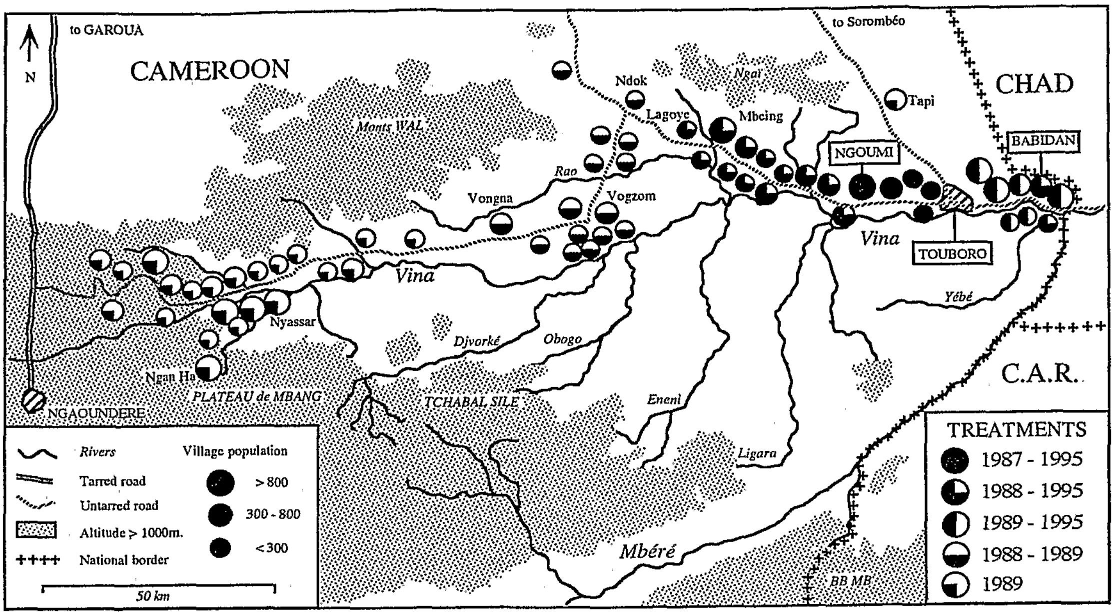

Figure. Map of the Vina valley, Cameroon, showing the location of the villages and the dates of ivermectin treatments for onchocerciasis.

formed in 31 villages between 1987 and 1989. Two skin snips (one at each iliac crest) were taken with a 2 mm Holth corneoscleral punch (Storz Instrument GmbH, Heidelberg, Germany) from all patients 5 years of age and older who came to receive their first ivermectin treatment, and who consented to be examined. The snips were left to incubate in saline for 24 h, and the emerged microfilariae were counted under a microscope. For each subject, we calculated the individual microfilarial load, defined as the arithmetic mean of the microfilarial counts from the 2 skin snips.

The pretreatment level of endemicity in the villages examined was evaluated by means of 2 parasitological indices used in OCP, i.e. the age- and sex-standardized prevalence of microfilaridermia in people 5 years of age and older (SPMF) and the community microfilarial load (CMFL). The SPMF was calculated using the known age and sex distribution in the OCP area (MOREAU *et al.*, 1978). The CMFL is the geometric mean number of microfilariae per skin snip among adults 20 years of age and older, including those with counts of zero. This mean was calculated using the log $(x+1)$ transformation, where x is the individual microfilarial load (REMME *et al.*, 1986). The levels of endemicity were classified according to the OCP definitions of hypo-, meso-, and hyperendemicity, corresponding to SPMF<35%, 35%≤SPMF<60%, and SPMF≥60%, respectively (PROST *et al.*, 1979).

Treatment

As shown in the Figure, the number of villages treated at each treatment round varied from 1987 to 1995. The first treatment round in the Vina valley was carried out in 1987, and concerned only 5 contiguous localities, including Ngoumi, located immediately west of Touboro. These villages constituted the initial treatment area. Six months later, in 1988, these 5 villages were treated again, and a first treatment was organized in 29 other localities—27 located west of the initial treatment area, and 2, including Babidan, located east of Touboro, near the boundary with Chad. In 1989, one year after the second treatment round, the treatment area was extended again, and ivermectin was distributed in all the villages of the valley. From 1990 to 1995, annual distributions were restricted to the most severely affected villages, those located in the eastern third of the valley.

Ivermectin was given at a dose of 150 µg/kg of body weight, which is the dose recommended for treatment of onchocerciasis. Pregnant women, mothers breastfeeding babies less than one month of age, children less than 5 years of age, and patients with severe clinical illness were excluded from treatment. Ivermectin was given free by a medical team which included physicians and nurses. The tablets were swallowed by the subjects in front of the drug dispenser so that the drug could not be taken away and given to people ineligible for treatment. Each village was treated in one day. The full name, sex and age of every treated patient was registered in a book, and then entered into a computer file. Reactions to treatment were monitored and treated during the 48 h following dosing. In the Vina valley, ivermectin was available only through the distributions organized by the team involved in the present study, and no diethylcarbamazine had been available since 1987.

Treatment coverage in each village during the successive treatment rounds was assessed by calculating the ratio between the number of people treated and the total population. The latter value was estimated from the nationwide census of 1987 and the annual rate of increase in the Cameroonian rural population which is, according to the Ministry of Planning, 2·5%.

Parasitological examinations in 1995

In 1995, skin snips were prepared in Ngoumi and Babidan by the same investigator as in 1987, 1988, and 1992, and using the method described above.

In both villages, children 5–7 years of age were examined after questioning the parents about the previous ivermectin treatments given to their children. The answers were checked after the examination round by checking the children's names in the computer files of the people treated during the previous years. This method allowed us to establish the list of those children who were examined in 1995 and had not received any treatment previously.

Evaluation of the impact of the repeated treatments on the transmission of onchocerciasis

At each examination round, 2 indices were calculated in the untreated children: the prevalence of microfilaridermia (PMF), and the geometric mean microfilarial density per skin snip (MFD). The MFD was calculated using the log (x+1) transformation, where x is the individual microfilarial load. The PMF and MFD were calculated separately for the children aged 5, 6 and 7 years, and for the total number of 5–7 years old children examined at each round.

The pretreatment parasitological indices measured in 1987 in Ngoumi in children 5–7 years of age were compared with the indices measured in 1992 and in 1995 in untreated children living in the same village and belonging to the same age group. The indices measured in 1988 and 1995 in children of Babidan were compared similarly. The PMFs measured at successive examination rounds were compared using the χ^2 test or Fisher's two-tailed exact test and the MFDs were compared using the Mann–Whitney test. In all tests, the differences were considered significant when $P<0{\cdot}05$.

Results

Pretreatment endemicity levels

During the pretreatment parasitological survey, a total of 7274 people, including 3959 subjects 20 years of age and above, was examined in 31 villages. The results demonstrated that the prevalence and intensity of onchocercal infection in the Vina valley generally increased from west to east. Among the 15 villages examined and located between Ngaoundere and Ndok, in the western two-thirds of the valley, only 4 were hyperendemic, whereas 7 were mesoendemic and 4 hyperendemic. Conversely, all the villages located east of Ndok were hyperendemic. Amongst the latter localities, which are the only ones that had been treated between 1990 and 1995, intensity of infection increased progressively from west to east, and 3 groups of villages could be distinguished according to the CMFL. In the 5 communities examined and located between Sora Mboum and Mbeing, the CMFL ranged from 20 to 40 microfilariae per skin snip (mf/ss), and the 9 villages located in this area were considered 'mildly hyperendemic'. In the 8 villages located between Touboro and Reh, including Ngoumi, the CMFL ranged between 50 and 120 mf/ss, and the villages located in this area were considered 'moderately hyperendemic'. The 8 communities located between Touboro and the boundary between Cameroon and Chad, in the most eastern part of the valley, were considered as 'highly hyperendemic', with CMFLs probably exceeding 150 mf/ss. This assumption was based on the results recorded in the only 2 villages examined in this area, Babidan and Koubao, where the CMFLs were 216·4 and 303·3 mf/ss, respectively.

In Ngoumi, a total of 762 people, including 517 subjects 20 years of age and above, was examined in 1987. The pretreatment SPFM and CMFL in Ngoumi were 87·6% and 83·7 mf/ss, respectively. In Babidan, a total of 246 people, including 125 subjects 20 years of age and above, was examined in 1988. The pretreatment SPMF and CMFL in Babidan were 92·5% and 216·4 mf/ss, respectively.

Drug coverage

In 1987, the total populations recorded in Ngoumi and Babidan were 1735 and 392, respectively. The estimated population living in these villages from 1987 to 1994, and the number of people treated each year, are shown in Table 1.

In Ngoumi, the drug coverage tended to decrease progressively during the first 6 distribution rounds, and to increase in 1993 and 1994. In Babidan, the general trend was similar to that in Ngoumi.

Table 1. Population and ivermectin coverage from 1987 to 1994 in the Vina valley, Cameroon

	1987	1988	1989	1990	1991	1992	1993	1994
Ngoumi								
Population	1735	1778	1823	1868	1915	1963	2012	2062
No. treated	1312	1175	1144	847	987	816	1189	1403
Coverage (%)	75·6	66·1	62·8	45·3	51·5	41·6	59·1	68·0
Babidan								
Population	392	402	412	422	433	444	455	466
No. treated	0	246	215	190	158	236	287	312
Coverage (%)	–	61·2	52·2	45·0	36·5	53·2	63·1	67·0

Table 2. Prevalence of *Onchocerca* microfilaridermia and geometric mean microfilarial density per skin snip in untreated 5–7 years old children in Ngoumi in 1987, 1992 and 1995

Age (years)	No. examined 1987	1992	1995	Prevalence (%) 1987	1992[a]	1995[a]	Density[b] 1987	1992[a]	1995[a]
5	5	20	15	60·0	5·0*	0**	2·96	0·08**	0**
6	21	37	23	57·1	27·0*	8·7***	2·97	1·09*	0·25***
7	16	10	9	75·0	30·0*	0***	6·61	0·28**	0***
Total	42	67	47	64·3	20·9***	4·3***	4·08	0·60***	0·12***

[a]Significant differences from the corresponding 1987 values are indicated thus: *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$.
[b]Microfilariae per skin snip.

The dispersal range of *Simulium* may exceed 10–20 km, and the populations of Ngoumi and Babidan during the study were exposed to flies infected in neighbouring areas. Consequently, the impact of repeated treatments on the transmission of onchocerciasis depended not only on the drug coverage in the villages studied but also on the coverage in the neighbouring localities. The mean drug coverages obtained between 1989 and 1994 in the mildly, moderately, and highly hyperendemic villages defined previously were 49·0% (range 33·5–65·9), 50·1% (range 41·7–58·3) and 42·2% (range 34·7–47·8), respectively.

The coverage in Ngoumi between 1987 and 1992 was similar to that in the other moderately hyperendemic villages, but it was higher in Ngoumi in 1993 and 1994. The coverage in Babidan was generally higher than in the other highly hyperendemic villages, and this difference was particularly marked in 1992, 1993 and 1994.

Parasitological indices in untreated children

Ngoumi. The PMF and the MFD in the 5–7 years old children decreased significantly beween 1987 and 1992 and between 1987 and 1995 (Table 2). Considering the children aged 5, 6 and 7 years separately, the PMF and the MFD also decreased significantly between 1987 and 1992, and between 1987 and 1995, in each of the 3 age groups. The PMF in the 5–7 years old children decreased significantly between 1992 and 1995 ($P<0·02$) but, when evaluated separately for the 5, 6 and 7 years old children, the decrease was not significant in any age group. The MFD did not decrease significantly between 1992 and 1995 in either the total number of 5–7 years old children ($P=0·07$) or in the 3 age groups separately. Table 2 shows that, in 1995, none of the 5 and 7 years old children had microfilariae in their skin snips and only 2 of the 23 children aged 6 years did so. The microfilarial loads of the 2 latter children were 0·5 and 122 mf/ss, respectively. The significant decrease in the PMF and the general trend in all the indices strongly suggest that a further decrease in the transmission of *O. volvulus* occurred in Ngoumi between 1992 and 1995, but the non-significant results regarding the MFD do not permit a definite conclusion on this point.

Babidan. In Babidan, the PMF in the 5–7 years old children decreased significantly between 1988 and 1995, but when evaluated separately for the 5, 6 and 7 years old children, the decrease was significant only for those aged 6 years (Table 3). The overall MFD in the 5–7 years old children decreased significantly, but there was no significant decrease within each individual age group.

Table 3. Prevalence of *Onchocerca* microfilaridermia and geometric mean microfilarial density per skin snip in untreated 5–7 years old children in Babidan in 1988 and 1995

Age (years)	No. examined 1988	No. examined 1995	Prevalence (%) 1988	Prevalence (%) 1995[a]	Density[b] 1988	Density[b] 1995[a]
5	10	12	50·0	25·0	5·79	1·20
6	19	11	78·9	36·4*	11·90	3·39
7	11	2	81·8	50·0	23·60	12·34
Total	40	25	72·5	32·0**	12·12	2·45**

[a]Significant differences from the corresponding 1988 values are indicated thus: $*P<0·05$, $**P<0·01$.
[b]Microfilariae per skin snip.

Discussion

Previously, in Africa, only 2 studies have evaluated the long-term impact of successive annual ivermectin treatments on the transmission of *O. volvulus* in areas where no vector control has been undertaken. One of these studies was performed after 5 successive distributions in hyperendemic villages in the Vina valley (BOUSSINESQ *et al.*, 1995), and the other in mesoendemic or mildly hyperendemic villages in the Bakoye and Faleme basins in the OCP area. In the latter, all the untreated 5 years old children had negative skin snips after 5 successive annual ivermectin distributions (WHO, 1995). The present study confirmed that repeated ivermectin treatments, even at 60% coverage, may bring about a marked reduction in the transmission of onchocerciasis even in areas with considerable initial intensity of infection. In addition, the results in Ngoumi strongly suggest that the decrease in the incidence of infection already recorded in 1992 after 5 repeated distributions continued between 1992 and 1995. The fact that the MFDs recorded in 1992 and 1995 did not differ significantly was probably due to the relatively small sample of children examined.

It is most unlikely that the decrease in the incidence might have been related to a reduction in the vector density, because no significant climatic change occurred between 1987 and 1995.

The decrease in the parasitological indices in untreated children was less notable in Babidan than in Ngoumi. Several factors may have accounted for this difference. First, in 1995, the population in Babidan had received only 7 successive treatments, whereas Ngoumi had been treated on 8 occasions. Second, the pretreatment level of endemicity was much higher in Babidan than in Ngoumi. Third, the mean drug coverage between 1989 and 1994 was only 42·2% in the villages adjacent to Babidan, whereas it reached 50·1% in the villages near Ngoumi. Lastly, Babidan is only 2 km from Chad, and 30 km from the CAR. The hyperendemic areas located in these countries along the boundary with Cameroon benefited from ivermectin distribution only since 1992. Consequently, highly infected *Simulium* from Chad and the CAR probably entered Babidan until 1992, and participated in the transmission of onchocerciasis in the latter locality.

The reduction in the transmission recorded in the Vina valley has been assisted by the fact that this area is geographically isolated by 2 ranges of mountains on the north and south, which limited the invasion of the study area by flies which had acquired their infection elsewhere. Moreover, as the populations living outside the valley on the north and south are sparsely distributed and some distance from *Simulium* breeding sites, they probably constituted only a moderate reservoir of infection, even before they were first treated in 1992. Besides this, ivermectin distribution also started in 1992 in the hyperendemic areas east of the Vina valley in Chad and the CAR, and consequently it is probable that the infection rate in the flies which dispersed from these areas to the Vina valley was reduced. This might have brought about a further decrease of transmission in the Vina valley since 1992.

Besides these favourable factors, the high intrinsic vector competence of *S. damnosum s.s.* and *S. sirbanum*, which transmit *O. volvulus* in the area, makes the results recorded in the Vina valley remarkable; in these species, the fewer the microfilariae that are ingested, the greater the proportion of those ingested that survive (BAIN, 1971). In contrast, in forested areas where onchocerciasis is transmitted by other species, reduction in the microfilarial reservoir may result in a proportional decrease in the intensity of transmission. Despite low drug coverage (30%), such an effect has been demonstrated by CHAVASSE *et al.* (1995) in Sierra Leone in an area where onchocerciasis is transmitted by *S. leonense*, an excellent vector of *O. volvulus*, and where 5 successive ivermectin distributions were carried out at intervals of 6 months.

Several mechanisms may be responsible for the decrease in the *O. volvulus* microfilarial reservoir in areas treated repeatedly with ivermectin. The direct microfilaricidal effect of ivermectin in treated people is reinforced by the fact that repeated doses have a cumulative effect on the fecundity of adult worms (WHITWORTH, 1992). Data from Asubende, Ghana, suggested that after each treatment the fecundity level of adult worms was permanently reduced by 30% (WHO, 1995). On this assumption, the reproductive capacity of the adult worms is reduced by 92% and 94% in individuals who received 7 and 8 successive annual treatments, respectively. The remarkable decrease in the transmission of *O. volvulus* recorded in the Vina valley supported these predictions. The assumption that the fecundity level is permanently reduced may explain why such a marked decrease was recorded in Ngoumi, despite only moderate drug coverage. It is likely that most of those individuals who missed one distribution would have attended the next treatment round. Consequently, the fact that treatments were taken irregularly by some individuals may have had a relatively small influence on the final impact on transmission. Such a conclusion had been drawn from a previous study which showed that microfilarial loads recorded 5 years after the first dosing were not significantly different in patients who had received 3, 4, or 5 treatments during this period (BOUSSINESQ *et al.*, 1993).

At present, it is considered that ivermectin cannot interrupt the transmission of onchocerciasis in hyperendemic areas (DUKE, 1990; WHO, 1995). However, the results recorded in the Vina valley suggest that the potential of the drug for reducing transmission may be greater than predicted, and studies should be performed in other areas to see whether they reproduce the trend recorded in northern Cameroon. The community self-treatment strategy that will be developed in the APOC area may increase the drug coverage and the impact on the transmission of *O. volvulus*.

Acknowledgements

This work was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases and the River Blindness Foundation.

We thank Messrs A. Amadou, J. Baldjagai, B. Bouchité, Drs F. Chandre, J. Dinga, J. C. Ernould, P. Fagot, J. Gardon, N. Gardon-Wendel, C. Godin, B. Kollo, Messrs P. H. Legros, J. M. Macé, Dr C. Malagal, Mr T. Madi, Drs R. Moyou, S. Ranque, P. Richard, Mr M. Thézé, and the staff of *Centre Pasteur*, Yaoundé, for their help in the field and assistance with data analysis. The co-operation of the Cameroon Ministry of Public Health is gratefully acknowledged. Thanks are also due to Dr R. Le Berre and the late Dr D. Quillévéré for their invaluable encouragement since the outset of this study.

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Received 26 June 1996; revised 12 September 1996; accepted for publication 12 September 1996