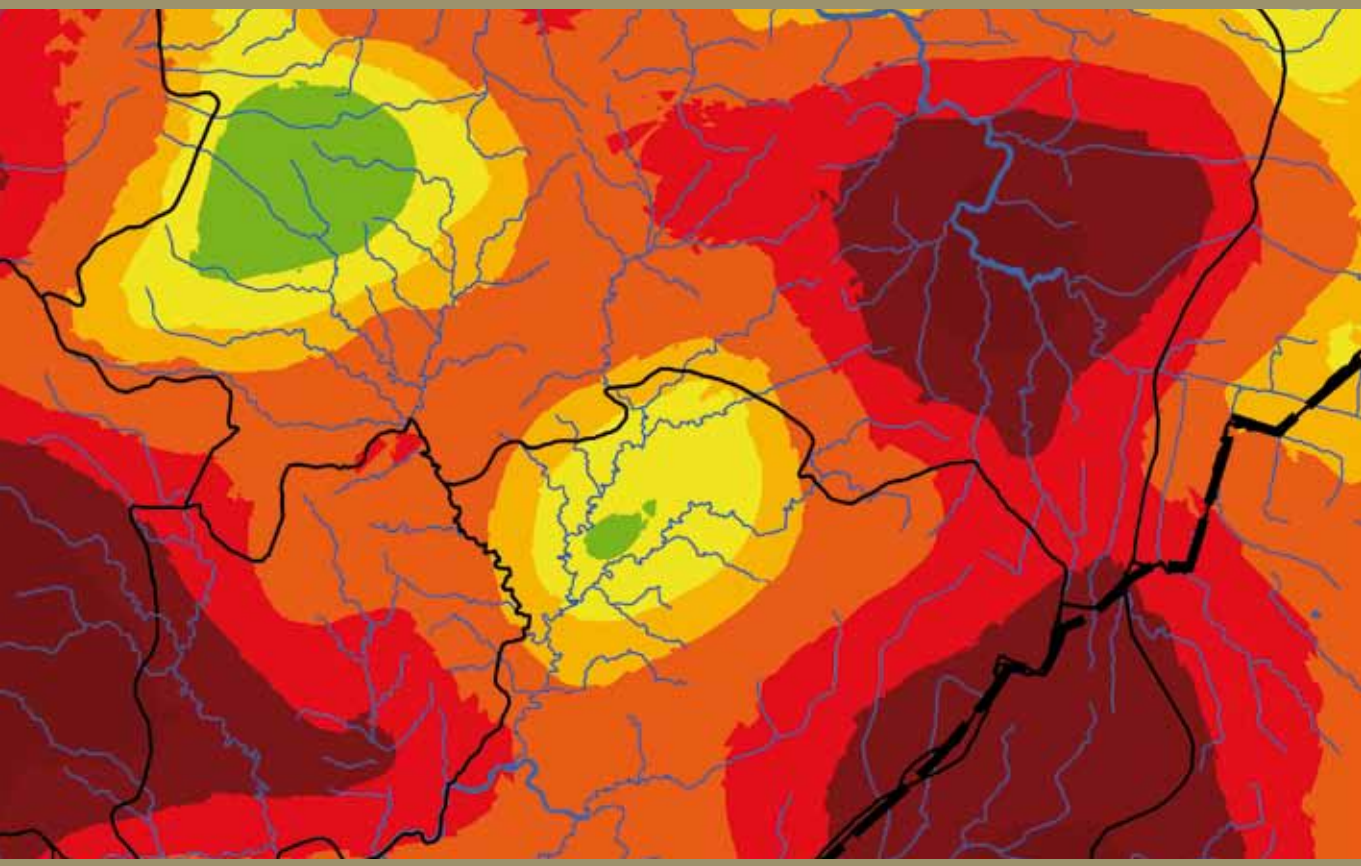
AFRICAN PROGRAMME FOR
ONCHOCERCIASIS CONTROL

Conceptual and Operational Framework of Onchocerciasis Elimination with Ivermectin Treatment



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African Programme for Onchocerciasis Control,
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List of acronyms

APOC	African Programme for Onchocerciasis Control
CDTi	Community-Directed Treatment with Ivermectin
CMFL	Community Microfilarial Load
GPS	Global Positionning System
LF	Lymphatic filariasis
LGA	Local Government Area
mf	microfilaria
mf/s	microfilaria/snip
OCP	Onchocerciaisis Control Programme in West Africa
REMO	Rapid Epidemiological Mapping of Onchocerciasis

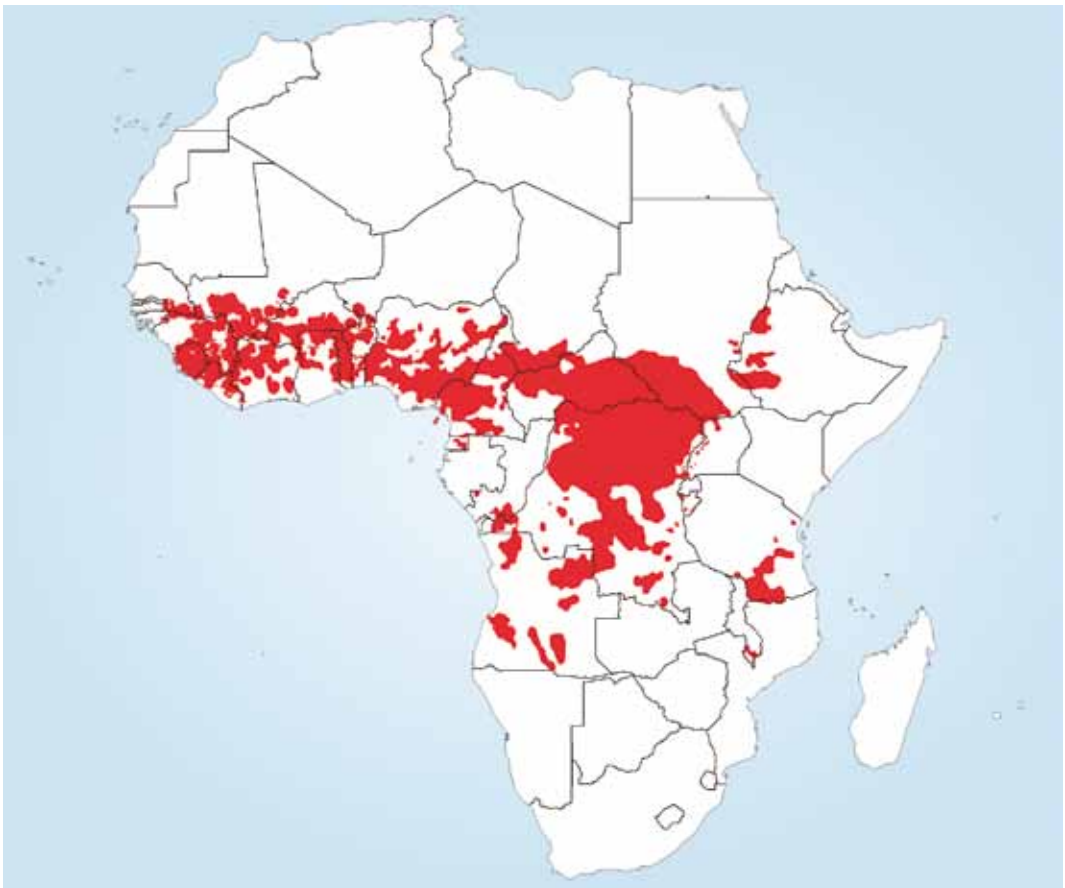
Introduction

Onchocerciasis used to be an important public health problem in Africa (figure 1), with over 37 million people infected and millions suffering from debilitating skin disease, terrible itching, impaired vision and blindness. But the epidemiological situation has improved dramatically over the last two decades. Community directed treatment with ivermectin has effectively brought the disease under control in most endemic areas where onchocerciasis is no longer a public health risk.

Recent studies in West Africa have shown that in the long term even more can be achieved with ivermectin treatment: elimination of the parasite and transmission appears possible in many, if not all, affected areas so that treatment can ultimately be stopped. Based on these new research findings, the board of the African Programme for Onchocerciasis Control (APOC) has directed the Programme "to determine when and where ivermectin treatment can be safely stopped and to provide guidance to countries on preparing to stop ivermectin treatment where feasible".

Onchocerciasis elimination by ivermectin treatment is a complex issue, and much is still to be learned. This document provides an overview of the current state of the art and describes the main conceptual and operational issues in onchocerciasis elimination with ivermectin treatment.

Figure 1 Pre-control: Areas where onchocerciasis was a public health problem

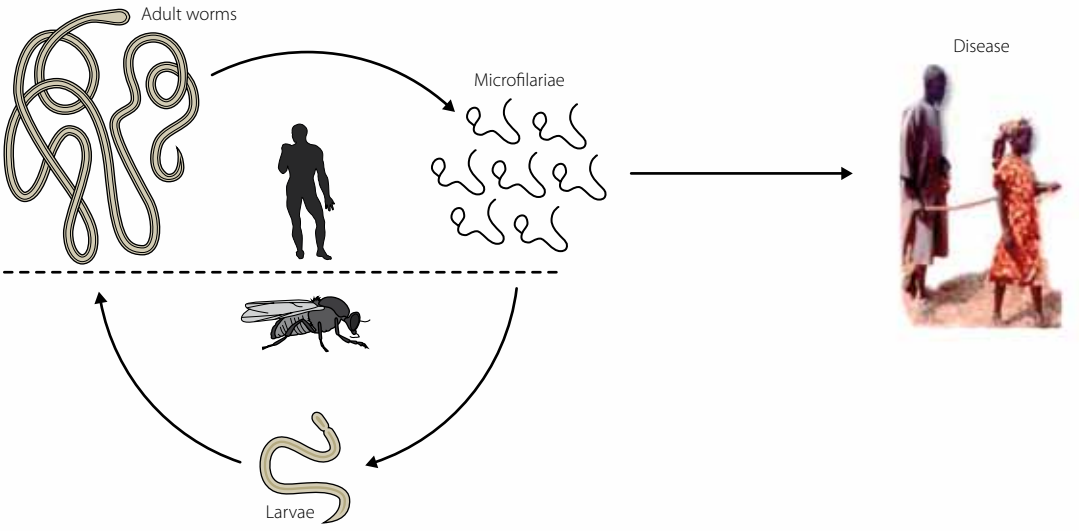


Infection, disease and transmission

Onchocerciasis is caused by infection with a filarial worm, *Onchocerca volvulus*, which only infects humans. The adult worms are found in nodules under the skin of infected persons and they can live up to 14 years. They produce thousands of small microfilaria that migrate through the skin and that are responsible for the main clinical complications as a result of inflammatory reactions to microfilaria in the skin and in the eyes. Intensity of infection is an important risk factor: the larger the number of adult worms, the larger the number of microfilaria and the more severe the disease.

The parasite is transmitted by blackflies which ingest microfilaria during a blood meal on an infected person and inject some of these parasites after their development into infective larva, into another person during a subsequent blood meal. The greater the number of blackflies is relative to the human population, the greater is the intensity of transmission, the higher the endemicity level (i.e. the prevalence and intensity of infection in the human population), and the more serious the disease in the affected community. Onchocerciasis is considered an important public health problem when the prevalence of microfilaria in the skin exceeds 40% of the total population of a community, or when the Community Microfilarial Load (CMFL; a measure of the intensity of the infection in the community) exceeds 5 microfilariae per skin snip (mf/s).

Figure 2 Main stages in the life-cycle of *Onchocerca volvulus*

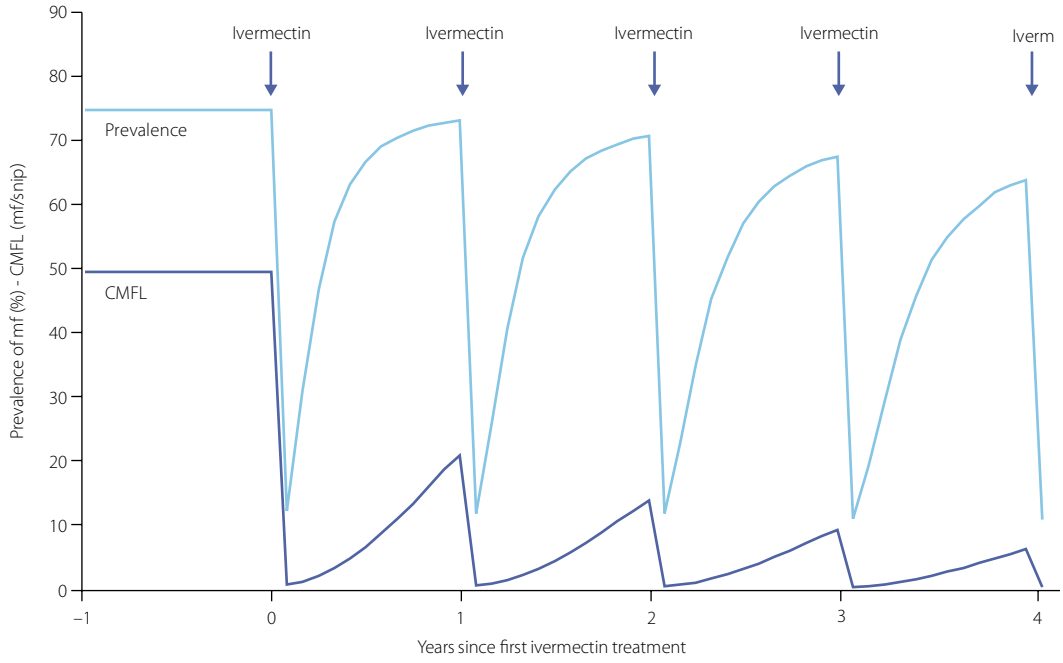


Ivermectin treatment

Ivermectin is a very effective microfilaricide that kills 99% of microfilariae with a single treatment. Since the microfilaria are the main cause of disease, ivermectin treatment has an immediate health benefit. Ivermectin does not kill the adult onchocercal worms and most adults worms start producing microfilaria again a few weeks after treatment, causing microfilarial loads to rise again. However, ivermectin does affect the viability and reproductivity of the adult worms and the rate of increase in microfilarial loads is less after each treatment. Figure 3 shows a computer simulation of the impact of four annual rounds of ivermectin treatment on the prevalence and intensity of microfilaria in the skin in a hyperendemic village with a precontrol CMFL of 50 mf/s. After each treatment, the prevalence bounces back fast, but the microfilarial loads increase much more slowly and to maximum levels that are lower after every treatment. After four treatments the CMFL remains below the threshold of 5 mf/s, indicating that onchocerciasis infection does not longer pose a significant public health risk in this community.

Because of the reduction in microfilarial loads, transmission will also be significantly reduced though not yet interrupted over the four years period. But computer models have predicted that in the long term interruption of transmission and elimination of the parasite reservoir might be possible with ivermectin treatment. These predictions were made in the 1990s, long before there was any empirical evidence to show that elimination was possible.

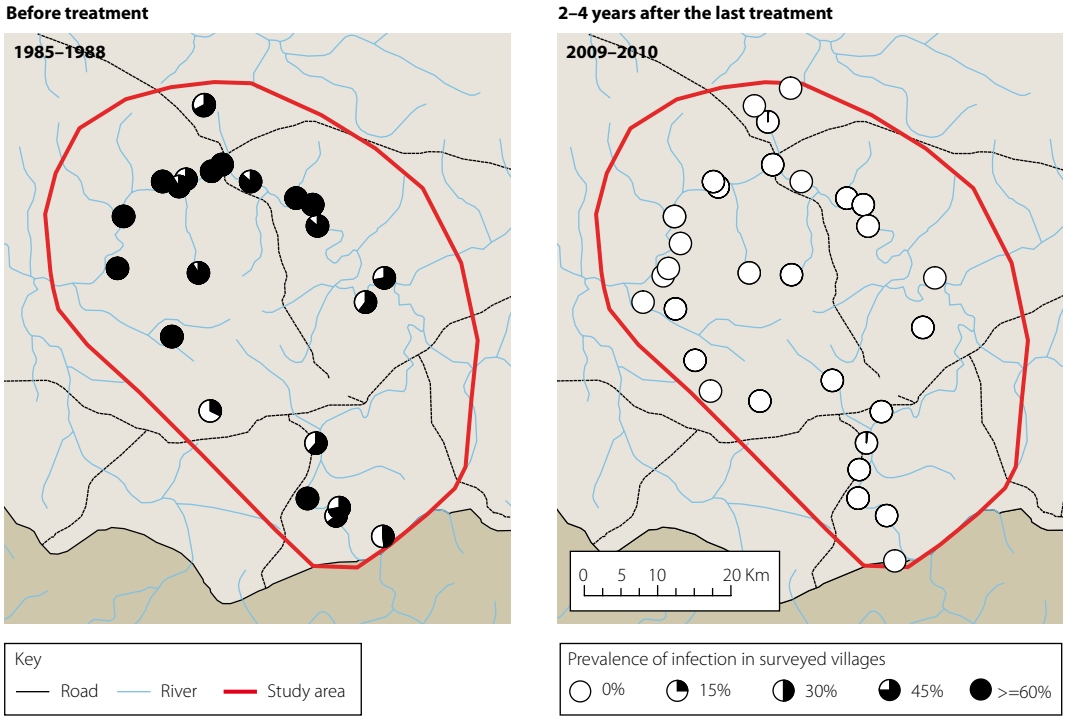
Figure 3 Predicted trends in prevalence of MF and CMFL after annual ivermectin treatment



Feasibility of elimination

The first empirical evidence on the feasibility of onchocerciasis elimination with ivermectin treatment is now available from studies in three onchocerciasis foci in Senegal and Mali. These studies showed that after 15 to 17 years of treatment (annual treatment in two foci and six monthly treatment in one focus), the prevalence of infection and the intensity of transmission had fallen below postulated threshold values for elimination (see example of River Gambia focus in figure 4). Treatment was then stopped and follow-up data over a period of three years showed no evidence of new infection or transmission. This provided the first evidence that ivermectin treatment can eliminate onchocerciasis infection and transmission, and that treatment can be safely stopped.

Figure 4 Prevalence of onchocerciasis infection in the River Gambia focus, Senegal



Conceptual framework of elimination

Once the study in Senegal and Mali had provided the proof of principle that elimination with ivermectin treatment is feasible in endemic foci in Africa, it became urgent to consider the implications of these findings for onchocerciasis control in the rest of the continent. An international group of experts was therefore convened in early 2009 to review the state-of-the-art of onchocerciasis elimination in Africa with current tools, and identify critical issues for elimination in different epidemiological settings. The expert group provided a definition of onchocerciasis elimination (see box below) and developed a conceptual framework that was subsequently refined by the Technical Consultative Committee of APOC.

Definition of onchcerciasis elimination

The reduction of infection and transmission to the extent that interventions can be stopped, but post-intervention surveillance is still necessary

Operational definition

(i) Interventions have reduced *O. volvulus* infection and transmission below the point where the parasite population is believed to be irreversibly moving to its demise/extinction in a defined geographical area;

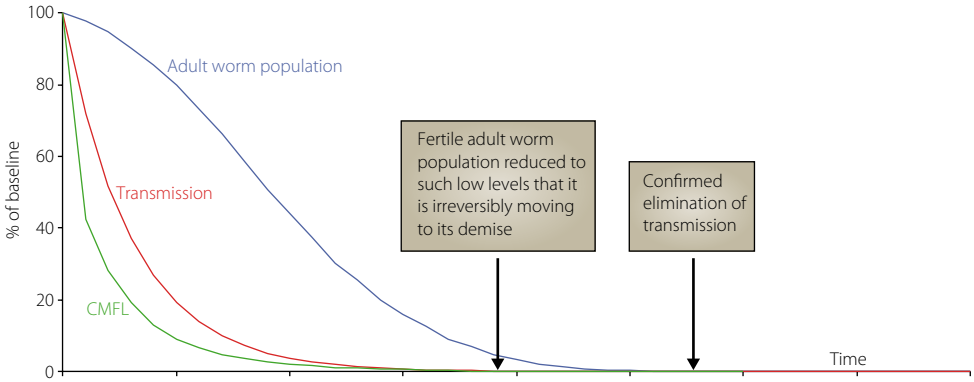
(ii) Interventions have been stopped;

(iii) Post-intervention surveillance for an appropriate period has demonstrated no recrudescence of transmission to a level suggesting recovery of the *O. volvulus* population; and

(iv) Additional surveillance is still necessary for timely detection of recurrent infection, if a risk of reintroduction of infection from other areas remains.

The conceptual framework is illustrated in figure 5. After the first round of ivermectin treatment in an onchocerciasis focus, the microfilarial loads decline dramatically, and this translates into a significant drop in the annual transmission rate. After each subsequent treatment round, the mean microfilarial load is further reduced and the annual level of transmission continues to decline. The adult worm population also shows a decline, although much more slowly, due to natural or treatment-induced

Figure 5 Conceptual framework of onchocerciasis elimination



	Phase 1	Phase 2	Phase 3
Intervention	Community-directed treatment with ivermectin	None	None
Transmission	Transmission declining towards negligible levels	Irreversibly approaching zero due to insufficient or absent adult worms	Zero
Evaluation	Monitoring & evaluation of progresss	Active surveillance to proof elimination	Surveillance for timely detection of a possible reintroduction of infection

death or sterilisation of old worms without replenishment. This continues till the fertile adult worm population has been reduced to such low levels that it will move irreversibly to its extinction, even without further ivermectin treatment. The parasite density is said to have fallen below its "breakpoint" and ivermectin treatment can be stopped, signalling the end of phase 1.

The concept of a breakpoint is operationally important: it means that infection and transmission does not have to be completely zero before treatment can be safely stopped. This concept has been proven in practice: in Senegal and Mali there were still several mf positive people in each of the three river basins but when treatment was stopped, there was no renewed transmission and infection. The same was observed in the Onchocerciasis Control Programme in West Africa where the prevalence of infection was still greater than zero in each river basin where vector control was stopped but, again, the cessation of control did not lead to renewed transmission and the infection died out.

In phase 2 the parasite numbers are now so low that any residual transmission is insufficient for the parasite population to survive: any remaining parasites have a too low chance of successful reproduction and eventually the parasite population becomes extinct. Epidemiological and entomological evaluations are needed during this phase to make sure that there is no recrudescence of the parasite population and transmission. If these evaluations show no recrudescence over a period of at least 3 years, elimination is taken as confirmed.

In phase 3, after achieving elimination, there is still need for a routine surveillance system for timely detection of the possible reintroduction of infection from other areas where the infection still occurs. Theoretically, this third phase continues until global eradication is achieved.

Required duration of treatment

In order to achieve elimination in an onchocerciasis endemic focus, many years of ivermectin treatment are required. One reason for this is that the adult onchocercal parasites live so long. But there are other factors that determine how many years of treatment are needed in a given focus. A critical factor is the precontrol endemicity level which reflects the initial worm load and the precontrol intensity of transmission. The latter depends on the local vector density and intensity of human/vector contact, and it is therefore also an indicator of the local potential of transmission during and after the control period. The higher the precontrol endemicity level, the more difficult it will be to interrupt transmission and bring the parasite population down to negligible levels. A second critical factor is the treatment coverage that is achieved during the control period.

The table below gives the results of computer simulations with the ONCHOSIM model that show how the required duration of treatment depends on precontrol endemicity level and treatment coverage. If the pre-control CMFL is 10 mf/s, then 10 years of treatment are predicted to be enough to be more than 95% certain of elimination. But if the precontrol CMFL is as high as 50 mf/s, the model predicts that it will take 20 years with 80% coverage to have a high probability of elimination. These simulations are based on an older version of the ONCHOSIM simulation model that will be updated in the near future using the APOC evaluation data. But the main principles will not change: the precontrol endemicity level is a very important factor that needs to be taken into account when planning for elimination and stopping treatment. Similarly, treatment coverage is critical. The table shows the predictions for 65% and 80% treatment coverage (most APOC projects have a therapeutic coverage within this range) which show that with 80% coverage elimination can be achieved several years earlier than with 65% coverage. Other simulations (not shown here) predict that if coverage falls below 50%, elimination may not be feasible at all.

The above predictions are fairly consistent with the empirical data that are available to date on onchocerciasis elimination in endemic foci in Africa. In a "hypo" endemic focus in Guinea-Bissau (CMFl < 6 mf/s), elimination was achieved with only six annual treatments. The studies in Senegal and Mali and the evaluation data collected by APOC to date suggest that elimination can be achieved in most foci after 13 to 17 years of annual treatment. The upper limit may be in the range of 20 to 25 years for foci with exceptionally high endemicity levels.

It is often assumed that if treatment is provided more frequently than once per year, elimination may be achieved within a shorter period, even though there is currently no empirical evidence from Africa to support this assumption. The critical question, however, is by how much the treatment period might be reduced and if more frequent treatment would be cost-effective. There is a need for proper comparative studies to clarify this issue. In the mean time, APOC intends to selectively use more intense treatment strategies in special areas, e.g. for mopping up of residual foci.

Table 1 Predicted probability of onchocerciasis elimination in relation to pre-control endemicity levels, treatment coverage and years of treatment

Pre-control endemicity level (CMFL)	65% treatment coverage				80% treatment coverage			
	10 yrs	15 yrs	20 yrs	25 yrs	10 yrs	15 yrs	20 yrs	25 yrs
10 mf/s	0.950	1.000	1.000	1.000	0.995	1.000	1.000	1.000
30 mf/s	0.042	0.887	1.000	1.000	0.401	0.997	1.000	1.000
50 mf/s	0.000	0.116	0.825	0.993	0.003	0.678	0.988	1.000
70 mf/s	0.000	0.000	0.191	0.757	0.000	0.111	0.846	0.990

Color codes: Green > 0.999, Yellow: 0.950 – 0.999, White <0.950

When to stop treatment: evaluation procedures and indicators

In each endemic focus there will be a need to evaluate the progress towards elimination, generate evidence to support decision making on stopping treatment, and ensure there is no recrudescence of transmission after cessation of treatment.

Phase 1

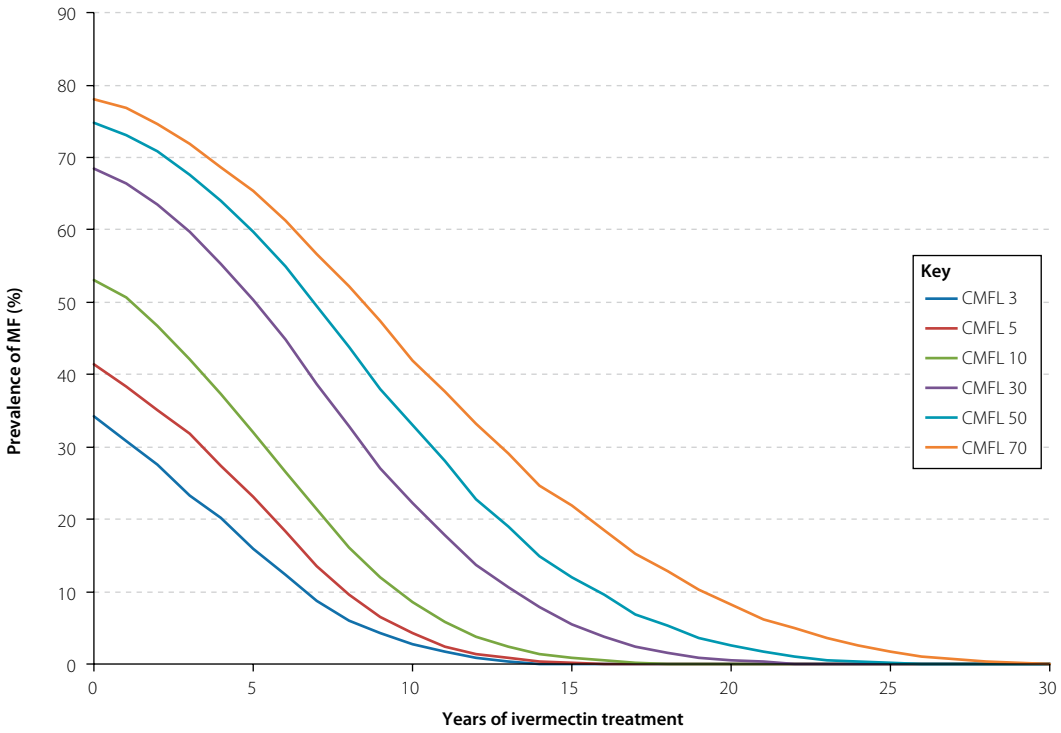
During phase 1, evaluations are needed to address two sequential objectives: a. to assess the decline in infection levels towards breakpoints, and b. to confirm that the breakpoint has been reached and that treatment can be safely stopped.

1.a. Assess the decline in infection levels towards breakpoints

This is the main evaluation activity for most of the first phase. It involves epidemiological surveys to determine the remaining levels of *O. volvulus* infection in a sample of communities from an endemic focus after a number of years of treatment and to compare the results with precontrol infection levels from the same villages in order to assess the trend towards breakpoint levels. Some 10 sample communities should be selected from from high risk locations near the river and the vector breeding sites in that part of the focus where the precontrol endemicity levels were highest. These should be communities for which precontrol epidemiological data (skin snip survey or REMO) exist. The surveys should be done 11 to 12 months after the last treatment and just before the next ivermectin treatment round. Until a new diagnostic of onchocerciasis infection becomes operationally available, the evaluations will be based on examination of skin snips for the presence and intensity of microfilaria in the skin. The main indicators are the prevalence of microfilaria (mf), standardised by age and sex, and the CMFL. Data on treatment coverage should be collected for each sample village, including information on the total village population and number treated each year according to the CDD record books. Community members should be interviewed whether they were treated during the last treatment round. Additional information on treatment history should be collected from other available sources for all preceding ivermectin treatment rounds, including any treatment provided before the period of APOC support. Finally, exact geographical coordinates should be taken for each sample village using a GPS.

The interpretation of the survey data is not straightforward. As mentioned above, the required duration of treatment, and thus the time needed to reach the breakpoint, varies between endemic foci according to their precontrol endemicity levels. Hence, also the declining trend in prevalence during the control period will differ between endemicity levels and this has to be taken into account in the interpretation of the survey results. This can be done by referring to ONCHOSIM predictions of the expected trends in prevalence for different precontrol endemicity levels. Figure 6 shows the predicted trends in prevalence of mf in endemic foci for which the precontrol endemicity levels range from a very low CMFL of 3 mf/s to a very high CMFL of 70 mf/s. This figure illustrates how important it is to take the precontrol endemicity level into account: after 10 years of treatment the predicted prevalence is below 5% in foci with a precontrol CMFL of 3-5 mf/s, but greater than 40% in foci with a precontrol CMFL of 70 mf/s.

Figure 6 Predicted trend in prevalence after ivermectin treatment (Onchosim simulations for annual treatment at 70% coverage)



Based on a comparison of the observed evaluation data and the predicted trends, the evaluation results are first classified for each focus as:

- Satisfactory: observed prevalence equal or lower than predicted prevalence
- Unsatisfactory: observed prevalence greater than predicted prevalence

In foci with satisfactory results, the computer predictions can subsequently be used to forecast after how many years the breakpoint is likely to be reached.

1.b. Confirm that the breakpoint has been reached and that treatment can be safely stopped

When reaching the predicted breakpoint, more surveys will need to be done to make sure that treatment can be safely stopped throughout the area. This will first require the delineation of the exact area where it is intended to stop treatment (see section 4 below). Epidemiological and entomological evaluations will be needed to assess residual infection and transmission levels throughout the area and confirm that these are below defined elimination thresholds. The epidemiological surveys will use the same skin snip methodology as in phase 1.a. but will have a wider spatial coverage (survey villages selected along the main rivers and affluents at a distance of no more than 20 to 30 km between villages) to ensure that infection levels throughout the area are below the threshold and that no pockets of infection remain that may cause recrudescence of transmission after cessation of treatment. The entomological evaluation will involve pool screening of blackflies collected throughout a full rainy season from a limited number of high risk locations along the principal rivers near major breeding sites of the vector, and analysis in a reference laboratory using an *O. volvulus* specific DNA probe. At least 10,000 blackflies should be collected and analysed for each catching point per year. The principal entomological indicator is the number of flies with infective 3rd stage larvae in the head per thousand flies (F3H/1000).

Based on experiences with cessation of onchocerciasis control in West Africa (vector control in the OCP and ivermectin treatment in the study in Senegal and Mali), together with ONCHOSIM model predictions, the thresholds for elimination

Table 2 Evaluation objectives and indicators

Phase	Evaluation objective	Indicator	Target
1	a. Assess decline towards elimination breakpoint	Prevalence of mf	≤ predicted prevalence
	b. Confirm that breakpoint has been reached and treatment can be stopped	Prevalence of mf	< 5% in all surveyed villages < 1% in 90% of surveyed villages
		Vector infectivity rate	< 0.5 infective fly per 1000 flies
2	Confirm there is no recrudescence of infection/transmission	Prevalence of mf	No increase/declining
		Vector infectivity rate	< 0.5 infective fly per 1000 flies
3	Detect possible recrudescence of infection/transmission	Prevalence of infection	< 1% in all villages
		Vector infectivity rate	< 0.5 infective fly per 1000 flies

for the epidemiological and entomological indicators have been provisionally defined as shown in table 2. It should be noted that the provisional threshold for vector infectivity, and the corresponding sample size requirement of 10,000 flies per catching site, is based on data for the savanna vector species, *S. damnosum* s.s. and *S. Sirbanum*, and may need to be adjusted for other vector species. With respect to the epidemiological indicators, further ONCHOSIM simulations are ongoing to define CMFL thresholds. All thresholds will be regularly reviewed and refined as further evidence becomes available.

Phase 2: confirmation of elimination

The aim of the evaluations during phase 2 is to confirm that the decision to stop treatment was correct, and that this has not resulted in recrudescence of infection and transmission. Phase 2 will last at least three years and involve entomological evaluations using the same methodology and catching points as in phase 1, and a final round of epidemiological evaluations. The entomological evaluations may be undertaken throughout the three year period, or only cover one full rainy season during the 3rd year. The epidemiological surveys will be done at the end of the three-year period in a sample of first line villages located at high risk locations along the rivers. The indicators for this phase are again the prevalence (or the incidence where longitudinal data exists) of MF and the vector infectivity rate.

Phase 3: routine surveillance

In phase 3, routine surveillance needs to be undertaken within the context of the national disease surveillance system in order to timely detect any possible recrudescence of onchocerciasis infection or transmission. The main indicators are the prevalence and incidence of onchocerciasis infection. It is hoped that by the time the surveillance would become operational at a large scale, a simpler and non-invasive diagnostic test would be available that could replace the skin snip. The surveillance could be organised as currently done in the ex-OCP countries where a small sample of indicator villages in high risk locations close to vector breeding sites are surveyed every 3 to 5 years. Entomological surveillance would also be valuable but might be difficult to organise at the required scale in all post-treatment areas. However, the system currently in use in ex-OCP countries may be a model for entomological surveillance in which pool screening is done in a few selected sentinel sites and results analysed centrally by the Multi-Disease Surveillance Centre in Ouagadougou.

Where to stop treatment

Another challenge is to determine where exactly treatment can be stopped. There is no single, standard answer to this question and it will be necessary for each area to carefully review all available data on onchocerciasis distribution, treatment coverage and impact before a decision can be made where to stop treatment. Based on the outcome of an informal consultation, during which participants from onchocerciasis control programs in several APOC countries went through this process for a number of foci that are close to elimination, it is recommended that the following steps are followed (see figure 7).

1. Delineate transmission zones

During its meeting in 2009, the expert group introduced the concept of a "transmission zone", which they defined as "a geographical area where transmission of *O. volvulus* occurs by locally breeding vectors and which can be regarded as a natural ecological and epidemiological unit for interventions".

Figure 7 Where to stop treatment

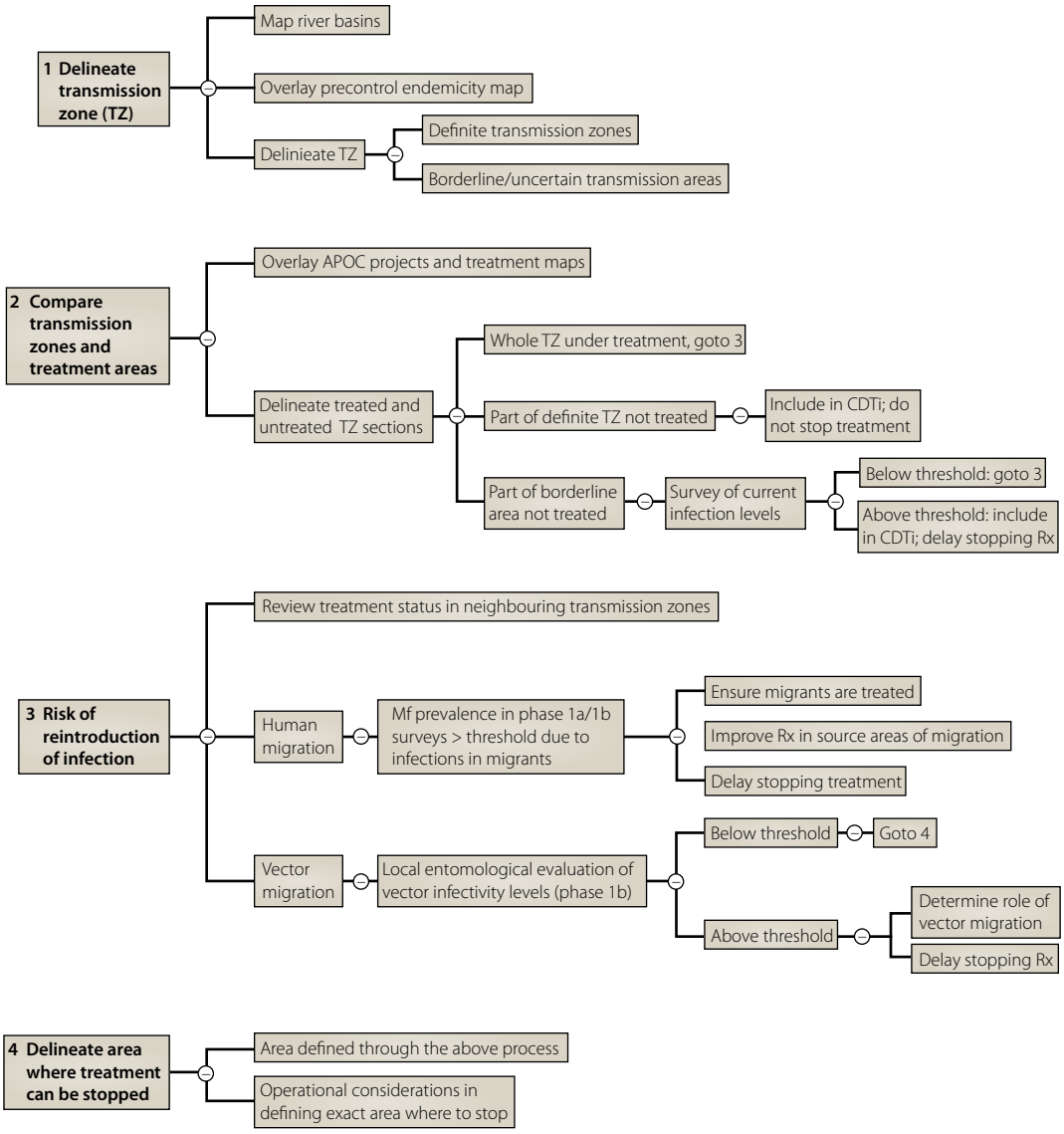
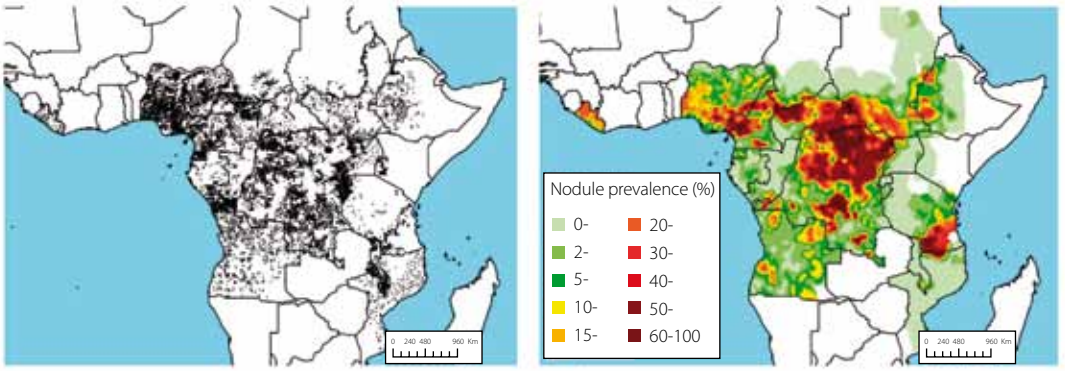


Figure 8 Villages surveyed for REMO and estimated prevalence of nodules in APOC countries

a Location of REMO survey villages

b Estimated prevalence of nodules in APOC countries



In practice, it is difficult to determine with a fair degree of certainty that the vectors in a given area are exclusively locally breeding. In this document, therefore, we operationally define a transmission zone as a river basin, or a major section of a river basin, where onchocerciasis is endemic and where the river is the core of the endemic area, with communities with the highest prevalence of infection generally located close to the river and infection levels falling with increasing distance from the river till they become negligible or reach a neighbouring transmission zone. The expert group noted that "the challenge is to define the geographical area where treatment is needed in order to move from control to elimination". This is an important qualification which implies that only communities that actively contribute to transmission should be considered part of a transmission zone, and that communities with isolated infections that on their own would not be able to maintain the transmission cycle, are not to be included.

The principle of river-centred onchocerciasis transmission zones forms the basis of the REMO method that has been used to map the geographical distribution of onchocerciasis in the APOC countries. Hence, as a first step we propose to use the same method to delineate river basins and river sections, and include in a potential transmission zone all communities within a distance of 20 km from the river or its affluents.

However, not all river sections contain Simulium breeding sites, and the next step is to determine which part of the river basin is endemic for onchocerciasis. For that we use the map of onchocerciasis endemicity levels in Africa that has been produced through a spatial analysis (using a statistical interpolation method called 'kriging') of the nodule prevalence data from REMO surveys in APOC countries (see figure 8b).

A limitation of REMO is that it only uses the prevalence of nodules to estimate the prevalence of onchocerciasis infection, and nodule palpation has poor sensitivity and specificity in low prevalence communities. On the other hand, the REMO surveys have generated a unique database with nodule prevalence data for a spatial sample of more than 13,000 villages and good geographic coverage of all potentially endemic areas in APOC countries (see figure 8a). For these countries, the REMO data provide the main information on the geographical distribution of the disease. Hence, it should be attempted to delineate transmission zones using the available map of precontrol nodule prevalence (and precontrol skin snip data for the few foci for which these are available) in APOC countries.

In the second step, therefore, the precontrol prevalence map is overlaid on the river basin map, and an attempt is made to delineate the transmission zones.

To illustrate this process, we will use the example of the endemic focus around Lere LGA in Kaduna state, Nigeria. Figure 9 shows the Lere focus, including the

boundaries of two river sections, the prevalence data for all villages where surveys were done before the start of ivermectin treatment, and the geographic distribution of the estimated prevalence of nodules obtained from a kriging analysis of the prevalence data.

In the centre of the map there is a cluster of endemic villages which clearly forms the core of a transmission zone that runs across the two river sections. Secondly, even though the data are limited, they also suggest that there is no transmission towards the West of the map, a conclusion that is consistent with the information that environmental conditions in this area are not favourable for vector breeding. The prevalence data also suggest that there is a limit to the transmission zone towards the South of the core area. It is however very difficult, based on the available data, to decide where exactly the limits of the transmission zone are located. The area with an estimated prevalence > 10% (yellow, orange and above) may be taken as a 'definite' transmission zone, but beyond this area it is difficult to say how much more should be included in the transmission zone. Clearly, there is a need for further surveys to clarify this issue.

This could be achieved by skin snip surveys in villages sampled along the main rivers at increasing distances downstream from the definite transmission zone. However, before any such additional surveys are undertaken, it is important to first review the ivermectin treatment map.

2. Compare transmission zone and CDTi zone

APOC's initial mandate was the control of onchocerciasis as a public health problem and CDTi has been targeted therefore to areas where REMO maps indicated that the disease was of public health importance (i.e. where there were at least some communities with a prevalence of mf > 40% or a CMFL > 5 mf/s). This criterion has been interpreted flexibly and many borderline areas have been included within the CDTi treatment zone to the extent that one third of all CDTi communities have a prevalence below the threshold of 40%. Nevertheless, the CDTi zone will often cover a more restricted area than the transmission zone, and there will be villages beyond the CDTi boundaries but still within the transmission zone that are not receiving ivermectin treatment. By definition, these are

Figure 9 Pre-control prevalence of onchocerciasis in Lere LGA, Kaduna State, Nigeria

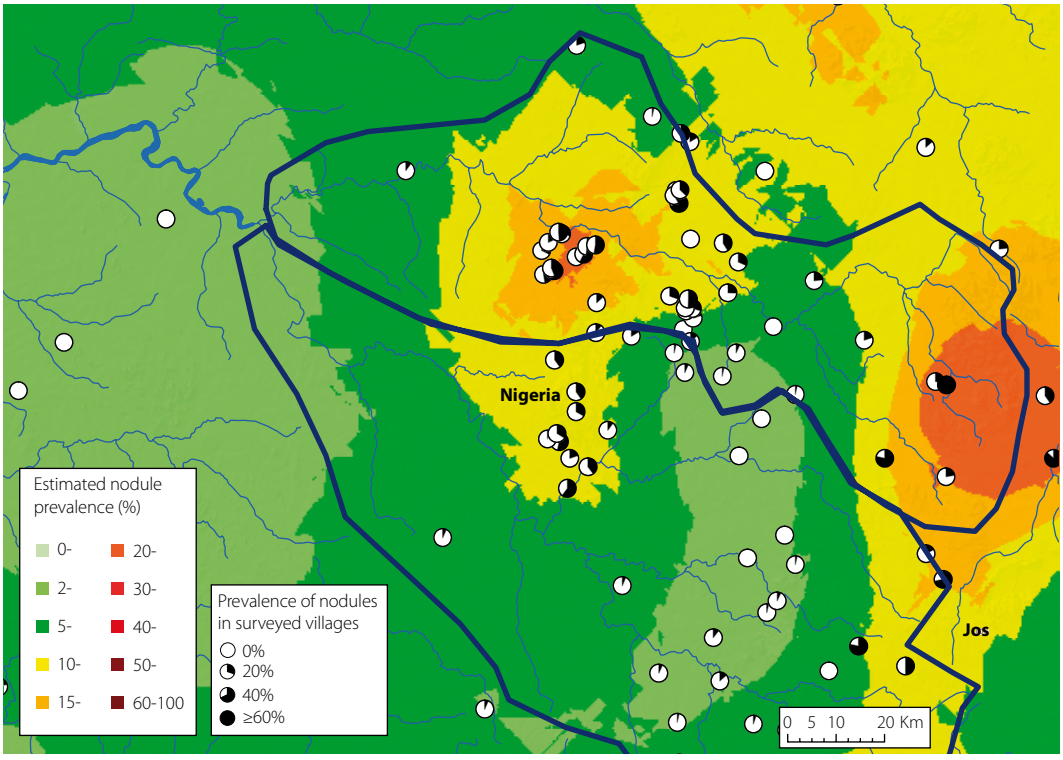
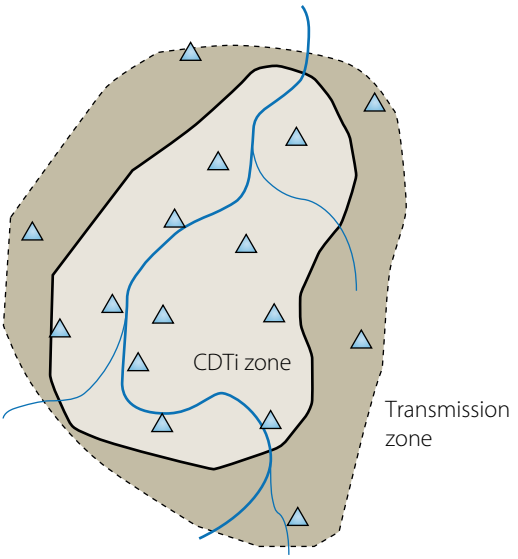


Figure 10 Schematic example of a transmission zone



villages that had a low level of endemicity before the start of control and, as illustrated in figure 10, they constitute the tail end of the endemic focus. It is important to note that these tail areas do not constitute endemic foci on their own, and that the infections in these areas were largely a result of transmission generated in the centre of the focus. Following the introduction of CDTi, the main source of transmission has been largely removed and after several years of CDTi, the infection levels in communities in the tail areas are therefore also expected to fall, even though they are not treated themselves. Hence, in the many areas where CDTi has been ongoing for many years, it will be important to assess also the residual infection levels just beyond the CDTi zone in order to determine whether an extension of the treatment area is required to achieve elimination or whether the current treatment zone is adequate.

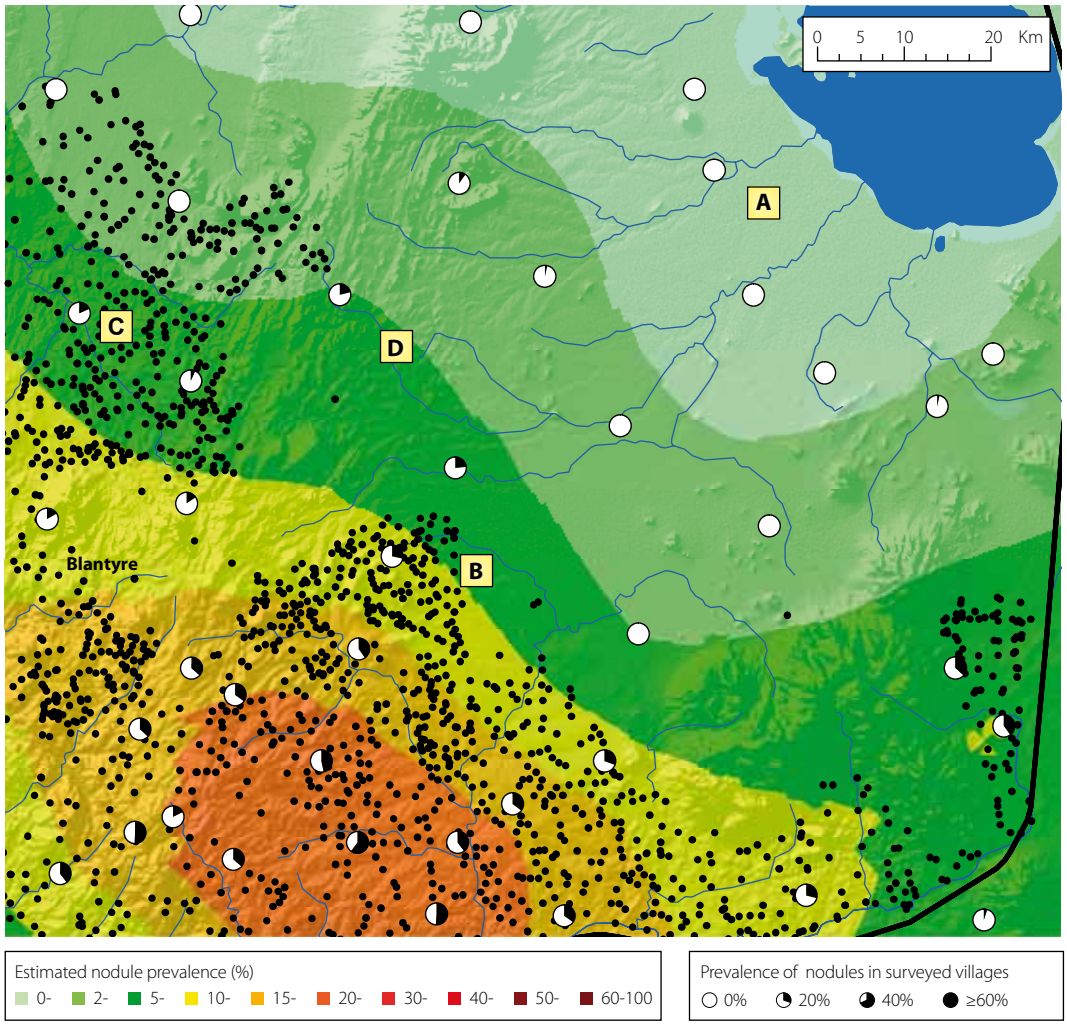
A different situation arises in transmission zones where there has been no CDTi treatment at all because the precontrol endemicity levels were considered too low for onchocerciasis to be classified as a public health problem. If there is evidence of continued transmission in such a zone, CDTi would be indicated within the context of the new elimination objective in order to avoid that low endemic onchocerciasis foci continue to exist and pose a potential threat to neighbouring areas where onchocerciasis has been eliminated. As the endemicity levels in these foci are by definition low, elimination should be relatively easy and take much less time than in the surrounding hyperendemic foci. This was shown in the Rio Geba focus in Guinea-Bissau where onchocerciasis endemicity was very low before the start of treatment (CMFL <6) and where elimination was achieved with six annual treatments only.

Some of the main scenarios, that may be encountered when overlaying prevalence and treatment maps, are illustrated in figure 11 for the North East boundary area of the main onchocerciasis focus in Malawi. For this area, detailed geographic information is available showing the location of all CDTi villages that are receiving annual ivermectin treatment (similar databases are under development for all APOC projects).

The main onchocerciasis focus is located in the south. From there, the prevalence of nodules declines when moving north and drops to 0 when reaching the flat plains near the lake where there are no vector breeding sites. Hence, the area marked A falls outside the transmission zone.

Area B is in a border area,`located just beyond the range of treated villages. The epidemiological situation in area B is not clear. This could be an example of a tail area where treatment over the last 10 years in the CDTi area has also affected onchocerciasis prevalence in the villages just beyond the treatment zone. It is quite possible that all villages where treatment is required to "move from control to elimination" are already covered. A prevalence survey in one or two villages along the river beyond the treatment zone should be able to clarify the current status of infection, and whether extension of treatment is required in this border area or not. According to the precontrol prevalence data, area C was apparently also an epidemiological tail area of the main transmission zone towards the south. However, this area is already fully covered by CDTi, and there is therefore no need for further investigations to determine the exact limits of transmission zone. A more problematic area is D where there are some villages with a low

Figure 11 Pre-control prevalence of onchocerciasis at the North-Eastern boundary of the onchocerciasis focus of Thyolo, Malawi



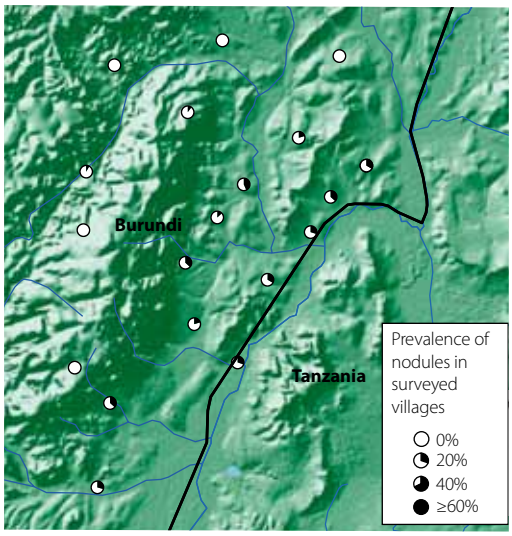
precontrol nodule prevalence between 2% and 10%, located along the upper stretches of rivers in a hilly area. It is not clear from the data if these positive prevalences are due to a spillover from the main transmission zone that is now under treatment or if these results reflect the existence of mini transmission zones in the hills where transmission continues independently. The only way to find out is through some epidemiological surveys in villages in area D for which precontrol prevalence data are available.

CDTi is provided through APOC projects that are closely linked to the national health systems in APOC countries. The boundaries of APOC projects therefore tend to follow administrative boundaries between health districts, regions and countries. Administrative boundaries frequently follow natural features, such as mountain ranges, lakes and, remarkably often, rivers. Hence there are many examples where the epidemiological centre of a transmission zone, i.e. the river with its vector breeding sites, forms the boundary between two APOC projects (or sometimes countries as in figure 12) that have different duration and coverage with ivermectin treatment. There are other examples where transmission zones fall into two or more APOC projects. Planning for elimination will therefore require an evolution from the current project orientation to thinking in terms of transmission zones, and cross-project/cross-border planning for elimination.

3. Assess the risk of reintroduction of infection from other endemic areas

Finally, the decision of where to stop treatment should also take account of the epidemiological and treatment situation in surrounding areas, and of the risk of reintroduction of the parasite through human or vector migration.

Figure 12 Example of a transmission zone that straddles the border between two countries



Human migration between onchocerciasis-endemic rural areas occurs usually only over limited distances and concerns mainly migration between neighbouring transmission zones. The main question to consider is whether the surrounding transmission zones are covered by ivermectin treatment, and whether the geographic and therapeutic coverage is adequate in these zones. If there is good coverage for a number of years, human migration may not pose a significant risk of reintroduction of the onchocercal parasite and recrudescence of transmission. But if treatment coverage is poor in the neighbouring transmission zone, or if there is no treatment at all, human migration could pose a risk. Figure 13 shows an example for an endemic focus in Kasese district in Uganda. Epidemiological evaluations undertaken in 2010 suggest that onchocerciasis has been virtually eliminated. However, of the few remaining MF positive people, the majority had migrated for a number of years to work as farmers in villages in onchocerciasis endemic areas across the border of the Democratic Republic of Congo before returning back to their original village in Uganda. These "migrants" had received much less treatment than the resident population of their village. Also in other countries it was found that treatment coverage among migrants is often very low whether because they are absent at time of treatment or because migrants are not included in the local census population and therefore excluded from the CDTi program. The cause for the onchocerciasis infections in migrants may be transmission in the source area of migration, inadequate treatment of migrants or a combination of these two. In such situations, the first priority should be to ensure that all migrants are properly treated with ivermectin. But if this doesn't solve the problem, and the prevalence of infection remains above thresholds for elimination because of importation of infection by migrants, it will be necessary to delay cessation of treatment until adequate treatment coverage has been ensured in the source area of migration.

Vector migration may be a serious problem. Experience in the OCP has shown that long distance migration of infective vectors can be a major threat in the West African Savannah where it has led to recrudescence of transmission in river basins where onchocerciasis had been effectively controlled. This long distance migration was characteristic of the savanna species of the vector, i.e. *S. sirbanum* and *S. damnosum* s.s., and it may be less of a problem for other vector species in forest areas and in East Africa. It will therefore be helpful to have a basic understanding of the presence and distribution of different vector species in the areas where cessation of treatment is being considered, and APOC is supporting cytotaxonomic studies to achieve just that. However, it will not be practically possible to study all vector migration patterns in detail in all APOC countries. The most practical way to assess whether there is a risk of reintroduction of the parasite through vector migration into an area where cessation of ivermectin treatment is being considered, is to evaluate vector infectivity rates in this area during the last year before stopping treatment. If vector infectivity rates are insignificant, it may be inferred that vector immigration does not pose a significant threat for transmission in this area and that treatment can be safely

stopped. If vector infectivity rates are still high, elimination thresholds have not yet been reached and further investigations are needed to determine the reason for the unsatisfactory entomological results.

Taking a wider geographic perspective will often simplify decision-making on transmission zones and where to stop treatment. There are vast areas where all river basins are highly endemic for onchocerciasis and where CDTi is provided everywhere. An example of such an area is the endemic belt that runs from South East Nigeria to South West Cameroon (see figure 14). In Cross River state and Ebonyi state in Nigeria, CDTi has been given for 13 or more years, and recent epidemiological evaluations (phase 1A) in three sites in these states have shown that onchocerciasis is close to elimination and that it is time to start planning for stopping treatment. Assuming that the good epidemiological results will be confirmed in the rest of these two states, there appears to be no need to worry too much about the exact delineation of transmission zones as onchocerciasis is endemic everywhere and CDTi is given throughout this part of South-East Nigeria and across the border in South-West Cameroon. In such situations it is better to be pragmatic and use operational considerations to decide on the area where treatment will be stopped first.

4. Delineate area where treatment can be stopped

The final step is to delineate the area where treatment can be stopped after taking all the above considerations into account and, if required, after collecting and analysing additional survey data. Above all, it will be important to be pragmatic and carefully review the treatment coverage data, both spatially to be clear where exactly treatment has been given, and temporally to review the consistency in treatment coverage. Operational consideration should also be taken into account, e.g. some national onchocerciasis control programs may prefer to stop by health district rather than by transmission zone which would be acceptable if the health district covers only part of the transmission zone and the remaining parts remains under treatment. Pragmatism will also be required in determining how much additional data needs to be collected, bearing

Figure 13 Onchocerciasis in Kasese district, Uganda

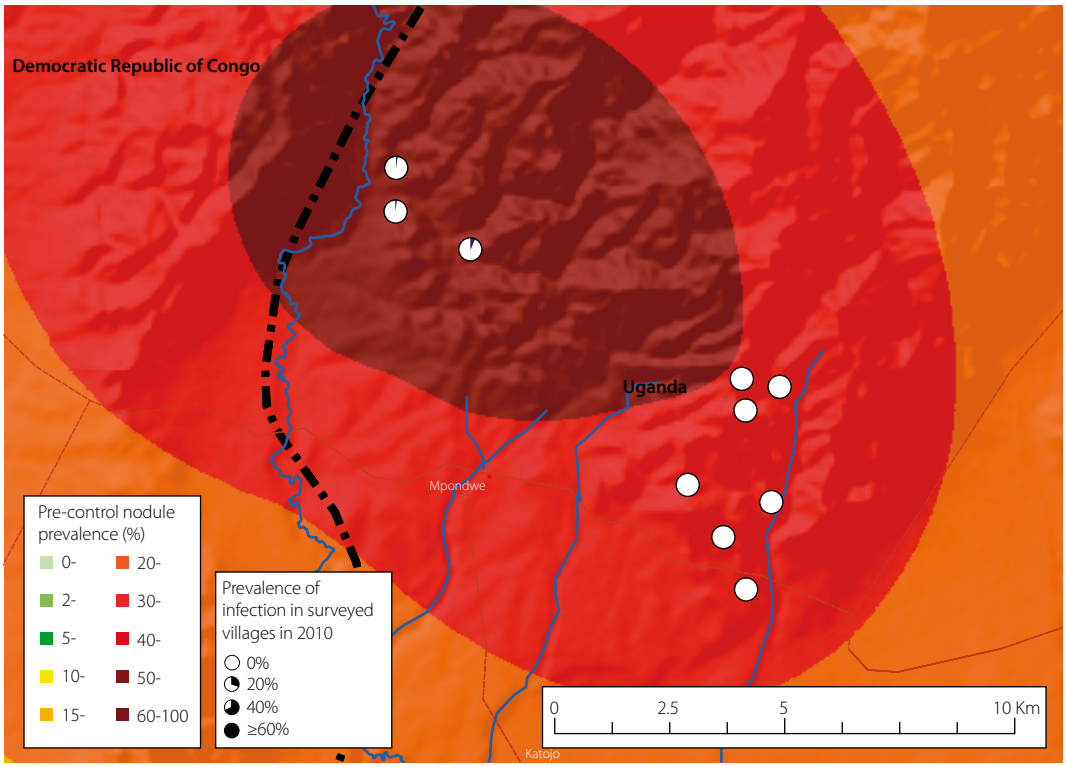
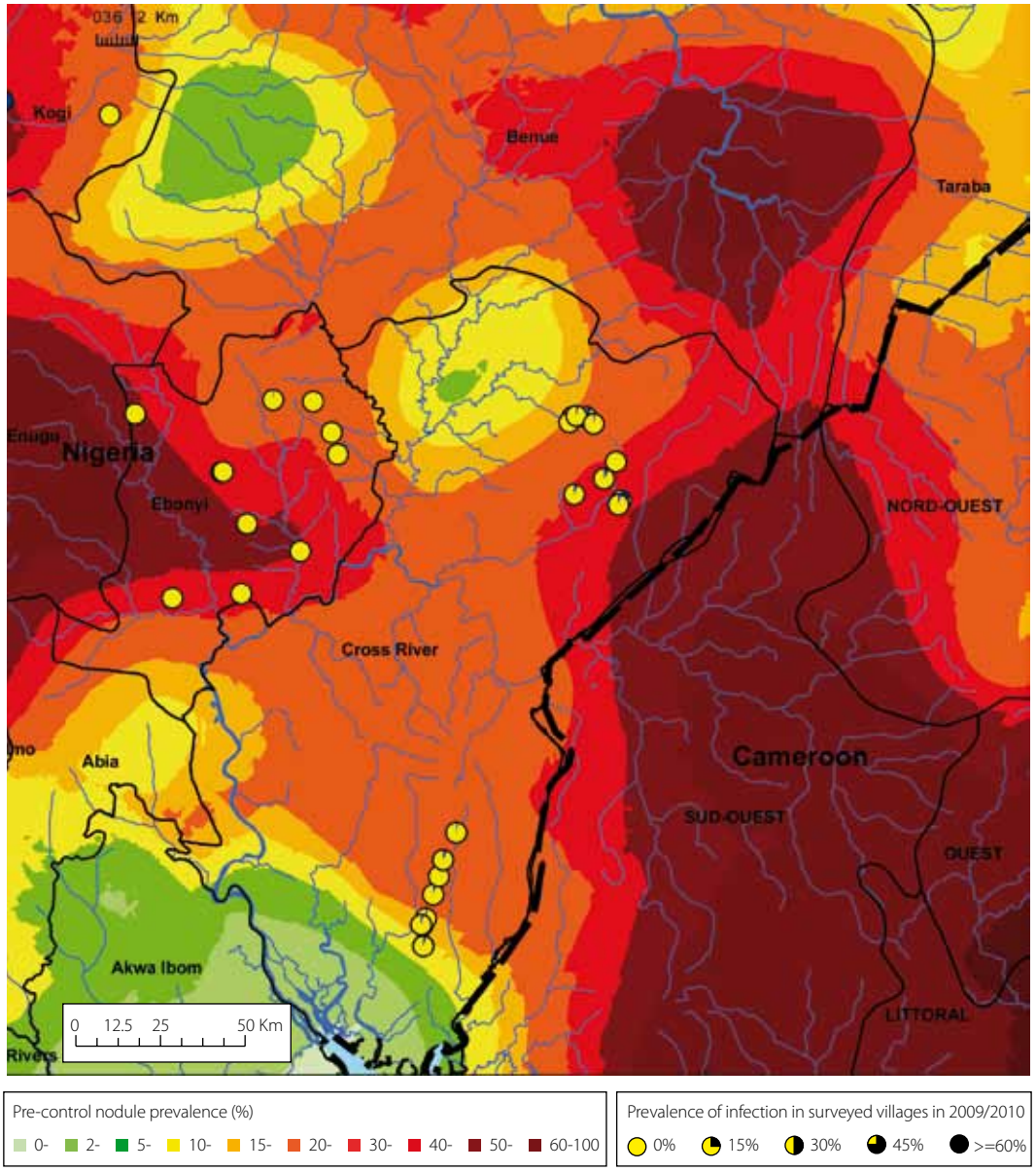


Figure 14 Onchocerciasis in South East Nigeria and South West Cameroon



in mind the need to be practical and cost-effective in operational decision making. The aim is not to map transmission zones in perfect scientific detail, but to make sound decisions on when and where ivermectin treatment can be safely stopped.

Lymphatic filariasis elimination is based on mass treatment with ivermectin and albendazole. LF treatment programs are planned or ongoing in several APOC countries, and it is possible that in areas where onchocerciasis elimination has been achieved and treatment can be stopped, ivermectin and albendazole treatment may be scheduled for some additional years for the purpose of filariasis elimination. This would not be a problem for onchocerciasis elimination but it would prolong phase 1 and the evaluations of phase 1B and phase 2 should be synchronised with the final year of filariasis treatment.

Another filarial infection, loiasis, may pose greater problems for onchocerciasis elimination. In areas with low level of onchocerciasis endemicity, but where the endemicity level of loiasis is very high, ivermectin treatment is contraindicated. If onchocerciasis transmission is locally maintained in such an area, onchocerciasis elimination may not be feasible with ivermectin treatment and other interventions may be needed.

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