Guidelines
for revising ivermectin treatment boundaries
within the context of onchocerciasis elimination
I. Purpose of the guidelines

The original aim of onchocerciasis control in APOC countries was to control the disease as a public health problem through community directed treatment with ivermectin in meso- and hyperendemic areas where there is a significant risk of onchocercal disease. This strategy has been successful and in the vast majority of high risk areas onchocerciasis is no longer a public health problem.

Recent studies in Mali and Senegal have shown that in the long run even more can be achieved with ivermectin treatment and that after multiple rounds of treatment onchocerciasis infection and transmission can be eliminated and treatment safely stopped. Subsequent epidemiological evaluations in advanced APOC projects have indicated that elimination may be feasible in most endemic areas in Africa. Based on this new evidence, the Joint Action Forum (JAF) of APOC has approved that APOC pursues the elimination of onchocerciasis in Africa.

This paradigm shift from control to elimination does not change the principal intervention strategy which remains based on community directed treatment with ivermectin (CDTi). But it requires a revision of current ivermectin treatment boundaries. These boundaries were initially drawn to ensure that all areas where there was a significant risk of onchocercal disease, i.e. where the prevalence of nodules was greater than 20%, would be covered by CDTi. For the purpose of elimination, the treatment boundaries need to be expanded to ensure that there remain no untreated onchocerciasis foci that might pose a future threat of reinfection to areas where treatment has been stopped.

**In order to achieve onchocerciasis elimination, ivermectin treatment needs to cover all areas where there is sustained local transmission.**

The vast majority of onchocerciasis transmission areas in Africa are already covered by ivermectin treatment for onchocerciasis control or ongoing/planned ivermectin treatment for lymphatic filariasis elimination. The present document describes a methodology to identify the remaining untreated areas where

- there might be local onchocerciasis transmission that would be able to sustain itself in the absence of local ivermectin treatment and
- where ivermectin treatment is therefore also needed.

This methodology was developed during a workshop held in March 2012 in Ouagadougou in which national onchocerciasis and lymphatic filariasis coordinators from 10 APOC countries, onchocerciasis experts and public health officials participated.
II. Indicator and Threshold

The geographic distribution of onchocerciasis is fairly well known. A detailed map of onchocerciasis prevalence and endemi city levels in APOC countries has been generated based on the results of Rapid Epidemiological Mapping of Onchocerciasis (REMO) surveys in over 14,000 villages (see figure 1). Areas where onchocerciasis is highly endemic and a public health problem are well defined on this map, and this information has been used to target CDTi projects to those areas.

Figure 1: Pre-control onchocerciasis endemi city levels

The recent move towards elimination has brought a new mapping challenge beyond high risk areas: to identify remaining foci where there is sustained local onchocerciasis transmission and where treatment is therefore also needed. To address this challenge, we will first use the existing onchocerciasis endemi city maps, based on the REMO data, to identify untreated areas where there might still be local onchocerciasis transmission. Although REMO was not specifically designed for this purpose, the extensive spatial information on onchocerciasis endemi city in the REMO maps can often be used effectively to exclude areas where onchocerciasis is not endemic and where no ivermectin treatment is needed.
**Minimum endemicity level for sustained local transmission.**

Onchocerciasis is a focal disease. Its geographic distribution is determined by the presence of vector breeding sites in rivers. In a typical onchocerciasis focus, the highest vector density and highest intensity of transmission are found close to the breeding sites. The villages near the breeding sites in the core of the focus tend to have the highest endemicity levels, with the prevalence of infection declining with increasing distance from the river and the breeding sites. Epidemiological surveys often target villages located at potential high risk locations close to rivers in order to estimate the maximum prevalence of infection in a focus as a measure of the local endemicity level.

Endemic onchocerciasis requires a minimum level of O. volvulus infection to be able to sustain local transmission. Simulations with the ONCHOSIM model suggest that a MF prevalence of at least 30% is needed for sustained local transmission, and the model is unable to simulate stable endemic situations where the prevalence of MF is less than 30% (corresponding to a prevalence of nodules of about 15% to 20%). This suggests that areas, where the maximum prevalence is below these levels, are whether unstable (increasing prevalence towards a higher stable level or decreasing to local extinction) or are receiving infection from elsewhere through vector or human migration and do not represent sustainable local transmission.

Available empirical data, though limited, are consistent with these model predictions. In Africa, the isolated onchocerciasis foci with the lowest documented endemicity levels are:

- The Rio Geba focus in Guinea-Bissau. In this focus the maximum village prevalence of MF was 25% of the population above the age of 5 years (corresponding to a nodule prevalence of about 10 to 15% among adult males\(^1\)).
- Central Gabon (Ogooue-lolo province). For this focus the REMO data show a maximum prevalence of nodules of 11% among adult males.

Hence, there is some evidence that from a nodule prevalence of 10% upward, local transmission may be possible. However there are no known foci with local transmission where the maximum prevalence of MF is less than 20% or the maximum prevalence of nodules less than 10%.

**Specificity of nodule palpation**

Nodule palpation is not 100% specific for identifying onchocercal nodules and onchocerciasis infection. In a recent analysis\(^1\) the specificity of nodule palpation has been estimated at 98% (lower limit 95%). This means that in areas without onchocerciasis, the prevalence of nodules is predicted to be on average 2% (upper limit 5%) even though there is no onchocerciasis infection and transmission. Given an average sample size of 40 persons per surveyed village, this implies that about one out of every three villages may have a positive nodule prevalence in non-endemic areas. This limitation of nodule palpation has to be taken into account when interpreting low prevalence values in nodule prevalence contour maps.

Threshold

In view of the above, it is recommended that prevalence contour maps are interpreted as follows when assessing the likelihood of sustained local onchocerciasis transmission in a given area.

<table>
<thead>
<tr>
<th>Maximum prevalence of nodules (contour map)</th>
<th>Likelihood of local transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20%</td>
<td>Local transmission - CDTi needed</td>
</tr>
<tr>
<td>[10 – 20%]</td>
<td>Local transmission possible - MF surveys needed</td>
</tr>
<tr>
<td>[5 – 10%]</td>
<td>Local transmission unlikely - MF surveys needed</td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>Local transmission highly unlikely</td>
</tr>
</tbody>
</table>

Hence, we conservatively define a threshold of 5% nodule prevalence as the prevalence level below which it is highly unlikely that there would be local onchocerciasis transmission that can sustain itself, and conclude that such areas can be considered non-endemic for onchocerciasis.

III. Algorithm

Based on the above reasoning, an algorithm has been developed for delineating the remaining areas where ivermectin treatment is needed for the purpose of onchocerciasis elimination. The algorithm consist of three main steps as described below.
Step 1: Complete CDTi coverage of high risk areas

CDTi covers currently nearly all areas where there is a high risk of onchocercal disease (prevalence of nodules greater than 20%), but there are still a few high-risk areas that are not yet treated (see figure 2).

The first step consists therefore of identifying the remaining areas that should be treated according to the current criteria for disease control and to ensure that they are included in the CDTi program.

1. **Display in a GIS the nodule prevalence contour map**
   - In some areas, e.g. in South East Angola, this step will first require the completion of REMO to cover the few gaps where there have been no REMO surveys yet.

2. **Overlay the latest map of CDTi treatment areas**
   - The current treatment maps used by APOC are based on hand drawn maps or other geographic information provided by national onchocerciasis control coordinators of APOC countries that has been incorporated in the GIS by APOC staff. These hand drawn maps were not always accurate and there exist many small inconsistencies between the digitised treatment maps and other spatial information such as administrative boundaries. It is therefore important that those responsible for the
local treatment maps are involved in this step to ensure that the treatment information is accurate and up-to-date.
  o For some CDTi projects there exists a complete spatial database with geographical coordinates of all CDTi villages. Where these data exist, they should be used to delineate the exact treatment boundaries.

3. **Identify high risk areas (prevalence of nodules > 20%) that are not yet treated**
   o the REMO map is based on a statistical process of spatial interpolation that predicts the prevalence of nodules between and around actual surveyed villages. Occasionally, these predictions extend into areas that are otherwise known to be onchocerciasis free, e.g. the peak of a mountain. All relevant environmental information and local knowledge should therefore be taken into account when interpreting the prevalence contours.

4. **Accelerate the inclusion of the identified high risk areas in the national CDTi programs**

After the completion of this first step, all remaining areas are by definition non-endemic or hypo endemic for onchocerciasis. Figure 3 shows the areas that are remaining after this step and where sustained local transmission cannot be excluded (i.e. areas with nodule prevalence > 5%).

*Figure 3: Nodule prevalence > 5% and no CDTi for onchocerciasis*
Step 2: exclude areas that are receiving ivermectin treatment for LF

Lymphatic filariasis elimination also uses ivermectin, in combination with albendazole, and the possible impact of LF treatment on onchocerciasis infection has to be taken into account. LF elimination requires at least 5 annual rounds of treatment and the LF coordinators that participated in the March 2012 meeting estimated that in their countries at least 6 to 7 annual rounds of treatment would be required. Such a treatment period would not be long enough to eliminate onchocerciasis in meso or hyper endemic areas, but it is probably sufficient to achieve elimination in hypoendemic areas where the prevalence of nodules is less than 15 to 20%. ONCHOSIM predictions indicate that ≤ 8 years are needed to eliminate such low level endemicity and in the Rio Geba focus in Guinea-Bissau, onchocerciasis was eliminated with only 6 annual rounds of ivermectin treatment. Hence, in areas that are low endemic for onchocerciasis, LF treatment will have a major impact on onchocerciasis infection and transmission, and probably achieve local elimination.

The workshop participants arrived at the following conclusion:

*It is expected that 6+ years of treatment for LF in hypoendemic onchocerciasis foci would eliminate the low local level of onchocerciasis infection and transmission. Hence, no separate CDTi for onchocerciasis would be needed in such areas. This assumption will need to be validated after the 6+ year LF treatment period through joint epidemiological surveys by the LF and onchocerciasis programmes.*

Figure 4: LF treatment in 11 APOC countries
Based on this logic, step 2 is defined as follows:

1. **Overlay the latest map for ongoing/planned LF treatment**
   - Figure 4 provides an example of an LF treatment map for the 10 countries that participated in the workshop, indicating areas that are (i) currently treated for LF, (ii) endemic for LF but not yet treated, (iii) nonendemic areas not targeted for treatment and (iv) areas still to be mapped.
   - A comparison with the map in figure 2 shows that in some countries there are significant areas of overlap between LF treatment areas and low endemic onchocerciasis areas where there is no treatment for onchocerciasis, e.g. in Malawi, Tanzania and central Nigeria.
   - The map in figure 4 is not complete nor up-to-date, and has only been included for illustrative purposes. Up-to-date and reliable LF treatment maps need to be provided at country level by the national LF programme. It is important therefore that LF programme staff actively participate in the revision of ivermectin treatment boundaries for onchocerciasis elimination.

2. **Identify areas without onchocerciasis treatment but where LF treatment is ongoing or planned.**
   - Where the nodule prevalence contours > 5%, and LF treatment is ongoing/planned, prepare for joint final surveys with the LF programme after the completion of LF treatment.
   - Where LF treatment is ongoing/planned but the nodule prevalence contours ≤ 5%, no further action is needed.

**Step 3: Remaining untreated areas**

In the preceding steps all areas were excluded where ivermectin treatment is ongoing or planned for the control of onchocerciasis as a public health problem or for LF elimination. The remaining areas are untreated areas that are nonendemic or hypoendemic for onchocerciasis where the prevalence of nodules < 20%. The aim of the third step is to further subdivide these remaining areas into two groups: (i) areas where local transmission is highly unlikely and no CDTi is needed, and (ii) areas where there might be sustained local transmission and where skin snip surveys are required to further clarify the situation before a decision on CDTi can be taken.

An important factor to take into account in this step is the distance to the nearest CDTi project. Areas that are bordering a CDTi project may constitute a “tail” of an onchocerciasis focus located within the project area. In such situations, ivermectin treatment in the core of the focus would in the long term also reduce the prevalence of onchocerciasis infection in the untreated tail area by removing the source of infection. The aim of skin snip surveys in such border areas would be to assess that the prevalence of onchocerciasis infection has indeed dropped as expected since the start of treatment in the CDTi project, indicating that transmission in the border area is not sustainable on its own. In isolated foci, the prevalence of infection will not have been affected by treatment in other areas.
Step 3 consists of the following:

1. **Display all relevant data in a GIS**
   - Display the nodule prevalence contours and prevalence pies for all REMO survey villages
   - Display other relevant spatial information: rivers, lakes, mountains, vegetation, national boundaries, other relevant administrative boundaries, ivermectin treatment boundaries etc
   - Exclude areas that are unsuitable for onchocerciasis transmission or for which there is evidence that there are no onchocerciasis vectors
     - refer for these exclusion areas also to the results of the original zoning exercise that was undertaken during REMO

2. **Differentiate untreated areas by distance to the nearest CDTi project**
   - Areas bordering CDTi projects, i.e. that are within 40 km from the nearest CDTi project
   - Isolated areas, i.e. that are > 40 km from the nearest CDTi project

3. **Decide on follow-up action using the decision chart and scenario table below**

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### Table 1: Decision Chart

<table>
<thead>
<tr>
<th>Highest pre-control prevalence of nodules in the area (according to nodule prevalence contour map)</th>
<th>&lt;5%</th>
<th>&gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated area</td>
<td>- In general: no treatment needed</td>
<td>- Treatment may be needed</td>
</tr>
<tr>
<td></td>
<td>- For clusters of nodule positive REMO villages, check by MF surveys (scenario 1 - 2)</td>
<td>- MF surveys to confirm and define treatment limits (scenario 4)</td>
</tr>
<tr>
<td>Borderline area with CDTi</td>
<td>- No treatment needed</td>
<td>- Check current status by MF surveys in selected villages, giving priority to REMO villages with highest pre-control nodule prevalence (scenario 5)</td>
</tr>
<tr>
<td></td>
<td>- Include in phase 1A/1B evaluations of CDTi project (scenario 3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 lists some specific scenarios for the different categories in table 1, indicating for each scenario what action should be taken, whether further surveys are needed, how the results of such additional surveys should be interpreted and if CDTi is indicated or not.
Table 2: Specific scenarios and corresponding follow-up action

<table>
<thead>
<tr>
<th>Nodule prevalence contour</th>
<th>Scenario</th>
<th>Action</th>
<th>Survey result</th>
<th>Follow-up Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>1. Single village with positive nodule prevalence but surrounded by zero prevalence villages</td>
<td>No CDTi needed</td>
<td>N/A</td>
<td>N/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample one village with highest nodule prevalence &amp; do skin snip survey</td>
<td>MF prevalence &lt;10%</td>
<td>No CDTi needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MF prevalence ≥ 10%</td>
<td>i) Re-assess remaining villages</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ii) Further assessment within 20km radius of the village with &gt;10% mf prevalence to map out treatment boundaries, then launch CDTi.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>iii) May need to do entomological assessment to confirm source of infection and deal with the source too to avoid re-inversion.</td>
</tr>
<tr>
<td></td>
<td>2. Cluster of 2 or more REMO villages with a positive nodule prevalence but surrounded by zero prevalence villages</td>
<td>Include in phase 1B surveys</td>
<td>Use phase 1b criteria</td>
<td>i) If phase 1B criteria met in total area (CDTi + border area), stop treatment and proceed with phase 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ii) If phase 1B criteria not met, continue treatment</td>
</tr>
<tr>
<td>&gt; 5%</td>
<td>4. Cluster of 2 or more REMO villages with a positive nodule prevalence &gt; 5% but surrounded by zero prevalence</td>
<td>Spatial sample of (2 or more) villages for skin snip survey (20 km between villages)</td>
<td>Sampled villages both have MF prevalence &lt;10%</td>
<td>No CDTi needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One or both villages have MF prevalence of ≥ 10%, then re-assess remaining villages</td>
<td>iii) Further assessment within 20km radius of the village with &gt;10% mf prevalence to map out treatment boundaries then launch CDTi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>iv) May consider entomological assessment to confirm source of infection and deal with the source too to avoid re-inversion</td>
</tr>
<tr>
<td></td>
<td>5. Bordering area (&lt;40 km) from of ongoing CDTI</td>
<td>Spatial sample of (2 or more) villages for skin snip survey (20 km between villages)</td>
<td>Sampled villages both have MF prevalence &lt;10%</td>
<td>No CDTi needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One or both villages have MF prevalence of ≥ 10%, then re-assess remaining villages</td>
<td>i) Further assessment within 20km radius of the village with &gt;10% mf prevalence to map out treatment boundaries then launch CDTi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ii) May consider entomological assessment to confirm source of infection and deal with source in case of reinvasion</td>
</tr>
</tbody>
</table>
IV. Example

This section gives examples of the implementation of step 3 using data for Malawi.

Figure 5: Environmental and REMO data

Figure 6: Nodule prevalence contours

Figure 7: Examples of the five scenarios (see table 2)
Figure 5 displays a map of the landscape of southern Malawi and neighbouring areas in Mozambique, showing the main rivers and watersheds, and the variations in altitude, both important factors for the distribution of onchocerciasis vectors. The map also displays the results of the precontrol REMO surveys. A large number of REMO surveys were done both in Malawi and Mozambique, and in most of the surveys, the prevalence of nodules was zero or very low.

Figure 6 shows the results of the spatial analysis of the REMO data. There is a clear zone of mesoendemic onchocerciasis running across southern Malawi from the border with Mozambique in the East to the border in the West. The border with Mozambique to the west of the endemic zone follows a mountain ridge that separates the watersheds in Malawi and Mozambique. In the East, there is no natural division that would provide an obstacle to onchocerciasis. Quite the contrary, the border itself follows a river with onchocerciasis endemic villages on the right bank in Malawi.

Figure 7 shows the CDTi treatment area. Malawi has a spatial database which includes the geographic ordinates of all CDTi villages in the country and the treatment map is therefore quite reliable. As the map shows, CDTi covers all areas where the prevalence of nodules is >20%.

Figure 7 also shows some examples for each of the five scenarios in table 2.

Scenario 1: for most of Malawi, the prevalence contour map shows a predicted prevalence of 0% to 2%, indicating the absence of endemic onchocerciasis. In some isolated REMO villages in this low prevalence area, there were still one or two persons nodule positive during the REMO examination. That was also the case for the village in the example of scenario 1 in figure 7 where palpable nodules were reported for 1 out of 50 examined adults. Given the specificity of nodule palpation of 98%, such occasional positive prevalences are to be expected in oncho free areas. The prevalence contour and the REMO data for the surrounding villages indicated onchocerciasis is not endemic in this area, and no ivermectin treatment is needed.

Scenario 2: this scenario shows 2 nodule positive villages in an area where the prevalence contours are below 5%. The two villages had a prevalence of about 10%, with 9 out of 92 persons examined in the two villages combined reported positive during the REMO surveys. However, the prevalence of nodules in the surrounding REMO villages, some located at only 5 to 10 km distance, were all zero. It is therefore highly unlikely that these two villages represent an onchocerciasis focus with sustained local transmission. Other explanations, e.g. specificity issues, problems during the execution of the REMO surveys, human migration from endemic areas, etc may be more plausible. Nevertheless, it might be considered prudent to check one of the two villages, if possible by a skin snip survey or otherwise by nodule palpation done by an experienced examiner, to make 100% sure that this area is free of local onchocerciasis transmission.
Scenario 3: this scenario concerns an area with a prevalence contour of 2% to 5% bordering the main CDTi zone. There are two nodule positive villages in this area, one with 3 nodule positives out of 50 examined, and one with 1 nodule positive out of 50 examined. Beyond these villages, away from the CDTi zone, all REMO villages have zero prevalence. This area is a good example of a borderline area where there is probably no local transmission and where a few precontrol infections may have been the result of transmission in the main endemic zone that since then has been covered by CDTi. Since the CDTi program in Malawi has been ongoing for more than 10 years, it is probable that the untreated borderline area is now onchocerciasis free. This needs to be confirmed and this confirmation can be logically done as part of the phase 1B surveys that will be soon be undertaken in Malawi to determine if the elimination threshold has been reached and treatment can be safely stopped.

Scenario 4: this is an area where the nodule prevalence contour is between 5% and 10%, and where there is a cluster of four villages that had a precontrol nodule prevalence of 10 to 13%. These four villages are located upstream of a river that flows down from the border mountains with Mozambique. The cluster of villages is located at more than 50 km from the nearest CDTi area and it is therefore not likely that the infections in these villages originate from the meso/hyper endemic area that is currently under treatment (even though migration of infected person has reportedly been important in Malawi in the past and responsible for the expansion of the initial onchocerciasis endemic zone to the West). It is possible that the data for this area represent an isolated focus with local transmission and this should be investigated as soon as possible. Skin snip survey should be done in 2 REMO villages with the highest nodule prevalence. In order to ensure a distance of at least 20 km between the two selected villages, the most northern village should be selected and one of the three other REMO villages.

Scenario 5: this example concerns an area just across the border in Mozambique, adjacent to the main CDTi area in Malawi. The border between the two countries follows a river that probably contains breeding sites as evidenced by the endemic villages on the right bank of the river in Malawi. The nodule prevalence contour just across the border in Mozambique is greater than 20% but there are no REMO villages in this area. The nearest REMO villages in Mozambique are located at > 30 km from the border but these had a very low or zero nodule prevalence. The available data suggest that just across the border in Mozambique there probably exists a small area with endemic onchocerciasis. Indeed, according to anecdotal reports, people from across the border in Mozambique cross the river every year to obtain ivermectin treatment in the villages in Malawi. To ensure that is no endemic onchocerciasis focus persists just across the border, it is urgent to undertake skin snip surveys in at least 2 villages located near the river in Mozambique at a distance of 20 km from each other.

The above scenarios are not exclusive, and slightly different situations may be encountered in other countries. However, the general principles in the decision chart and the type of reasoning used in the above examples should facilitate decision-making in all situations.
V. Follow-up surveys and treatment

When the above analysis indicates that additional epidemiological surveys are needed in a given area, it is recommended that such surveys are done using the skin snip method\(^3\) as a measure of active onchocerciasis infection, as well as nodule palpation to facilitate a comparison with the precontrol REMO data. These surveys should follow the standard epidemiological evaluation protocol prepared by APOC (see Annex 1). However, to simplify the surveys and limited the number of people to be examined, it is recommended that the examination be restricted to the examination of high risk age groups, i.e. adults above the age of 20 years.

In order to determine whether any MF positives that are detected during these surveys represent local or imported infections, it will be important to take a full migration history for all MF positives. The epidemiological evaluation protocol of APOC includes guidelines for taking such a migration history.

Finally, it should be recalled that ivermectin treatment cannot be used in areas that are hypoendemic for onchocerciasis but hyperendemic for loiasis. Hence, such areas are not a priority for the current exercise of revising treatment boundaries until a practical intervention method has been developed that can be safely used in such co-endemic areas.

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\(^3\) or an alternative diagnostic test for active infection, such as the DEC patch test, when such test becomes available and has been adequately validated