The impact of Mectizan on the transmission of onchocerciasis

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For many years there was no suitable drug available for the control of onchocerciasis. The advent of Mectizan (ivermectin, MSD; an effective microfilaricide), its registration in October 1987 for the treatment of human onchocerciasis, and its suitability for large-scale application were major break-throughs in the control of human onchocerciasis via chemotherapy. Several studies, both fly-feeding experiments and community trials, have established that Mectizan treatment causes a significant reduction in the transmission of infection. Although long-term treatment in some isolated foci (such as occur in the New World and in some hypo- and meso-endemic areas elsewhere) appears to interrupt transmission, more prolonged treatment is required to prove if transmission can be stopped. Advantage could be taken of the significant impact of Mectizan on transmission by giving treatment while or just before transmission by blackflies is most intense.

Until the late 1980s the only drugs available for the treatment of onchocerciasis were suramin and diethylcarbamazine (WHO, 1987). Although suramin has been shown to be macrofilaricidal (Ashburn et al., 1949) and has been used successfully in limited mass treatment (Dawood, 1978: Rougemont et al., 1980, 1984), the difficulties associated with its mode of administration and its toxicity have limited its usefulness (Awadzi et al., 1995). Diethylcarbamazine only has microfilaricidal action, has to be given over several days and also produces severe, adverse (Mazzotti) reactions (Awadzi and Gilles, 1980) These drawbacks have excluded the use of suramin and diethylcarbamazine for the routine treatment of onchocerciasis.

The advent of an effective microfilaricide called Mectizan® (ivermectin, MSD) and its registration in October 1987 in France for the treatment of human onchocerciasis were breakthroughs in the control of onchocerciasis. The suitability of Mectizan for large-scale

treatment (Awadzi et al., 1985; De Sole et al., 1989; Remme et al., 1989; Prod'hon et al., 1991; Whitworth et al., 1991; Collins et al., 1992) opened up prospects for the control of onchocerciasis through chemotherapy. One of the most important and striking characteristics of Mectizan is that, despite its short half-life, a single dose not only eliminates skin microfilariae (mff) but also provides long-lasting suppression of microfilaridermia (Awadzi et al., 1985; Greene et al., 1985); this phenomenon might be attributable to the development of a partial, drug-facilitated immunity (Schulz-Key et al., 1992). Repeated treatments cause massive reduction in the number of multicellular embryonic stages of worms (Duke et al., 1991; Chavasse et al., 1992). In the light of such findings, it seemed plausible that treatment with Mectizan would cause a certain amount of reduction in transmission by virtue of its temporary elimination of skin mff. Thus, one of the hopes that was entertained when Mectizan treatment was introduced was that it would have a lasting impact on, or interrupt transmission.

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In the present review, an attempt is made to bring together the results and conclusions of the many different studies that have sought to evaluate the impact of Mectizan on transmission of *Onchocerca volvulus*. The potential of Mectizan treatment for the control of transmission and how this could be best exploited are discussed.

ENTOMOLOGICAL EVIDENCE FOR IMPACT ON TRANSMISSION

Fly-feeding Experiments
Some of the initial studies on the impact of Mectizan on transmission were fly-feeding experiments in West Africa and Guatemala.

LIBERIA
Cupp et al. (1986) examined the quantitative effects of Mectizan treatment on: (1) the level of infection of a normally efficient vector, *Simulium yahense*, by *O. volvulus* mff; and (2) the development of the mff in the blackflies. They examined and fed flies on human volunteers 3 and 6 months after each volunteer had received a single dose of drug (at 200 µg/kg) or placebo. In general, treated subjects had far lower densities of mff in their skin at 3 or 6 months post-treatment than the subjects given placebos and flies fed on treated subjects at these times were not only less likely to be infected than those fed concurrently on members of the placebo group but, if infected, carried much smaller loads of parasites (see Table 1). Cupp et al. (1986) concluded that Mectizan treatment should limit the incidence and prevalence of infection in blackflies (because it cuts the densities of mff in the skin drastically) and may therefore be effective in interrupting transmission of *O. volvulus* for epidemiologically important periods of time.

MALI
Bissan et al. (1986), who carried out their year-long experimental studies using *S. sirbanum* (an important savanna vector) and 12 onchocerciasis patients, observed that individuals who were given a single dose of Mectizan remained non-infective to *S. sirbanum* flies for up to 6 months. However, infection rates in

flies fed on the subjects 1 year post-treatment were considerably higher than those fed on the subjects just 2 months post-treatment. The conclusion was that transmission was reduced considerably for an interval of time that was longer than the 3-month period of intense transmission in the study area. A potentially useful operational strategy to adopt in planning Mectizan treatment then became evident: give treatment just before the start of the seasonal vector-breeding period, as this is likely to have maximum impact on transmission.

IVORY COAST
In a similar trial in Ivory Coast, eight subjects were studied in an experiment which lasted 180 days (Prod'hon et al., 1987). The mean numbers of ingested mff and developing larvae in *S. soubrense* and *S. sanctipauli* engorged on treated and non treated-patients were recorded. Not only were the infection rates in the flies fed on the treated subjects significantly lower than those in the flies fed on the untreated, but larval development was retarded in flies fed on the treated subjects at any time up to 6 months post-treatment.

GUATEMALA
In the New World, Cupp et al. (1989) showed that there was interruption of uptake of *O. volvulus* mff by *S. ochraceum* from a group of volunteers living in a meso-endemic focus in Guatemala who were treated with oral Mectizan at 200 µg/kg on two occasions, 7 months apart, and then followed-up for a period of 15 months. Since microfilarial uptake by *S. ochraceum* is strongly predictive of thoracic infection and subsequent production of *O. volvulus* infective-stage larvae (L_3; Collins et al., 1977), Cupp et al. (1989) concluded that regularly spaced Mectizan treatments at the community level would result in the elimination of infective blackflies. This, by extension, would cause an abrupt decrease in the annual transmission potential (ATP; Duke 1968).

Although all of these initial studies (and many of the subsequent ones on this topic) involved small numbers of volunteers, they

TABLE 1

Uptake of microfilariae (mff) by Simulium yahense *from onchocerciasis patients receiving placebo or Mectizan, 3 and 6 months post-treatment (from Cupp et al., 1986)*

Group	No. of subjects	Mean skin infection (mff/mg)	No. of flies dissected	Mean fly infection (mff/fly)	(thoracic mff/fly)	Thoracic infection (% of flies)
FLIES FED 3 MONTHS POST–TREATMENT						
Placebo	4	40.77	28	34.80	14.10	96.4
Mectizan	3	0.54	25	0.32	0.10	12.0
FLIES FED 6 MONTHS POST–TREATMENT						
Placebo	4	49.63	48	10.52	3.06	75.0
Mectizan	3	8.6	34	2.28	0.56	32.4
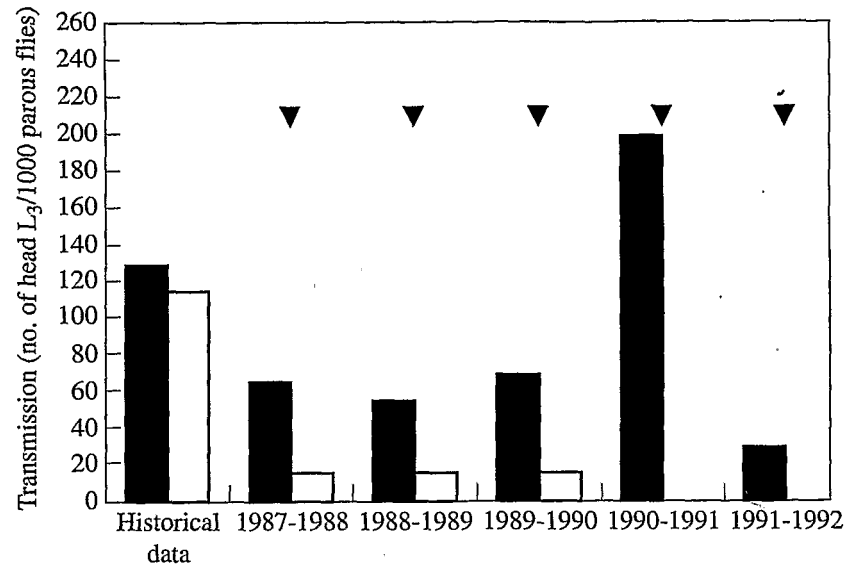
Fig. 1. Changes in transmission in Asubende, Ghana, after five rounds of Mectizan treatment (▼), as measured by the numbers of infective-stage larvae (L₃) in the heads of 1000 parous blackflies caught in September–October (■) and November–February (□).

were enough to show that Mectizan treatment affected the parasite–vector relationship, significantly decreasing the number of mff available for ingestion by blackflies, reducing production of L₃ and consequently reducing transmission. As a result, the expectation was that mass treatment with Mectizan would result in an immediate period of reduced *O. volvulus* transmission.

Community-based Trials in Ghana, Liberia and Guatemala

Various community trials have been conducted in an attempt to establish the effect on transmission of mass treatment with Mectizan as: (1) a single, annual dose; (2) multiple doses per year (at various frequencies); and (3) treatment over many years.

GHANA

The community trial with Mectizan in the Pru basin in Ghana (Remme *et al.*,1989) was one of the earliest and largest of a series that was undertaken in the area monitored by the Onchocerciasis Control Programme of West

Africa (OCP) in 1987. The study area was ar isolated focus of hyperendemic, savanna onchocerciasis in Asubende in Ghana, and the aim was to assess the effect of mass treatmen with Mectizan on the transmission o *O. volvulus.* Well over 14 900 people wer treated once with a single dose of Mectizan (a 150 μg/kg) and then again, at the same dose 1 year later. The total reservoir of skin ml was reduced by an estimated 68%–78% months after the initial treatment. This obser vation was consistent with the entomologica results, which showed a reduction in trans mission of 65%–85% in the first 3 month after treatment ('transmission' being measure as the mean number of L₃ in the head of parous, female fly; Fig. 1). Although the stud was the first to show that mass chemotherap could significantly reduce *Onchocerca* tran mission, the remaining level of transmissic was unacceptably high. In fact, preliminar mathematical models predicted that annu Mectizan treatment would not eradicate tl parasite from an endemic area within a peric of 25 years (Habbema *et al.*, 1992) and initi results of studies after the second treatme

TABLE 2
Monthly transmission potentials of Onchocerca volvulus by Simulium yahense on the rubber plantation of the
Liberian Agricultural Company, before and after the distribution of Mectizan (from Trpis et al., 1990)

Area	Pre-treatment (1986)	Post-treatment (1988)	Reduction (%)
Central camps	22.9	5.8	74.6
Peripheral camps	146.2	68.0	53.5
Outside villages	210.0	158.8	24.4

round failed to show any evidence of an additional reduction in transmission.

LIBERIA

In the Liberian trial, in an exclusively *S. yahense* focus (Trpis et al., 1990), subjects from a plantation with a total population of about 14 000 were each given two treatments with Mectizan (each of 150 μg/kg), one in 1987 (7699 subjects; 56% of target population) and the other 12 months later, in 1988 (8068 subjects; 58% of target population). Although biting intensities before and after each treatment were similar (2.1–2.4 bites/man-hour), transmission of *O. volvulus* after the second treatment fell by 63.0%–96.8% compared with that pre-treatment. Although monthly transmission potentials fell in the untreated, control areas (from 210 to 158; a 24.4% reduction), the fall was much (and significantly) less than that seen in the treated areas (22.9 to 5.8; a 74.6% reduction; Table 2). As in Ghana, transmission had thus been drastically reduced but not completely interrupted by chemotherapy.

GUATEMALA

A biannual, community-wide, Mectizan treatment over a 30-month period provided the opportunity to measure the effect of this regime of treatment on vector infection over a relatively long time, in an area of Guatemala where *S. ochraceum* was the vector (Cupp et al., 1992). The most important results were that significant reductions occurred in: (1) the prevalence and intensity of infection in *S. ochraceum* in all three study sites (the numbers of females carrying L_3 being reduced by

76%, the number of *O. volvulus* L_3/1000 parous flies falling by ≥92% and prevalence of fly infection at one site being reduced by 89%); (2) infecting biting density (IBD) and transmission potential (both of which fell to zero at one site; Fig. 2). That this is the first and only report of Mectizan causing all transmission potential to be eliminated perhaps reflects the low efficiency of *S. ochraceum* as a vector (compared with its counterparts in West Africa, where all the other, related studies have taken place; Cupp, 1992).

OCP Comparative Studies in Guinea (Combined Mectizan Treatment and Vector Control) and the Original OCP Area (Vector Control Alone)

Within the OCP, Mectizan treatment has not only been used widely as an adjunct to vector control but has also been used on its own in some areas (in the northern part of the western extension and in Sierra Leone). A comparative study, to assess the impact on transmission under operational conditions of vector control combined with Mectizan treatment given annually at 150 μg/kg, was undertaken in 1994 by Guillet et al. (1995). Data from the Niger basins in Guinea (where Mectizan treatment and vector control have been combined) were compared with those from the original OCP area (where there has only been vector control). The principal vectors were *S. sirbanum* (both countries), *S. damnosum* s.s. (both countries) and *S. squamosum* (Guinea only; Fig. 2).

At the eight selected catching points in the original OCP area, larviciding had been fully on course from 1977. Data collected from
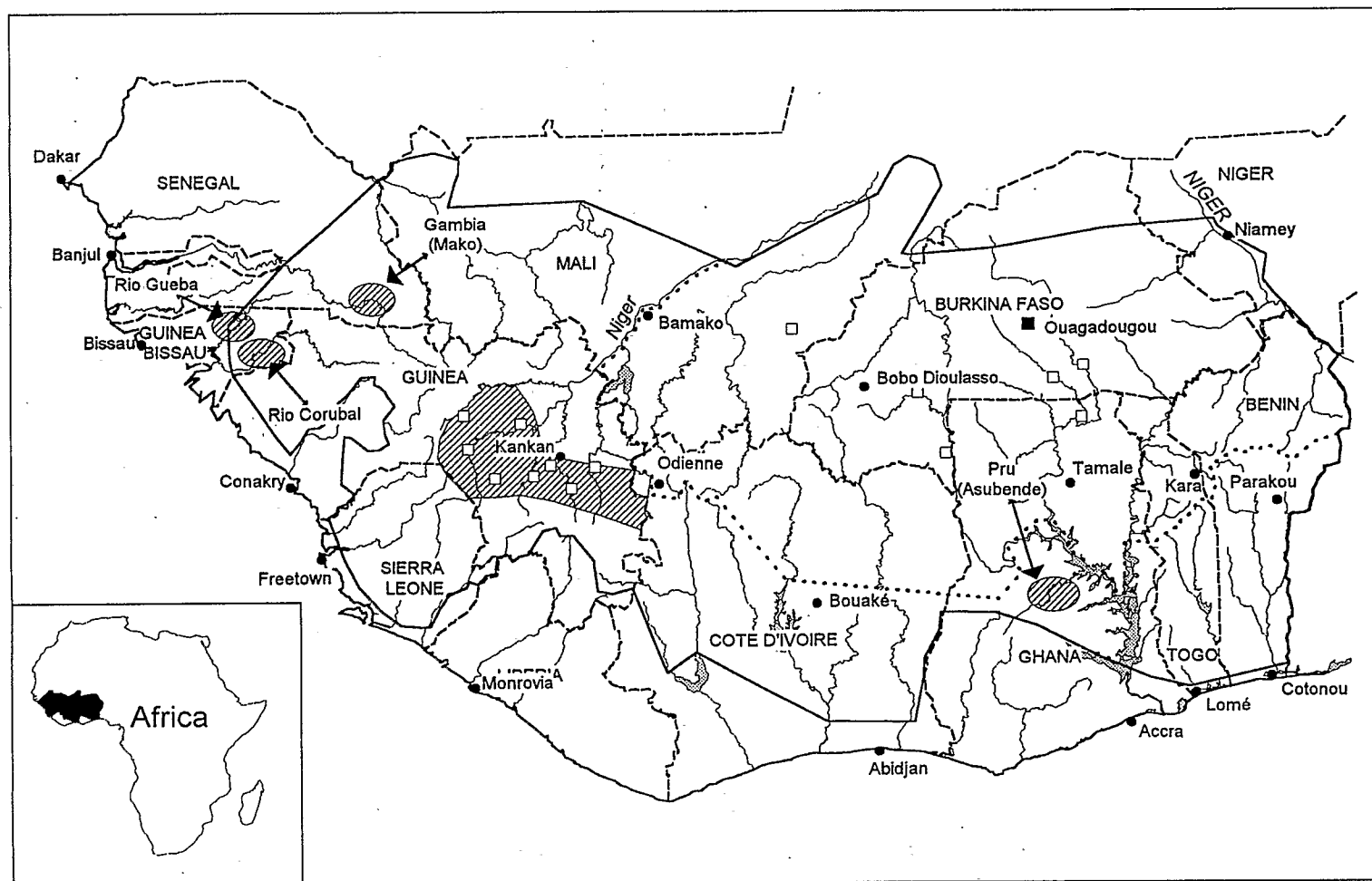
Fig. 2. Map showing some of the study sites (▨) within the area monitored by the Onchocerciasis Control Programme of West Africa (OCP). Catching points (□), the boundaries of the current (—) and original OCP areas (··········) and national boundaries (-------) are indicated.
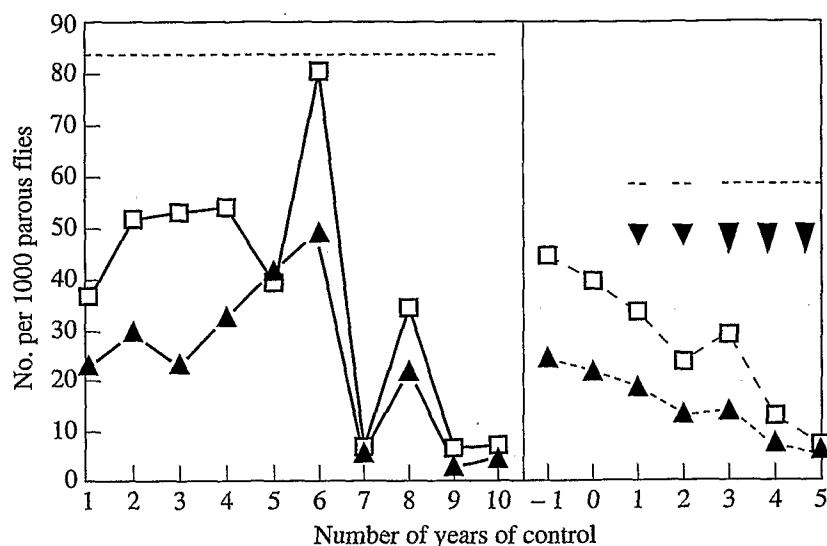
Fig. 3. Numbers of infective flies (▲) and numbers of infective-stage larvae (□) in collections of parous flies from the original area monitored by the Onchocerciasis Control Programme of West Africa (left-hand panel) and from Guinea (right-hand panel). In Guinea, the first two Mectizan rounds were limited to a few villages (▼) whereas the rest were on a much larger scale (▼). The levels of transmission observed when vector control was used alone are indicated by the horizontal, dashed lines.

> 34 000 blackflies caught at these sites over a 10-year period were analysed.

In the Niger basins, larviciding had begun in 1988 and Mectizan treatment had started in 1988, in the Milo basin, and then been extended to the other basins between 1989 and 1990, when all the basins relevant to the comparative study were fully covered. Treatment coverage was generally > 65%. Overall, data from > 20 600 blackflies caught at eight points in the Niger basins over a 6-year period were available for study.

Significant reductions in the numbers of L3/1000 parous flies were seen after just 3 years of combined Mectizan treatment and vector control but only after 7–10 years when larviciding was the only control measure (Fig. 3). Furthermore, it took 10 years of effective and continuous larviciding to achieve the same loads of L3 in parous flies as was achieved with 5 years of combined Mectizan treatment and larviciding. Although it is difficult to disassociate the effect of Mectizan from that of vector control, the evidence that

Mectizan has had a direct effect on transmission in the Niger basin is strong.

Until Mectizan's registration for human use in 1987, the only method for large-scale control of onchocerciasis was larviciding. The OCP embarked on the control of onchocerciasis in 1974, initially intending to use larvicides for a period of 20 years (the current estimate of the life-span of the adult worm at that time). After Plaisier et al. (1991) stated that the mean reproductive life-span of the adult worm was only 9–11 years, the planned maximum period of larviciding was brought down to 14 years. Mathematical models have now been used to predict that only 12 years of a combination of Mectizan treatment and larviciding would be enough to meet the OCP's goals.

Conclusions from the Entomology

The evidence that emerges from fly-feeding experiments and the small-scale and community-based trials is that mass treatment with Mectizan significantly reduces the numbers of infective blackflies and the

transmission of *O. volvulus*. The drug's clearance of skin mff is probably the main cause of its impact on transmission, uptake of mff by blackflies increasing with increasing microfilarial density in the skin of the bloodmeal source, up to a point of saturation (Duke, 1962; Basanez *et al.*,1994). However, Mectizan appears to have other, less obvious effects which reduce transmission (Chippaux *et al.*, 1995). For example, the mff that survive in a subject treated with Mectizan tend to migrate deeper into the dermis than normal and therefore become inaccessible to the feeding flies (Jurgens and Schulz-Key, 1990). The surviving mff that are ingested by a fly feeding on an Mectizan-treated individual also seem less able to cross the fly's peritrophic membrane than those from an untreated individual (Boussinesq and Prod'hon, 1990).

There is considerable inter-study variability in the observed impact of similar doses of Mectizan, transmission generally being reduced by 65%–97%. This variation may be attributable to any of several factors or a combination of them: variation in the competence of local blackflies as vectors; differences in treatment coverage; and different levels of endemicity pre-treatment. The level of treatment coverage necessary to reduce transmission significantly has still to be established. Treatments targeted at individuals with high densities of mff in their skin (indicating exposure to intense transmission) are likely to have the greatest impact. However, Chavasse *et al.* (1995) observed a 21% reduction in the numbers of infective flies 8 months after unselective treatment with a coverage of only 30%.

The early community studies in the Asubende focus showed that, although there was a considerable reduction in transmission during the year after first treatment with Mectizan, no additional reduction was observed after the second and third treatment rounds. However, other studies that have stretched over a relatively longer period, both in West Africa and Central America, have shown further declines in transmission after several years of annual Mectizan treatment. Despite this encouraging trend, none of these studies

has gone on long enough to show complete interruption, to the extent that Mectizan treatment could be stopped. As there is an estimated 30% reduction in the fecundity of the adult worms after each treatment (Plaisier *et al.*, 1995), long-term treatment could so weaken the adult worms, by attrition, that production of mff stops.

The observation that people treated with Mectizan may remain non-infective for 6 months (Bissan *et al.*, 1986) indicates that treatment just before the period of the year when the adult blackflies are most active would have the most profound impact on transmission.

EPIDEMIOLOGICAL EVIDENCE FOR IMPACT ON TRANSMISSION

The purely entomological assessment of the impact of Mectizan on transmission in Liberia (Cupp *et al.*, 1986) is complimented by a epidemiological study in the same area. In the, latter study, Taylor *et al.* (1990) tested whether treating a large population with Mectizan would decrease transmission sufficiently to reduce the incidence of human infection. As Mectizan has a prolonged effect on skin mff and all adults in the study area were and are given Mectizan routinely, incidence of infection was assessed in children aged < 12 years (who were not treated with Mectizan during mass treatments), over a 3-year period. The overall incidence of infection in children aged 5–12 years fell from a baseline level of 14.9% in 1988 to 9.7% in 1989 (following three annual treatments of individuals aged ≥ 12 years). The age-adjusted incidence of infection in children aged 7–12 years fell from 16.4% in 1988 to 9.1% in 1989 (Table 3) and prevalence of infection in 5-year-old children dropped from 23.7% in 1987 to 19% in 1989 (Table 4).

Effects of Long-term Use of Mectizan on Transmission

As Mectizan is essentially a microfilaricide it needs to be given for a long period, presumably for as long as the life-span of the

TABLE 3

Incidence of onchocercal infection in the 1987 cohort of Liberian children followed-up in 1988 and 1989 (modified from Taylor et al., 1990)

Incidence	1988			1989			Incidence reduction (%)
	No. of subjects		Incidence (%)	No. of subjects		Incidence (%)	
	Snipped	Positive		Snipped	Positive		
Overall	931	139	14.9	516	50	9.7	35*
Age-adjusted (7–12-year-olds)	742	122	16.4	481	44	9.1	45†

* $\chi^2 = 12.3$; $P < 0.001$.
† $\chi^2 = 12.6$; $P < 0.001$.

TABLE 4

Prevalence of positive skin-snips in Liberian children aged 5 years (from Taylor et al., 1990)

| Year | No. of children | | Prevalence (%) |
	Examined	Positive	
1987	396	94	23.7
1988	452	109	24.1
1989	480	91	19.0

adult worm. Mectizan does cause some attrition in adult worm numbers and the viability of the survivors after multiple doses (Duke et al., 1990) and may have a cumulative effect (Remme et al., 1990). The results of the study in the Asubende focus in the OCP (Alley et al., 1994) emphasised that even a single treatment with Mectizan has a significant, medium-term (2–4-year) impact on microfilarial loads (i.e. the impact of the drug on production of mff by female parasites is fairly long lasting). Simulations from the ONCHOSIM epidemiological model have shown that, in the West African situation, Mectizan would have to be given for >20 years to achieve the same results as vector control (Plaisier et al., 1990). A few studies have been conducted in Cameroon (Boussinesq et al., 1995, 1997) and in the OCP area in an attempt to assess the medium- to long-term impact of Mectizan on the transmission of onchocercal infection in areas where Mectizan is the only means of control. Unlike the earlier trials, in which the impact of Mectizan treatment on transmission was assessed mainly by entomological parameters, these recent studies assessed the changes in prevalence, incidence and intensity of infection over several years, as was first done in Liberia (Taylor et al., 1990).

The initial trial in Cameroon demonstrated that five, successive, Mectizan treatments brought about a marked decrease in the prevalence in untreated children aged 5–7 years. The change was significant in the 6-year-olds and highly significant for the combined results for all the 5–7-year-olds (Table 5).

In the OCP area, the follow-up studies were carried out in several basins in the western extension of the programme. The basins concerned were the Gambia basin in Senegal (hyperendemic focus) and the Rio Corubal (hypo- to meso-endemic) and Rio Geba (hypo-endemic) basins in Guinea Bissau (Fig. 2). In all three areas, Mectizan was given at the recommended dose of 150 μg/kg body weight to all individuals that were eligible for treatment, children aged ≤5 years old were not treated, and the study ran for 4–5 years. However, the frequency of treatment per year was different in each area. The available results show a marked decrease in the overall prevalence of infection in all three basins concerned (by almost 100% in the Rio Geba basin). Remarkably, not a single infection was detected in any of the children aged 0–5 years living in the study areas. Entomological assessments showed an 88% reduction in the numbers of infective flies.

Transmission to humans appears to have been totally interrupted in the hypo-endemic Rio Geba basin, as the prevalence of infection in the total population was reduced by almost 100% and the incidence of infection in the 5-year-olds who were receiving Mectizan for the first time was zero. Whilst it is clear that there is a profound reduction in transmission following Mectizan treatment in this area, further follow-up studies will be needed to confirm these findings.

The results from the Rio Corubal basin, where Mectizan was given three times a year for 3 years following 2 years of annual

TABLE 5

Prevalence of positive skin-snips in untreated children aged 5–7 years and
living in Babidan village, Cameroon, in 1988 and 1995 (modified from
Boussinesq et al., 1997)

Age (years)	No. of children examined		Prevalence (%)	
	1988	1995	1988	1995
5	10	12	50.0	25.0
6	19	11	78.9	36.4*
7	11	2	81.8	50.0
5–7	40	25	72.5	32.0†

* Significantly different from 1988 value ($P < 0.05$).
† Significantly different from 1988 value ($P < 0.01$).
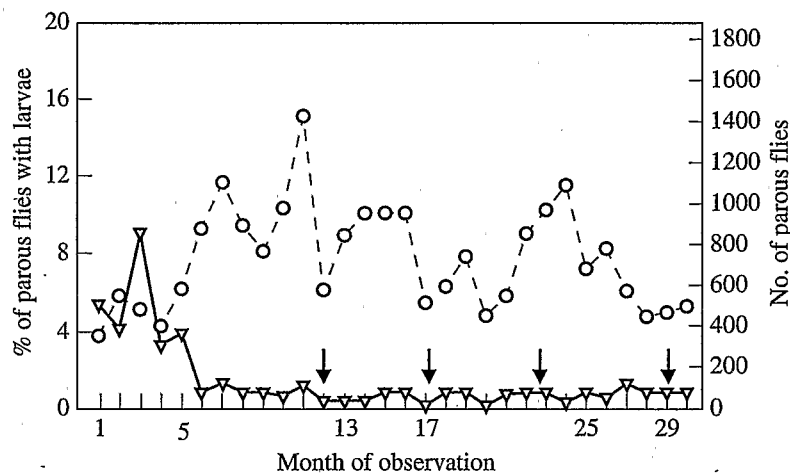
Fig. 4. Prevalence of Onchocerca volvulus infection (all larval stages; ∇) in parous Simulium ochraceum collected at Finca Los Andes from 1 January 1988 (month 1) to 30 June 1990 (month 30). During this period, Mectizan was administered at the community level four times (arrows). The numbers of parous flies collected are also shown (O). From Cupp et al. (1992).

treatment, were equally remarkable, indicating a trend towards a virtual interruption of transmission in this area also, where there was 89% reduction in infective flies.

A progressive decline in transmission over 2.5 years of biannual treatment was observed in the Central American studies (Fig. 4). Whereas there was no complete interruption of transmission, the decline observed in the level of transmission supports the idea that Mectizan treatment caused irreversible damage to the adult worms (Duke et al., 1991; Plaisier et al., 1995).

Model Predictions

Following the community trials undertaken in the OCP area, the results of which showed considerable reduction in transmission after a single Mectizan treatment (Remme et al., 1989b), the ONCHOSIM mathematical model was used to investigate the long-term consequences of such responses (Habbema et al., 1992). Model simulations based on various strategies and scenarios of Mectizan in a holo-endemic area with a treatment coverage of 65% were made. The results indicated that long-term Mectizan treatment would not be

appropriate for eradicating the parasite in such an area, because of rapid repopulation of the skin by mff after treatment and incomplete population coverage. Although subsequent ONCHOSIM modelling, based on additional data collected over 5 years of Mectizan treatment (Plaisier *et al.*, 1995), has indicated that annual Mectizan treatments not only kill the mff but reduce the viability of the adult female parasites (leading to an irreversible reduction in fecundity of about 30%), the problem of inadequate coverage remains. In the early years of large-scale, Mectizan treatment by mobile teams, a coverage of 65% of the total population was considered optimistic. Plaisier *et al.* (1995) argue that even at a coverage of 65%–70%, which is considered excellent in community health, transmission will continue, albeit at a lower level, leading to new infections. Coverage of >75% is, however, becoming a more reasonable target in certain areas because of the trend towards community-directed treatment. It will be interesting to observe what predictions can be made using the ONCHOSIM model and the new parameters now at play.

CONCLUSIONS

The evidence available so far firmly confirms the significant impact of Mectizan treatment on transmission of *O. volvulus*. In some isolated situations, particularly in meso-endemic and hypo-endemic areas, repeated annual treatments or repeated treatments each year may interrupt transmission completely. Treatment targeted at the beginning of the period of intense transmission by the vectors will have the maximum impact on transmission. Combining Mectizan treatment with vector control maximizes the effect of the vector control, leading to a more rapid decline in the transmission of infection.

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