A rapid health impact assessment of APOC: technical report

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Dec 2007

A rapid HIA

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A RAPID HEALTH IMPACT ASSESSMENT OF APOC

EXECUTIVE SUMMARY & TECHNICAL REPORT

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Final version : December 2007

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EXECUTIVE SUMMARY

Background
Onchocerciasis is responsible for a considerable burden of disease, mainly because of visual impairment, blindness, skin lesions and severe itching as a result of heavy continuous infection. The World Health Organization (WHO) estimated that 17 million people were infected and that 900,000 disability adjusted life years (DALYs) were lost due to onchocerciasis in 1990 (World Health Organization 1995). However, the latest epidemiological mapping data indicate that the disease is much more widespread than assumed previously and that the number of people infected and the number of DALYs lost are more than twice as high as originally estimated (Remme et al. 2006).

The African Programme for Onchocerciasis Control (APOC) aims to eliminate onchocerciasis as a public health problem, which will also aid socio-economic development of the affected regions. The main strategy consists of the implementation of sustainable mass treatment with ivermectin, via a community-directed treatment approach. APOC is organized in projects by the participating countries and it involves a great effort of many people. Policy makers, programme managers and donors therefore request proof of APOC’s effectiveness, and the Joint Action Forum of APOC requested that APOC sharpened its focus on results and on the impact on the populations concerned. It was concluded that a health impact assessment (HIA) of the APOC was strongly indicated.

A HIA tries to assess the potential effects of projects, programmes and policies on health (Lock 2000). It involves identifying disbenefits and benefits to health, interpreting health risk and potential health gain. It assesses the potential effect on the health of the population, and the distribution of those effects within the population. As a first step, the present report concerns a rapid HIA of APOC based on data available by 2006. The study gives first estimates of the health impact of APOC on the population concerned and also explores the requirements for a comprehensive HIA. Details on data, methods and findings of the HIA are presented in the technical background report (Habbema et al. 2007).

Objectives of the rapid HIA

- To assess the impact of the African Programme for Onchocerciasis Control (APOC) by 2005 on skin and eye problems and on the burden of disease caused by onchocerciasis, as measured in disability adjusted life years (DALYs) lost due to the disease;
- To predict the health impact of APOC by 2015, when the programme has continued for 10 more years;
- To explore possibilities of a comprehensive health impact assessment (HIA) of APOC.
Steps in the impact assessment
First, we determined the size of the population targeted by APOC mass-treatment. The total population is categorized by type of onchocerciasis (two types: savannah, and forest or mixed forest-savannah), and by the onchocerciasis endemicity level before the start of APOC (4 categories: non-, hypo-, meso-, and hyperendemic, respectively covering areas with nodule prevalence (NP) = 0%, 0% < NP < 20%, 20% ≤ NP < 40%, and NP ≥40%). Combining the population numbers with literature-based estimates of the prevalence of onchocerciasis-related disease in each category of endemicity and onchocerciasis-type, we calculated the total number of people with onchocerciasis-related clinical manifestations in the APOC area and the number of DALYs lost.
Subsequently, we determined the operational effectiveness of APOC, investigating how many mass-treatments were done in the different project areas and what the overall average population coverage was per round.

The computer simulation model ONCHOSIM (Plaisier et al. 1990) was used to simulate how the prevalence of infection and disease decline, depending on the number of treatment rounds provided and the proportion of people treated per round. Predictions were done for each relevant treatment scenario, and were done separately for each of the two types of onchocerciasis and the four endemicity levels. Results were then aggregated to estimate the trend in the overall prevalence of infection and disease in the APOC area.
The number of DALYs lost due to onchocerciasis in the APOC area was calculated for each year, using the predicted trends in disease manifestations and DALY-weights for these different manifestations (Shibuya et al. 2006). We calculated the difference with the pre-APOC situation.

Data sources
The following data from the African Programme for Onchocerciasis Control (APOC) were the basis for our analysis:
- Data from Rapid Epidemiological Mapping of Onchocerciasis (REMO) nodule prevalence surveys (Noma et al. 2002);
- Project data on population size, the timing of treatment, and the proportion of the population treated per round;
- Data from impact assessment studies in sentinel sites.
In addition, we used:
- Data about the prevalence of blindness and low vision in savannah areas before and during the Onchocerciasis Control Programme (Remme et al. 1989);
- Published data from various studies about the prevalence of blindness in forest areas and in forest/mixed areas;
Results

The population targeted by APOC: size, type of onchocerciasis, and endemicity level.
APOC is active in 108 projects in 15 countries (Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, DR Congo, Equatorial Guinea, Ethiopia, Liberia, Malawi, Nigeria, Sudan, Tanzania, Uganda). In 2005, the total population size in the project areas was about 88 million. For comparability of results over time, all results have been standardized to the 2005 population of 88 million.

On the basis of the results of the Rapid Epidemiological Mapping of Onchocerciasis (REMO) it was estimated that the population was evenly distributed over the 3 endemicity classes: 32% of the APOC population lives in a hyperendemic community, 33% in a mesoendemic community and 30% in a hypoendemic community. The remaining 5% lives in a non-endemic community that is surrounded by meso- or hyperendemic areas. Concerning the type of onchocerciasis it is estimated that a quarter of the APOC population lives in savannah areas and three quarters in forest or mixed forest-savannah areas.

Pre-treatment burden of onchocerciasis-related disease: eye and skin problems.
The most important health consequences of onchocerciasis are loss of vision and skin problems. Before the start of APOC, about 400,000 people (0.4%) of the total APOC population were blind because of onchocerciasis, and another 900,000 (1.1%) suffer from low vision. The most important skin manifestation is troublesome itch, which leads to sleeplessness, tiredness, lack of concentration, and absenteeism from work or school. We roughly estimated that 15.3% people in the APOC area suffered from troublesome itch. According to earlier work, blindness reduces the quality of life by 60% and low vision and itch lower the average quality of life by 28.2% and 6.8% respectively (Shibuya et al. 2006). Moreover, blindness reduces the remaining life expectancy by 50%. As a consequence, every year a total of 1.7 million DALYs were lost due to onchocerciasis before the start of APOC: 860,000 due to troublesome itch, 580,000 due to blindness and 260,000 because of low vision (Figure 1).
Operational effectiveness of APOC: treatment rounds and coverage
Forty-one percent of the APOC population lived in a project area in which 7 to 9 annual rounds of mass treatment with ivermectin (CDTI) had taken place by the end of 2005, 16% in areas with 4 to 6 rounds, and 17% in areas with 1 to 3 rounds; 27% of the APOC population lived in areas where CDTI was yet to start. Because of the gradual build up of geographical coverage in project areas, the proportion of the population that receives treatment increased with the number of rounds; from 32% in the rounds 1-3 of mass treatment, to 55% in rounds 4-6, and 70% in rounds 7-9.

Trends in infection and disease during and after APOC
All clinical manifestations show a continuously decreasing trend since the start of APOC, but with distinct patterns (Figure 2). The prevalence of infection has declined to about 73% of its pre-CDTI level by the year 2005 and we expect it to decline further to 14% of the pre-CDTI level in the year 2015. Because it is closely related to infection and improves after treatment, we also predict a very strong decline in the prevalence of itching: its prevalence is already halved by the year 2005 and it will be nearly eliminated by the 2015. Reduction in blindness and low vision goes slower, because of the irreversibility of these consequences of onchocerciasis. These problems were reduced to respectively 77% and 88% of the pre-CDTI levels in the year 2005, and to 32% and 49% 10 years later. More detailed information about predicted trends in the prevalence of infection and clinical manifestations in the period from 1995-2015 can be found in Figure 3.
Figure 2. Prevalence of onchocerciasis infection and clinical manifestations in the APOC population in 2005 and 2015, compared to the pre-APOC level (=100%).

Figure 3. Predicted trends in the prevalence of onchocerciasis infection and related clinical manifestations in the APOC population, during the execution of the APOC programme. The left axis shows the absolute level and the right axis the relative level (taking the pre-APOC level as 100%). The percentages displayed on the curves are relative to the pre-APOC level.
Health impact

The burden of disease due to onchocerciasis in terms of annual number of DALYs lost is almost halved in the APOC areas by 2005 and by 2015, a reduction of the DALY loss of 86% could be achieved (Figure 4).

Before the start of APOC, about 1.7 million DALYs were lost each year due to onchocerciasis. Thanks to APOC, many DALYs are 'regained'. The annual number of DALYs regained by APOC, compared to the pre-control situation, has gradually increased and is estimated for 2005 at >700,000 DALYs. With continuation of APOC, and especially by inclusion of the 27% APOC population not yet treated in 2005, this figure of DALY-gain may be doubled by 2015. The total (cumulative) number of DALYs regained by APOC is estimated at 3 million by the end of 2005 and could rise to 15 million in 2015 (Figure 5).

Because of the irreversible nature of eye disease and the gradual implementation and up-scaling of the CDTI programmes the total impact of APOC by 2006 on eye-disease is limited.

In a hypothetical scenario in which the whole target population was covered from the start onwards, more health impact would be achieved in 5 years than the actual APOC programme achieved in the first 10 years.
Uncertainties in the results
The presented estimates are rough estimates of APOC’s health impact. They are subject to considerable uncertainty, mainly because of data limitations. For example, only few studies have examined the relationship between mf-prevalence and the occurrence of skin- or eye-disease. Moreover, interpreting and combining these studies is difficult, because they used different definitions of infection and disease. Similarly, little information is available about the short and long term effects of mass ivermectin treatment on the severity and prevalence of skin problems. Reported coverage levels should be interpreted cautiously because the quality of reporting is uncertain. Moreover, we had no information about the number of people who never participated in mass treatment. These people are pivotal in keeping transmission going.

Because the model-predictions are uncertain, validation of predictions against actual observations from CDTI programmes is crucial. Such data were available from APOC’s impact assessment studies in about 10 sites. For ethical reasons, skin mf counts were not assessed in these studies. This precluded direct comparison of the model predictions about infection prevalence with empirical data. Data about the nodule prevalence were available, but after a number of CDTI rounds this is no longer a useful measure of infection. The prevalence of clinical manifestations showed so much unexpected and difficult to explain variability that it is not possible to use them for model-validation.
Towards a comprehensive health impact assessment (HIA)

A more exhaustive literature review might help to find more data about the relationship between infection and disease prevalence and about the effects of ivermectin, but will not solve the main uncertainties. We recommend the inclusion of a larger number of sentinel sites in evaluation studies of APOC. Collecting information about skin mf counts to correlate infection with clinical manifestations would be very helpful. Nevertheless, uncertainty will always remain in estimates of the health impact. A comprehensive HIA should therefore include a sensitivity analysis to test the robustness of health impact estimates to underlying assumptions.

A comprehensive HIA should include the impact of CDTI on onchocerciasis-related disease manifestations not included in this rapid HIA (reactive skin lesions other than itch, depigmentation, epilepsy, dwarfism), and the impact of ivermectin treatment on other diseases than onchocerciasis (lymphatic filariasis, loiasis, strongyloidiasis). Side effects of ivermectin, the broader health services impact of APOC, and socio-economic impact of the control programme should also be considered in a comprehensive HIA. Also, results should not only be calculated for the total APOC region, but also for countries and projects separately.

ONCHOSIM will have to be adapted for its use for a comprehensive HIA. The current ONCHOSIM computer program is transmission-oriented and is developed for a hyperendemic savannah population. A HIA is health-oriented, and the APOC area has savannah, mixed forest-savannah regions with different degrees of endemicity. ONCHOSIM should take this into account. Moreover, the current ONCHOSIM does not allow the linking of multiple diseases to the (cumulative) exposure to the parasite, while this is needed for simultaneous prediction of all disease manifestations. Also the computer program should be adapted such that training and transfer is simplified.

A key-question to be addressed in further studies is whether CDTI could eventually eliminate the infection completely, which would clearly maximize its impact on future generations. When the results of the HIA are combined with the results of ongoing studies on transmission in Senegal, Mali and Guinea Bissau, ONCHOSIM could be used to develop criteria for determining the best moment to stop CDTI, and to develop surveillance strategies and criteria to decide when surveillance results are such that action is needed because of a likely recrudescence of the onchocerciasis epidemic.

Conclusion

The APOC strategy can effectively reduce the burden of onchocerciasis-related disease. The overall impact of the programme by 2005 has been limited by the incomplete geographic coverage in the past. Nevertheless, the burden of onchocerciasis-related disease in DALYs has almost halved by 2005. By 2015, the burden can be reduced to less
than 15% of the pre-APOC burden, if the programme continues to expand and reaches its full scale in a few more years. For a complete and accurate account of APOC’s health impact with proper sensitivity analysis and consideration of APOC’s impact on other onchocerciasis-related disease manifestations and other diseases than onchocerciasis, a comprehensive HIA is recommended. This comprehensive assessment will require additional data collection.

References
TECHNICAL REPORT
1 Overview: steps in estimating APOC’s health impact

In this technical report, we provide a detailed description of the steps in the calculation of APOC’s health impact. This report is to serve as a reference for those who want to have more background about the methods used in the rapid Health Impact Assessment of APOC.

A schematic representation of the whole process is provided in Figure 1, showing the steps that were taken and the relation between the steps.

Firstly, we studied the APOC target population, using project-data about the population size, results of rapid epidemiological mapping, and treatment reports. Chapter 2 provides information about the population size, the distribution in the target population of the two main types of onchocerciasis (savannah or forest/mixed infections) and the distribution of endemicity levels. Chapter 5 gives information about the number of treatment rounds provided to the population. Based on this information, we determined the treatment scenario’s that had to be simulated by ONCHOSIM. Information about the number of people per category (defined by onchocerciasis-type, endemicity level and number of treatment rounds provided) was used in the post-processing of simulation results in order to estimate the number of people with onchocerciasis-related morbidity before APOC and after the start of CDTI.

Chapters 1 and 4 respectively provide information about the relationship between infection and disease prevalence levels and the effects of ivermectin on the prevalence and severity of disease. This information was needed to quantify the ONCHOSIM model parameters that relate to these issues, so that the model provides accurate predictions of the prevalence of disease before and after start of CDTI. Some of the information was needed in the post-processing of simulation results.

Chapter 6 and 7 provide information about the input for the ONCHOSIM simulation model. Chapter 6 focusses on the parameters related to transmission dynamics and development of clinical manifestations. Chapter 7 summarizes the treatment scenario’s that were simulated by ONCHOSIM. We ran many different scenario’s with the model, to predict trends in the prevalence of infection and disease by type of onchocerciasis, endemicity level and the number of treatment rounds provided.

Post-processing of the ONCHOSIM output is described in chapter 0. This chapter describes how we calculated the prevalence of different clinical manifestations from simulation results and how we aggregated the results to estimate the total number of people with onchocerciasis-related morbidity before and after the start of CDTI. This was translated into an overall measure for the burden of disease in Disability Adjusted Life Years (DALYs).

Results are summarized in Chapter 9 and in Chapter 10 we briefly discuss the results.
§ 2: APOC target population
- Total population of APOC’s target area
- Categorization of the target population by type of onchocerciasis
- Categorization of the target population by endemicity level

§ 3: Empirical data on the pre-treatment relationship between infection and disease
- Relationship between mf and nodule prevalence
- Relationship between nodule and itch prevalence
- Relationship between eye-disease and infection prevalence
- Calculation of Disability Adjusted Life Years (DALYs)

§ 4: Empirical data on the effects of ivermectin on infection and disease
- Effects of ivermectin on the parasite
- Effects of ivermectin on eye disease
- Effects of ivermectin on skin disease (itch)

§ 5: History of CDTI in APOC target population
- Categorization of the target population by number of treatment rounds
- Population coverage

§ 6. Input assumptions for ONCHOSIM, for use in APOC
- ONCHOSIM version used in the analysis
- How is disease simulated by ONCHOSIM?
- Quantification of parameters related to transmission
- Quantification of parameters about the relation between infection and disease
- Quantification of parameters about the effects of ivermectin on infection and disease

§ 7. Simulated treatment scenario’s
- Scenario’s to be simulated with ONCHOSIM

ONCHOSIM input

ONCHOSIM SIMULATIONS

ONCHOSIM output

§ 8: Post-processing of simulation results
- Overview
- Estimate the prevalence of itch from the predicted female worm prevalence

§ 9: Results: predicted trends in burden of disease
- Trend in prevalence of infection and disease
- Trend in burden of disease in DALYs lost

Input for calculations

Input for calculations

Figure 1. Schematic representation of the main activities in the health impact assessment of APOC, with references to the chapters in this report that describes the corresponding methods and results. The boxes relate to the main activities, while the arrows indicate the relation between these activities. In blue boxes: literature review and data-analysis to obtain input for the ONCHOSIM model and post-processing calculations. In yellow boxes: conclusions regarding input for the ONCHOSIM model. The pink boxes show the steps where taken in post-processing of simulation results and the eventual results.
2 APOC population by type of onchocerciasis and endemicity

2.1 Total population of APOC’s target area

- APOC is active in the following 15 countries:
  1. Angola
  2. Burundi
  3. Cameroon
  4. CAR
  5. Chad
  6. Congo
  7. DR Congo
  8. Equatorial Guinea
  9. Ethiopia
  10. Liberia
  11. Malawi
  12. Nigeria
  13. Sudan
  14. Tanzania
  15. Uganda

- The original project area of APOC also included Gabon, Kenya, Mozambique and Rwanda.
  - In Gabon the endemicity level was found after the REMO to be hypoendemic. Therefore, APOC supported the project for one year only. Clinic-based treatment method is being applied in the country (19 villages under treatment).
  - REMO surveys showed that the nodule prevalence in adult males in Kenya, Mozambique, Rwanda was always <20%, so that CDTI was not necessary (Noma et al. 2002).

- 108 projects were started to implement CDTI in all areas that needed CDTI (nodule prevalence in adult males >= 20%).

- Information about the population size in each project area was available from reports of the National Onchocerciasis Taskforces (NOTF). We obtained an excel file with summary data from APOC that contains data for each year about the total number of communities in the project areas and the number of communities where treatment was implemented; similarly the database contained estimates of the total population size in the project area and the numbers of people treated. (NB. these data were later used to estimate the coverage in CDTI projects; see 0). We were particularly interested in the population size by project in the year 2005, to which we scaled all results.

  The reported data are somewhat difficult to interpret. Reason for this is that CDTI often started in only a part of the area and some projects reported the number of villages and population estimates for the selected part, rather than for the whole area that has to be targetted eventually. Thus, data about the ‘total number of communities in the area’ and ‘total population size’ were often unreliable. To estimate the population size for a particular year, we had to make several assumptions:
  1. Data from the most recent treatment round provide the best estimate of the number of village and population size in the target population.
  2. The number of villages in a project area has not changed during the CDTI period, i.e. the boundaries of the project area have not moved and there were no new villages or disappearing villages.
  3. The number of people in a project area grows at a rate equal to the average national growth rate (unless we know otherwise and have good data).
  4. Population is equally spread over the villages. This last assumption ignores migration, which in some areas may be massive because of violent conflict. There might also be migration from APOC areas to urban areas, which lowers population growth in the project areas. However in the absence of estimates of the size of that effect we could not correct for it.

- With the above assumptions, we did not always obtain realistic figures of the population size in different years. For some countries the NOTF-data had to be corrected, because of unrealistic changes in population size (Cameroon, Nigeria). For some projects (namely most projects in
Angola, Burundi, Congo DRC, Liberia and Sudan) the population estimates from the project proposals had to be used instead. [d]

- The total population targeted by APOC was estimated at 88.5 million in the year 2005 (taking account of population growth as estimated by UNDP). The following table summarizes the results by country:

<table>
<thead>
<tr>
<th>Country</th>
<th>Population in APOC target areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>1,153,584</td>
</tr>
<tr>
<td>Burundi</td>
<td>809,029</td>
</tr>
<tr>
<td>Cameroon</td>
<td>4,361,810</td>
</tr>
<tr>
<td>CAR</td>
<td>1,319,888</td>
</tr>
<tr>
<td>Chad</td>
<td>1,607,692</td>
</tr>
<tr>
<td>Congo</td>
<td>607,635</td>
</tr>
<tr>
<td>Congo DRC</td>
<td>30,850,128</td>
</tr>
<tr>
<td>Equatorial Guinea</td>
<td>72,498</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>4,981,358</td>
</tr>
<tr>
<td>Liberia</td>
<td>2,954,713</td>
</tr>
<tr>
<td>Malawi</td>
<td>1,628,602</td>
</tr>
<tr>
<td>Nigeria</td>
<td>28,785,819</td>
</tr>
<tr>
<td>Sudan</td>
<td>5,534,246</td>
</tr>
<tr>
<td>Tanzania</td>
<td>1,943,428</td>
</tr>
<tr>
<td>Uganda</td>
<td>1,848,752</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88,459,182</strong></td>
</tr>
</tbody>
</table>

No CDTI in Kenya, Mozambique, Rwanda, Gabon.

- More detailed data, of population size by project, is available in an excel file. [e]

### 2.2 Categorization of population by type of onchocerciasis

- The impact of community-directed mass treatment with ivermectin (CDTI) depends on the type of onchocerciasis, i.e. the blinding or ‘savannah’-type of onchocerciasis or the forest-type that causes much less blindness. People in African savannah areas are only exposed to the savannah-type. In other areas, the forest type is usually predominant, although mixed infection often occurs.

- The areas in which the savannah-type is predominant are known, but exact delineation of forest and mixed infections is difficult (and may vary over time). Assuming that the disease patterns in areas with forest and mixed infections are not so different, we took them together.

- The delineation of savannah and forest/mixed areas was based on the following figure (courtesy Hans Remme [f]):
We categorized the 108 CDTI projects as ‘savannah’ or ‘forest/mixed’ by estimating whether they were above or under the dividing line in the above picture. This was cross-checked by the APOC staff and judged acceptable. Adding up the population numbers showed that about 25.5% of the population that is targeted by APOC lives in areas where the savannah-type of onchocerciasis is predominant (i.e. 22.5 million people). The remaining 74.5% (66 million) live in mixed or forest areas.

### 2.3 Categorization of population by endemicity level

- The impact of community-directed mass treatment with ivermectin (CDTI) depends on pre-treatment endemicity level.
- Communities are usually categorized as non-, hypo-, meso- or hyper-endemic based (Noma et al. 2002), based on the prevalence of nodules in 30-50 adult males:
  - 0 Nonendemic
  - 1-19.9 Hypoendemic
  - 20-39.9 Mesoendemic
  - 40+ Hyperendemic

  NB. the target number of 30-50 adult males was not always achieved. The nodule prevalence levels are based on very small numbers in some villages, which may have led to misclassification.

- APOC intends to treat all people living in meso- and hyperendemic villages. However, the areas that are targeted by APOC also contain some hypo- and non-endemic communities that are located in the same reservoir.

- From the REMO data, we selected all villages that fall in a project area and we classified them as non-, hypo-, meso- or hyperendemic according to the REMO guidelines. The data were analyzed in SPSS to estimate for each project the proportion of villages that non-, hypo-, meso- and hyper-endemic (according to REMO guidelines).
- The calculated proportions were used to calculate the numbers of people in each endemicity class by project. We thereby assume that the proportion of communities in each endemicity category is the same as the proportion of people in each endemicity category. In other words, we assumed that there were no systematic differences in the average size of the community by endemicity level.

- The REMO database contains duplicates, which were usually not filtered out. This is unlikely to have a major effect on the overall outcomes. We ignored missing entries and corrected the percentages to add up to 100%.

- Combining this information with the results from section 2.2, the total APOC population was categorized as follows:

  **Table 2. The target population of APOC, categorized by type of onchocerciasis and endemicity level.**

<table>
<thead>
<tr>
<th></th>
<th>Forest/mixed</th>
<th>Savannah</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-endemic</td>
<td>4,045,525 (6.1%)</td>
<td>640,157 (2.8%)</td>
<td>4,685,682</td>
</tr>
<tr>
<td>hypo-endemic</td>
<td>19,195,986 (29.1%)</td>
<td>7,544,890 (33.5%)</td>
<td>26,740,876</td>
</tr>
<tr>
<td>meso-endemic</td>
<td>20,316,492 (30.8%)</td>
<td>8,947,023 (39.7%)</td>
<td>29,263,515</td>
</tr>
<tr>
<td>hyper-endemic</td>
<td>22,383,162 (33.9%)</td>
<td>5,385,946 (23.9%)</td>
<td>27,769,108</td>
</tr>
<tr>
<td>total</td>
<td>65,941,165 (100%)</td>
<td>22,518,016 (100%)</td>
<td>88,459,181</td>
</tr>
</tbody>
</table>

- The numbers by project are available in an excel spreadsheet.\(^e\)
3 Empirical data on the pre-treatment relationship between infection and disease

3.1 Relationship between the prevalence of mf and nodules

- Quantitative information about the relationship between mf and nodules is required because:
  o We need to estimate the pre-control prevalence of clinical manifestations in the 4 endemicity categories. This requires quantitative information about the relationship between the prevalence of nodules and the prevalence of disease. This information is not always available. For example, the most important data about the relationship between eye-disease and endemicity are based on mf prevalence levels or CMFL. Quantitative information about the relationship between mf and nodule prevalence is required to link the prevalence of eye-disease to the prevalence of nodules.
  o ONCHOSIM is used to make predictions of trends in infection and disease for areas with different endemicity levels (non-, hypos-, meso- or hyper- endemic). However, the output of ONCHOSIM simulations provide no information about the nodule prevalence in the simulated population; it only gives information about mf prevalence and CMFL. This means that observed nodule prevalence levels have to be translated into mf prevalence levels, before we can calibrate the model (vice versa, predicted mf prevalence can be translated into expected nodule prevalence).
  o We also need to test whether the ONCHOSIM-predicted relationship between infection and disease is correct. Predictions therefore needs to be validated against data. The best available dataset about skin disease unfortunately does not provide information about mf prevalence and intensity. To compare model predictions with the data, we either have to translate the observed nodule prevalences in expected mf prevalences (or vice versa, translate predicted mf prevalence into expected nodule prevalence).

- Remme has recently analyzed data from different locations, to quantify the relationship between nodule and mf prevalence levels (Remme 2004). Data are summarized in Figure 3.

Figure 3. The relationship between the prevalence of nodules in adult males (y-axis) and the prevalence of mf among the total population aged 5 yrs and older. The horizontal and vertical lines indicate the threshold values for meso- and hyperendemicity.
• The 4 categories of endemicity were defined by nodule prevalence levels. Based on Figure 3, we estimated the mf prevalence levels that corresponded to the boundaries of the 4 categories. This resulted in the following categorisation:

<table>
<thead>
<tr>
<th>Endemicity level</th>
<th>Nodule prevalence (males aged 20+)</th>
<th>Mf prevalence (total population aged 5+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non endemic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypo endemic</td>
<td>1 – 20*</td>
<td>1 – 40*</td>
</tr>
<tr>
<td>Meso endemic</td>
<td>20 – 40*</td>
<td>40 – 60*</td>
</tr>
<tr>
<td>Hyper endemic</td>
<td>40+</td>
<td>60+</td>
</tr>
<tr>
<td>midpoint hyperendemic</td>
<td>60</td>
<td>73</td>
</tr>
</tbody>
</table>

* upper boundaries excluded from the interval

• The results of this analysis have later been used to translate ONCHOSIM-predicted pre-treatment mf prevalence levels in corresponding predicted nodule prevalence levels, according to the following relationships:

<table>
<thead>
<tr>
<th>mf prevalence</th>
<th>corresponding nodule prevalence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nd</td>
</tr>
<tr>
<td>1-39.9</td>
<td>Nd</td>
</tr>
<tr>
<td>40-59,9</td>
<td>mf prevalence – 20</td>
</tr>
<tr>
<td>60+</td>
<td>(4/3)*mf prevalence – 40</td>
</tr>
</tbody>
</table>

Nd: Not done. Without additional assumption on migration of infected humans or flies, ONCHOSIM predicts that onchocerciasis would be cleared from hypo-endemic areas without any intervention.

3.2 Relationship between the prevalence of nodules and itch

• From APOC’s impact assessment studies, pre-treatment data were available about the relationship between nodules and itch.

• Few or no studies of itch has been carried out in savannah-areas. Based on expert opinion (personal communication dr. J.H.F. Remme, 2006), we assume that the pre-treatment relationship between itch and infection prevalence is the same for the savannah and forest type of infection.

• There are three major datasets about onchocerciasis-related skin problems including itch that use the Murdoch classification of cutaneous changes due to onchocerciasis (Murdoch et al. 2002):
  o Data from (Murdoch et al. 2002)\([i]\)
  o Data from (Brieger et al. 1998)
  o Data from APOC’s impact assessment studies, phase I.\([k]\)
The data from Murdoch and Brieger were considered most reliable. Unfortunately, we did not have a codebook to the the data from Brieger. Therefore we have used only the data from Murdoch for our analyses.

Murdoch included various measures of itch in the questionnaire. We used the data for “troublesome itch”, considering that the available disease weights are for troublesome itch (see paragraph 3.4). Murdoch had used the same indicator in her work.

Murdoch presented only aggregated data for groups of villages in her paper. We analysed the original raw data to obtain village-specific estimates for the nodule prevalence in adult males and the prevalence of itch in the whole population. The data provide valid estimates of the nodule prevalence in adult males, but crude estimates of troublesome itch in the whole population were biased because younger age groups were underrepresented and elderly were overrepresented in the data. We standardized the data to the UNPP standard population for Sub Sahara Africa (2003 Revision). The results are summarized in Figure 4. The standardized prevalence levels are always lower than the crude ones.

The Annex to 3.2 provides a more detailed description of the analysis.

Figure 4. Crude and standardized estimates of the prevalence of troublesome itch in relation to the nodule prevalence. Based on data from Murdoch et al (2002).

The standardized data were further analysed to fit a curve through the data, in order to stimate the prevalence of itch in non-endemic areas (‘intercept’), i.e. itch that is not caused by onchocerciasis.

Analyses are done in MS Excel. The results are summarized in Figure 5, with:

- a curve with a slope zero in the origin and an estimated point of inflection (solid black line)
- a curve with a slope zero in the origin and an fixed point of inflection at 50% (dotted black line)
- Deming regression (red line), assuming that the variance in measurements on the X- and Y-axis is equal, i.e. lambda = 1

The results of Deming regression were used for further analyses. We selected the Deming results because Deming regression corrects (to some extent) for non-systematic misclassification of...
exposure, which leads to a dilution-bias. Ignoring this non-systematic misclassification leads to an underestimation of the strength of the relationship between onchocerciasis infection and itch and an inflated estimate of the background non-onchocercal itch. The estimated equation was: \( y = a + bx \), with

- \( y \) = itch prevalence (%) (onchocerciasis-related + other itch)
- \( x \) = nodule prevalence in adult males (%)
- \( b = 0.416 \)
- \( a = 5.888 \)

**Figure 5. The relationship between nodule prevalence in adult males (x-axis) and the prevalence of troublesome itch (y-axis) as based on REMO results.**

- The background prevalence of itch was therefore estimated at 5.9%. In calculating the prevalence of onchocerciasis-related itch, we need to take into account that some of the people with itch from other causes may in addition get itch from onchocerciasis. Therefore, we cannot simply subtract the 5.9% background prevalence from the prevalence of all itch. Assuming that the proportion of people suffering from onchocerciasis is independent of the presence of other itch, we used the following equation to calculate the proportion of people with onchocerciasis-related itch:
  
  \[
  \text{prevalence} = \frac{bx \times 100}{(100 - a)}, \]

  where
  
  - `prevalence` indicates the prevalence of onchocerciasis-related
  - `a` and `b` are parameters of the Deming regression line describing the relationship between the prevalence of nodules and itch from all causes
  - `x` = nodule prevalence

Results are summarized in Table 5.
Table 5. Estimates of the prevalence of troublesome itch, due to all causes and onchocerciasis-related, by endemicity level.

<table>
<thead>
<tr>
<th>endemicity</th>
<th>prevalence of troublesome itch</th>
<th>onchocerciasis-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>non</td>
<td>5.9%</td>
<td>0%</td>
</tr>
<tr>
<td>hypo (for nodule prevalence 10%)</td>
<td>10.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>meso (for nodule prevalence 30%)</td>
<td>18.4%</td>
<td>13.2%</td>
</tr>
<tr>
<td>hyper (for nodule prevalence 60%)</td>
<td>30.8%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

* equal to the intercept of Deming regression.

- The onchocerciasis-related itch should be used in estimates of the burden of onchocerciasis and should be compared with model-predictions of itch.

- The results of this analysis have later been used for two purposes:
  1. To provide a rough estimate of the baseline itch prevalence by endemicity level, for back-of-the-envelope calculations
  2. More importantly, to translate ONCHOSIM-predicted mf prevalence into the corresponding onchocerciasis-related itch prevalence levels (via an intermediate step that relates nodule prevalence to mf prevalence; see section 3.1). After completion of this step, the (pre-treatment) predictions of nodule prevalence could be related to other indicators of infection.

3.3 Relationship between the prevalence of eye-disease and infection

- Information about the quantitative relationship between prevalence of infection and eye-disease was required to validate ONCHOSIM predictions (see section 6.3).

- We followed the WHO criteria that define blindness as visual acuity of less than 3/60 or a restriction of visual field to less than 10° of fixation in the better eye. Low vision is defined as visual acuity of less than 6/18 but better than 3/60 in the better eye (Remme 2004).

- The best data about the relationship between infection and blindness of onchocerciasis can be found in a series of papers by Remme and Dadzie (Dadzie et al. 1992; Dadzie et al. 1990; Dadzie et al. 1989; Remme et al. 1989).

- There is a clear relationship between the CMFL or mf prevalence level and the prevalence of blindness for savanna-type onchocerciasis. According to Remme & Dadzie, CMFL has a better (and linear) correlation with blindness than mf-prevalence. However, for the APOC area we have better information about the mf-prevalence than about the CMFL. We therefore used the data from a study on blindness in the OCP area that relate the prevalence of onchocerciasis-related blindness to the mf prevalence in the skin (Remme et al. 1989), which are provided in Figure 6:
• In hyper-endemic savannah areas of OCP the prevalence of low vision was about 1.8 times the prevalence of blindness (Shibuya et al. 2006).

• Much less information is available about the prevalence of eye-disease, in relation to endemcity levels, in forest areas. In addition, the available data from forest and mixed areas show wide variation without a clear pattern. In consultation with Hans Remme, we decided to group all non-savannah onchocerciasis (forest and mixed) together and estimate the relationship between infection and blindness (or low vision) for this group.

• The forest data about blindness and low vision come from various sources. Studies varied with respect to the methods to measure blindness, the age groups in which blindness prevalence was measured and the indicator of infection (mf or nodules). Therefore, standardization was required before the data could be compared and the model predictions could be fitted to these data. See Annex to 3.3. Figure 7 shows the corrected data.

• In analysing and standardizing the data of blindness, we took account of the measurement methods. In many studies only the central vision is tested, but onchocerciasis also affects the peripheral vision. According to the WHO criteria, persons can also be functionally blind if the peripheral vision is affected. If this is not taken into account, about 25% of functional blindness is missed (Remme 2004).

Figure 6. Prevalence of onchocerciasis-related blindness in relation to the prevalence of microfilariae in the skin. Source (Remme et al. 1989)
Figure 7. The relationship between the prevalence of microfilariae in the skin among the total population aged 5 and over, and the prevalence of blindness and visual impairment as it was found in several studies in the published literature, after correction for differences in the research populations and methodology.

- These data were used to quantify the relationship between infection and disease in ONCHOSIM. See par. 6.3.

3.4 Calculation of Disability Adjusted Life Years (DALYs)

- We quantify the burden of onchocerciasis-related disease in terms of Disability Adjusted Life Years (DALYs) lost.

- DALYs represent the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD), weighted for the loss in quality of life. One DALY represents the loss of one year of equivalent full health.

- For the calculation of the YLD ‘disability weights’ are needed. These are available for blindness, low vision and troublesome itch. We used the disability weights from the Global Burden of Disease 2000 (Shibuya et al. 2006). By multiplying these weights with the number of years lived with disability, we get an estimate of the YLD.
  - Low vision 0.282
  - Blindness 0.600
  - Itching 0.068

- Onchocercal blindness and reduced vision are associated with an increased risk of dying. The GBD 2000 used relative risks of 2.5 for blindness and 1.5 for low vision for both sexes (Shibuya et al. 2006). For onchocercal skin disease no excess mortality is known.

- A recent study suggested that mortality increase was related to mf-load rather than to blindness (Little et al. 2004). However, this may be confounded, e.g. if blindness was assessed less accurately than mf-load. There is also no plausible mechanism. We decided to link mortality to blindness and visual impairment, not to mf-load directly.
• YLL was estimated based on the average age of incidence of blindness predicted by the ONCHOSIM model and the corresponding life expectancy of the ONCHOSIM population (which has a life expectancy at birth of 44 years). This amounted to an average of 8 years lost per case of blindness. For more detail, see section 8.1.

• Health effects were not discounted and no age-weighting was applied (DALY[0,0]).
4 Empirical data on the effects of ivermectin on the infection and clinical manifestations

Ivermectin has an effect on the clinical manifestations of onchocerciasis via two mechanisms. Firstly, ivermectin may cause a direct improvement to some clinical manifestations via its effect on the parasite. Secondly, it has an indirect effect on the incidence and progression of disease, due to the reduction in transmission. The ONCHOSIM model takes account of this second mechanism. For the direct effects of ivermectin we studied the literature and based our assumptions on the results.

4.1 Effects of ivermectin on the parasite

- Ivermectin is primarily a microfilaricidal drug. It eliminates the microfilariae from the skin and, with some delay, the eye. It kills up to 100% of the skin load of microfilariae, though the effect of treatment varies by individual. In the course of months the levels climb again to a level that is about 40% lower than before the ingestion of ivermectin (Alley et al. 1994).

- Such a long-term reduction was found to be consistent with a model in which 28% of the female worms immediately and irreversibly lost their fertility and all other worms only temporarily lost their fertility and recovered completely (Plaisier et al. 1995). An alternative explanation assumes that there is no irreversible effect on fertility: all worms suffer from a temporary complete interruption in mf production; the per-worm mf productivity after recovery is 32% lower than the pre-treatment level.

- Early studies did not suggest a macrofilaricidal effect of treatment on the adult worms, but in a recent nodulectomy study Gardon et al. did find evidence for such an effect in a mass treatment trial from Cameroon (Gardon et al. 2002). Model-based analysis of these data suggested that each treatment kills about 11% of the adult worms, while another 15% of the worms permanently lose their ability to produce mf (Borsboom et al, unpublished data). For transmission, the distinction between these two effects is not relevant: overall 26% of worms stops producing mf. This estimate is close to the earlier estimate from Plaisier et al (Plaisier et al. 1995).

4.2 Effects of ivermectin treatment on eye disease

- Blindness due to onchocerciasis is irreversible and not cured by ivermectin.

- Low vision due to posterior segment lesions of the eye (optic nerve disease (OND) and choroidoretinitis (CR)) are also considered irreversible, but low vision due to anterior segment lesions (sclerosing keratitis (SK) and iridocyclitis (IC)) is considered partly reversible (Abiose 1998; Whitworth et al. 1991a).

- A key-question with respect to reversibility therefore is: what percentage of low vision is due to anterior segment lesions, and how much of these lesions are reversible by annual ivermectin treatment? Over what time period do they regress?\[n\]

- There is a considerable amount of literature on the subject. We primarily used two sources for this overview: a review by Abiose (1998) and a Cochrane review (Ejere et al. 2006).
In his review article Abiose gives percentages of anterior and posterior lesions in the OCP area (figure 9 of (Abiose 1998)) among a group of persons who completed eight annual treatments with ivermectin. Table 6 summarizes some of these data: both anterior and posterior segment lesions showed some regression (average weighted by prevalence: 44% reduction), though considerably more for anterior (72%) than for posterior (24%).

Table 6. Prevalence of anterior and posterior eye lesions in the OCP area and the effect of 8 annual treatments with ivermectin on the prevalence of these lesions.

<table>
<thead>
<tr>
<th></th>
<th>Posterior segment</th>
<th>Anterior segment</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>OND</td>
<td>both</td>
</tr>
<tr>
<td>Before</td>
<td>11.2</td>
<td>16.7</td>
<td>12.2</td>
</tr>
<tr>
<td>After 8 years</td>
<td>10.3</td>
<td>11.0</td>
<td>4.8</td>
</tr>
<tr>
<td>% reduction</td>
<td>8%</td>
<td>34%</td>
<td>24%</td>
</tr>
</tbody>
</table>

From these data it is not clear what the visual status of these persons was (blind, impaired vision, normal vision). It stands to reason that the more serious the lesion, the less reversible it is. Looking at these data, an assumption that about 40% of the low vision due to onchocerciasis is reversible over eight years does not seem unreasonable.

However, this may be overestimating the effect. Abiose cites Cousens et al. (1997) who found that annual dosing of ivermectin reduces the occurrence of visual field deterioration by 36%, and states (without reference) that “(…) ivermectin appears to have no significant benefit in terms of visual acuity, this is not surprising as visual acuity is a crude test of central vision which usually deteriorates late in the course of the disease.” If we take Remme’s estimate that 25% of blindness is due to visual field loss (Remme 2004) and assume that this goes down by 36% while central vision, once affected, does not recover, we come to only 9% reduction in visual impairment due to ivermectin distribution. (And a reduction in the incidence of new cases that might be at least 40%, considering the above table.) This low estimate of effect is supported by the Cochrane review (Ejere et al. 2006) in which placebo-controlled trials did not find any statistical beneficial effect for visual acuity loss. Two out of three trials did find a reduction in visual field deterioration (OR 0.55 and 0.33). The duration of the trials was mostly limited to one year.

An additional question might be if below the threshold for visual impairment there is any improvement in vision. Chippaux followed a cohort on annual ivermectin for up to eight years and measured a ‘Mean Visual Acuity’ index which included also less severe vision loss (Chippaux et al. 1999). The score on this index slightly decreased over time, indicating a worsening of vision. Of course the cohort also aged during this period, but a marked improvement in average vision was certainly not seen.

In conclusion, the effect of ivermectin on onchocerciasis-related visual impairment is only for about 9% reversible. The effect on specific ocular diseases is larger; overall about 40% may be reversible. However, the lesions that regress are the early lesions, while the definition of visual impairment only includes late stages of the disease processes that are not affected by ivermectin.

For the rapid HIA of APOC it was not feasible to include a reversible fraction of low vision, though this might have led to a slight underestimation of the ocular effects of ivermectin treatment. (See section 6.5).
4.3 Effects of ivermectin treatment on skin disease (itch)

- From the onchocerciasis-related skin manifestations, we only included troublesome itch in the rapid HIA. This is probably the most important skin lesion due to onchocerciasis and the only onchocerciasis-related skin condition for which a disability weight has been developed.

- The literature contains few well-conducted studies on the effects of ivermectin on itch. Especially about the longer-term effects little is known.

- Several authors note that the prevalence of onchocercal skin disease (OSD) fluctuates with time, simultaneously in groups on ivermectin and placebo. More than one dose annually does not seem to add to the reduction in disease manifestations.

- A useful study on the short-term effect of ivermectin on itch is the multi-country study by Brieger and colleagues (Brieger et al. 1998). This double-blind, placebo-controlled trial study shows that ivermectin reduces the prevalence of severe itch to about 50 to 60% of its previous value over the course of about 6 months. The level of itch then remains more or less stable for at least nine months with no perceptible downward trend.

- In a community trial in Sierra Leone, Whitworth and colleagues (Whitworth et al. 1992) conclude after four six-monthly doses of ivermectin that the clinical results are somewhat disappointing. The authors note reductions in the severity but not the prevalence of skin lesions. The prevalence of itching was lower but this effect did not reach statistical significance. Also noteworthy is the high prevalence of itching among those without nodules and clean skin snips: about 35%. This is likely due in large part to other causes than onchocerciasis, although in an earlier publication (Whitworth et al. 1991b) the authors found “a significant correlation between the prevalence of itching and density of microfilariae”. This correlation is not in itself at odds with a background prevalence of 35% of non-onchocerciasis-related itch in this population, but Murdoch and colleagues also find that non-onchocercal skin disease contributes very little to pruritus in seven communities in different countries (Murdoch et al. 2002). Another possible explanation mentioned is that the itching reflects the persistence of a small population of mf even after multiple doses of the drug. In a later publication (Whitworth et al. 1996), after one of the subgroups had received over 6 years of treatment, the picture is not much different. One third of the itching was alleviated (prevalence went from 60% to 40%). Beside reductions in serious hyperkeratosis and possibly depigmentation (leopard skin) no other skin problems seemed improved by ivermectin treatment.

- Brieger and colleagues find that in onchocercal skin disease-free individuals, administration of ivermectin at three-monthly intervals reduces by half the number of new cases of reactive skin disease (Brieger et al. 2001). This was studied in a population in which participants receiving ivermectin and placebo were mixed, so the effect cannot be attributed to a reduced exposure to infected blackflies.

- Ivermectin distribution programmes do also reduce transmission levels in an area, as evidenced by entomological indicators and a reduced prevalence of infection among children. After two years of ivermectin distribution, Taylor et al (Taylor et al. 1990) found a reduction in the incidence among 7-12 year olds of 45% and Boussinesq (1995) found that after 5 years prevalence of infection among 5-7 year old children had fallen by 55% (and mean mf skin density by 77%).

- The manuscripts on the impact assessment provided by APOC (Ozoh et al, unpublished manuscript): Long-term impact assessment of APOC activities: onchocercal skin disease in six countries 1998 and 2004,) in which the prevalence before the start of APOC and five years into the programme are compared, are consistent with a limited effect of APOC on disease prevalence. The dermatological effects vary considerably over the ten sites. Mostly so for severe itch; the
results vary from 8-fold reductions to 10-fold increases. Over nine sites, the geometric mean reduction is 36% (the remaining site went from 0 to 12% prevalence).
5 Implementation of CDTI by APOC

5.1 Categorization of the target population by number of treatment rounds

- To assess the impact of APOC until now, we needed to know how many treatment rounds have taken place in the different project and what the population coverage was.

- The information was provided by APOC. The file gives the following information, by project:
  - timing (calendar year) of each CDTI round
  - the number of villages that is included in the project area and the number that actually had CDTI. This is input for the calculation of geographic coverage.
  - the number of people in the project area and an estimate of the number of people who received treated per round. This is input for the calculation of therapeutic coverage.

The reported numbers are somewhat difficult to interpret. The intention was to calculate the geographical coverage as the number of villages that received mass treatment over the total number of villages in the project area. This would provide information about the rate of upscaling. However, several countries initially did not report the total number of villages in the project area, but gave the number for the initially much smaller targeted area where the intervention was started. Therefore, the ‘total number of communities in the area’ and ‘total population size’ from the first few years cannot always be used to calculate the geographical and therapeutic coverage. Sometimes the recent data were deemed reliable (although several assumptions had to be made in the analysis, see section 2.1); in other cases, we had to make use of estimates from countries project proposals, which were assumed to be less reliable. Table 7 summarises the results. No programme had given > 9 rounds by the end of 2005.

- The more detailed data by project can be found elsewhere. Additional information can be found in a working document.

Table 7. The total population in APOC-targeted areas, classified by type of onchocerciasis, endemicity level and the number of treatment rounds that were provided by the end of 2005.

<table>
<thead>
<tr>
<th>Type of onchocerciasis</th>
<th>no. of Rx rounds before 2005</th>
<th>non</th>
<th>hypo</th>
<th>meso</th>
<th>hyper</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>savannah:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21,047</td>
<td>1,047,123</td>
<td>1,145,767</td>
<td>351,838</td>
<td>2,565,776</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>99,569</td>
<td>1,810,104</td>
<td>1,440,784</td>
<td>565,762</td>
<td>3,916,220</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>13,636</td>
<td>913,879</td>
<td>1,747,602</td>
<td>186,415</td>
<td>2,861,532</td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>505,905</td>
<td>3,773,783</td>
<td>4,612,870</td>
<td>4,281,931</td>
<td>13,174,489</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>640,157</td>
<td>7,544,890</td>
<td>8,947,023</td>
<td>5,385,946</td>
<td>22,518,016</td>
<td></td>
</tr>
<tr>
<td>forest/mixed:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2,116,216</td>
<td>5,395,821</td>
<td>4,564,338</td>
<td>7,075,528</td>
<td>19,151,904</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>844,692</td>
<td>5,629,379</td>
<td>6,444,803</td>
<td>6,546,378</td>
<td>19,465,252</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>644,970</td>
<td>3,500,323</td>
<td>4,568,528</td>
<td>4,002,997</td>
<td>12,716,817</td>
<td></td>
</tr>
<tr>
<td>7-9</td>
<td>439,647</td>
<td>4,670,463</td>
<td>4,738,824</td>
<td>4,758,259</td>
<td>14,607,193</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4,045,525</td>
<td>19,195,986</td>
<td>20,316,492</td>
<td>22,383,162</td>
<td>65,941,166</td>
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<td>6,442,945</td>
<td>5,710,104</td>
<td>7,427,367</td>
<td>21,717,680</td>
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<td>7-9</td>
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<td>9,351,694</td>
<td>9,040,190</td>
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<td>Total</td>
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<td>26,740,876</td>
<td>29,263,515</td>
<td>27,769,108</td>
<td>88,459,182</td>
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</tbody>
</table>
5.2 Population coverage

- The uncertainties in the data also made it difficult to distinguish between geographical coverage and therapeutical coverage. In our analyses we used the overall coverage (geographic * therapeutic) which could be calculated as the number of people treated / population size.

- The average coverage level may vary between projects; it will also vary within projects between rounds and villages. We could not take account of all these sources of variation and instead worked with an average coverage level that is used in all our simulations. However, we do take account of a gradual increase in coverage that resulted from the upscaling of the project.

- The average coverage in rounds 1-3, 4-6 and 7-9 was calculated from the coverage data from 2005. To estimate the mean coverage in rounds 1-3, we looked at projects that were giving their 1\textsuperscript{st} to 3\textsuperscript{rd} round in 2005 and calculated the average coverage in that year. Similarly, we estimated the other coverage levels from the selections of projects that gave their 4\textsuperscript{th} – 6\textsuperscript{th} or 7\textsuperscript{th} – 9\textsuperscript{th} round in 2005. The results were as follows:
  - 1-3 rounds by 2005 \( \Rightarrow \) 32%
  - 4-6 rounds by 2005 \( \Rightarrow \) 55%
  - 7-9 rounds by 2005 \( \Rightarrow \) ~70%

- The calculated coverage was used as input for our simulation studies (see section 0.2).

- NB. It would be more accurate to distinguish between geographical and therapeutical coverage. The present analysis implied that all communities in a project are equally covered and with modest coverage, but in fact part of the villages received all the treatment rounds and had higher coverage while others were not covered at all. The epidemiological consequences of these two ways of treating coverage may not be the same.

- NB. For the estimation of the impact of upscaling on coverage, it would have been better to use data from all years and not only the data from 2005. For example, to estimate the average for projects that are providing round 1-3, we have now only used the information from projects that started recently. It would have been better to also use the information from earlier years, when other projects were providing round 1-3. However, this required a different organization of the data and was not done because of time constraints.
6 Input assumptions for ONCHOSIM, for use in APOC

6.1 ONCHOSIM version used in the analyses

- We chose to use the ONCHOSIM.EXE (155 KB, 21 March 1997), along with the user-interface that was developed for demonstration and teaching purposes. A corresponding input file for Asubende was available (asubende.oif). About the same quantifications were used in several simulation studies with ONCHOSIM (Borsboom et al. 2003; Winnen et al. 2002).

- In the current simulation study, we will leave most parameters unchanged: they keep the same value as in the Asubende simulations. The following parameters had to be adjusted to get a correct representation by the model of the dynamics of transmission and disease development:
  1. **Relative biting rate (RBR):** this parameter has to be changed to simulate the different endemicity levels.
  2. **Disease threshold:** this parameter will be adjusted so that the model accurately predicts the association between blindness and visual impairment and mf prevalence.
  3. **Reduction in life expectancy due to eye-disease:** this parameter needs to be adjusted so that the model accurately predicts the trend in the prevalence of blindness during control; its value also depends on the type of eye-disease that is simulated.
  4. **Exposure variability:** this parameter has to be changed to simulate the different endemicity levels.

- For simulating the impact of CDTI, we adjusted the following parameters:
  5. **Timing and coverage of ivermectin:** according to APOC experience / theoretical scenario.
  6. **Macrofilaricidal effects of treatment and effects on adult worm productivity:** this parameter is an important determinant of the long-term effects of treatment and transmission effects.

- We further changed the values with some general specifications about the simulation and simulation output:
  7. **Start, end and interval of monitoring:** depending on the application.
  8. **Starting year and stopping year of the simulation:** depending on the application.
  9. **Standard population:** we need output for entire populations, except 0-5 year-old children; the first row of values will be put to zero.

- An example input file is given in the Annex to 6.1. Most parameters have not been changed in our simulations and take the same value as in the Asubende file; only the parameters that are highlighted take different values and their value may differ between runs.

- Information of the new values of these parameters, which we used in our simulations, is given in the following paragraphs.
6.2 How is disease simulated by ONCHOSIM?

Eye-disease: blindness and low vision

- ONCHOSIM has frequently been used to assess the impact of interventions on infection prevalence and the CMFL, but it has not previously been used to predict the impact on clinical manifestations.

- Blindness is explicitly included in ONCHOSIM. The development of eye-disease is assumed to be related to the cumulative mf counts, reflecting an accumulation of damage in the eye. If an individual’s cumulative mf-count passes a critical threshold level, he or she gets blind. The actual threshold varies between individuals. Blind people experience considerable excess mortality in rural Africa. ONCHOSIM accounts for a reduction of the remaining life expectancy in people who have passed the threshold.

- Low vision is not included in the current version of ONCHOSIM. However, visual impairment (including blindness) can simply be modelled by choosing a lower value for the threshold. The excess mortality (specified as reduction in remaining life-expectancy) has to be adjusted accordingly.

- The applied version of ONCHOSIM only supports one threshold, which means that we can simulate either blindness or visual impairment (including blindness). The prevalence of low vision can be calculated by doing two series of runs, one with the threshold for blindness and one with the lower threshold for visual impairment. The mean prevalence of visual impairment (including blindness) minus the mean prevalence of blindness.

- Because of the change in threshold and associated change in excess mortality, the simulated populations with blindness and visual impairment are not exactly comparable. Differences are not large, however, and are deemed acceptable for the current rapid assessment. Nevertheless, we recommend the inclusion of two separate thresholds for low vision and blindness in ONCHOSIM for future work.

Skin-disease: itch

- With respect to onchocercal skin disease, we limited this rapid HIA to troublesome itch, presumably the most important skin-disease in terms of burden of disease. It also is the only one for which a disability weight has been developed.

- Skin disease and itch are not explicitly included in the current version of ONCHOSIM. From the model-predicted prevalence and intensity of infection, we had to make deductions about the itch prevalence.

- We made the following assumptions:
  - The onchocerciasis-related itch is caused by a reaction of the immune system to (dead) microfilariae in the skin.
  - The presence of at least one productive adult female worm is a prerequisite for having onchocerciasis-related itch in the long-term. The intensity of infection is not so important for the development of itch.
  - Some persons are vulnerable for development of itch, while others are less vulnerable.
In the ONCHOSIM-model we linked the prevalence of itch to the prevalence of female adult worms. A fixed proportion of people with female adult worms is assumed to have itch in a situation without treatment.

- The prevalence of onchocerciasis-related itch was calculated in several steps:
  - ONCHOSIM simulates the trend in female worm prevalence after the start of ivermectin treatment
  - From the female worm prevalence, we can calculate the proportion of people that would have itch in a situation without treatment (‘potential’ itch prevalence)
  - We assume that the real itch prevalence during intervention is lower than the ‘potential’ prevalence, as a consequence of treatment. That is: we multiply the potential itch prevalence with a correction factor to account for the fact that people may have worms but (temporarily) no mf.

- Section 8.2 provides more detailed information about the calculation of itch prevalence.

6.3 Quantification of parameters related to transmission

- There are 7 types of endemic situations in the APOC area:
  - Non-endemic
  - Hypo-endemic, savannah-type
  - Hypo-endemic, forest/mixed-type
  - Meso-endemic, savannah-type
  - Meso-endemic, forest/mixed-type
  - Hyper-endemic, savannah-type
  - Hyper-endemic, forest/mixed-type

- There is no need to make simulations for a non-endemic situation, and the current version of the model has difficulty in predicting a stable hypo-endemic situation (the infection usually dies out). Therefore, we will use the ONCHOSIM model only to simulate the 4 meso- and hyper-endemic situations. This concerns the following parameters, i.e.:
  - Relative biting rate (RBR)
  - Exposure variability

We quantified these parameters by fitting the model to data, as described below.

- An mf prevalence of 48% was taken as representative level for meso-endemic areas; an mf prevalence of 73% was used to represent hyper-endemic areas. These levels could be reproduced with the parameter values of Table 8:

<table>
<thead>
<tr>
<th>type of onchocerciasis</th>
<th>endemcity</th>
<th>RBR</th>
<th>exposure variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>savannah</td>
<td>hyper</td>
<td>0.40</td>
<td>4.237</td>
</tr>
<tr>
<td></td>
<td>meso</td>
<td>0.33</td>
<td>3.942</td>
</tr>
<tr>
<td>forest/mixed</td>
<td>hyper</td>
<td>0.40</td>
<td>4.237</td>
</tr>
<tr>
<td></td>
<td>meso</td>
<td>0.33</td>
<td>3.942</td>
</tr>
</tbody>
</table>
6.4 Quantification of parameters about the relation between infection and disease

- Parameters related to transmission and eye-disease need to be quantified for savannah and forest/mixed type of onchocerciasis. This concerns the following parameters:
  - Excess mortality: when the cumulative mf density in a person crosses the threshold, he is considered to have disease and consequently his remaining life expectancy may be reduced.
  - Disease threshold (+ variability): a person is blind in the model, when the cumulative number of mf in the body passes a critical threshold. The threshold value varies between individuals.

We need to specify separate thresholds for blindness and for visual impairment (including vision loss and blindness) and the excess mortality rates need to be adjusted accordingly.

- For details about the methods used to quantify these parameters, we refer to some other documents[^p]. Here only a brief description is given.

Thresholds for eye-disease: savannah type of onchocerciasis

- For the savannah-type of onchocerciasis, quite some data are available about infection and blindness. From OCP, we have data about the association between mf prevalence and blindness prevalence (see section 3.3). To fit the model to these data, we varied the RBR over a wide range of values and compared the resulting association between prevalence of mf and blindness (or visual impairment), in a standardized population of 5 years and older. We assumed that the variability in exposure increases when the RBR is lower (such an association appeared from old fits done by Anton Plaisier for Folonzo, Tiercoura en Asubende; such an increase in variability explains why there can be endemic situation with very low RBR’s). A good fit was obtained with a disease threshold for the cumulative mf count of 4000.

- There are less data about the association between visual impairment and mf prevalence. Reportedly, for the hyper-endemic savannah areas that the prevalence of low vision was about 1.8 times the prevalence of blindness (Shibuya et al. 2006). We used this information to adjust the threshold for visual impairment in the savannah. The ratio of low vision : blindness prevalence of 1.8 was exactly reproduced at an mf prevalence of 73% (which is representative for hyperendemic areas) when the threshold was 2800. NB. People who have crossed this threshold either have low vision or are blind. With this new threshold, we predicted the association between mf prevalence and visual impairment.

- The following graph shows the goodness-of-fit of the model to the OCP for the association between infection and disease. See section 3.3 for a description of the data (we had to read the data from the graph to be able to create the following graph in excel).
We also checked whether the predicted decline in blindness prevalence during OCP was comparable to the observed pattern for high endemic areas (initial mf-prevalence 70-90%). The next graph gives the trend in prevalence of blindness in the original OCP area (combined results for 10 villages from Burkina Faso, Côte d'Ivoire and Ghana). The blue lines give the observations. The red dotted lines give model predictions with various values of the RBR and exposure variability. The thick solid red line gives the average trend of the observations, which can be compared to the data. The goodness of fit is good.

**Figure 9. The trend in prevalence of blindness in the original OCP area (blue dotted line) and the trend as modelled for this study (red lines). See text for further explanation.**
The conclusion from the previous figure is that our assumption of 50% excess mortality in blindness is good enough to work with.

**Thresholds for eye-disease: forest/mixed type of onchocerciasis**

- We had much less information about the association between infection and blindness for the forest type of onchocerciasis than for the savannah type. Therefore, we first made sure that our model accurately simulated the situation for the savannah type. Only thereafter, we made further adjustment for application of the model in forest/mixed areas. Our considerations were as follows:
  - The relationship between infection prevalence and exposure is the same in savannah and forest/mixed areas. Therefore, we can use the same values for the RBR and exposure variability as in the savannah areas.
  - The prevalence of blindness is much lower in forest/mixed areas than in savannah areas, for the entire range of mf prevalence levels. This means that we need higher thresholds for blindness and visual impairment.
  - Blindness and low vision have the same impact on the remaining life expectancy in savannah and forest/mixed areas.

- Because of the scarcity of data on blindness and eye-disease, we had to use data from various studies, which had used different methods and definitions. Several correction and standardization steps were required to make the data comparable with each other and the model predictions (this was described in section 3.3). We fitted the model to the standardized data. All parameters remained the same as in the model for the savannah-type, except for the threshold levels for blindness and low vision. A good fit (predicted prevalence levels of these eye diseases matched the observations) was obtained with a threshold value of 10000 for blindness and of 5500 for visual impairment. Results of the Goodness-of-fit are shown in the following figure:

*Figure 10. The prevalence of blindness and low vision in the forest/mixed area of APOC, as modelled in this study. The open circles depict observed prevalences of blindness; the open triangles are observations on the prevalence of visual impairment (blindness and low vision combined); the blue squares are the model outcomes for blindness; the red squares those for visual impairment.*
**Excess mortality**

- The excess mortality has to be adjusted with the eye-disease threshold. We assume that blindness reduces the remaining life expectancy by 50%. Under this assumption, the model gives accurate predictions of the decline in blindness prevalence during a 100% successful vector control programme (see Figure 9). Assuming that there is no excess mortality in people with low vision, and taking account of the fact that the number of people with low vision is 1.8 times the number of blind people, we set the excess mortality for visual impairment at 20%, which is roughly equal to 50% * 1.0/(1.0+1.8).

**A remark about itch**

- Itch is not included in the ONCHOSIM simulation model that was originally developed for OCP. For the current analysis, we decided to estimate the prevalence of itch in processing the simulation outcomes (rather than changing the programme code to include it explicitly in the ONCHOSIM model, which was not feasible in the limited time frame of the rapid HIA). See section 8.2.

**6.5 Quantification of the effect of ivermectin on infection and disease**

**Impact on infection**

- Ivermectin treatment has strong impact on infection levels. One treatment clears all microfilariae from the blood and also affects the fertility or longevity of adult worms. We made the following assumptions about the effects of treatment on the parasite:
  - 5% of treatments have no effect due to malabsorption
  - Ivermectin always kills 100% of the skin load of microfilariae
  - Each treatment kills 25% of the worms on average. This is based on Gerard Borsboom’s analysis of the Gardon-trial data and was in agreement with earlier estimates from Anton Plaisier from analysis of the Asubende trial data.
  - The effect of treatment on adult worms varies by individual

- The exact specifications of the effect of ivermectin used in ONCHOSIM can be found in the example input file in the Annex to 6.1.

**Impact on eye disease**

- We assume that treatment does not cause a regression of visual impairment or blindness. Although it has been reported in the literature that pathologic changes in the eye are partly reversible, this only concerned early stages in which there was no visual impairment yet. More advanced stages appear to be irreversible. For a more thorough explanation, see section 4.2.

- Therefore, treatment only affects the prevalence of blindness and low vision indirectly through a reduction of the incidence (because of the reduction in mf counts). The impact of long-term ivermectin mass treatment on the prevalence of blindness and low vision is predicted by the model.
7 Simulated treatment scenario’s

- We decided to regard the situation in 1995 as the ‘baseline situation’, and assessed the situation in 2005 and 2015.

- We assessed two scenarios: ‘APOC’ and ‘IDEAL’. The ‘APOC’-scenario used treatment data as observed in APOC for the period from 1997 up to end 2005, and then assumed a gradual expansion of ivermectin distribution to all remaining APOC project areas, with ultimately 70% therapeutical coverage.

- The ‘IDEAL’-scenario has 15 rounds of CDTI, starting in the year 2000, with a coverage of 70% coverage for the entire APOC population.

- Technically, this required the simulation of 6 treatment scenarios with ONCHOSIM:
  - A. Theoretical scenario A: 15 rounds of CDTI with 70% coverage
  - B. Theoretical scenario B: 15 rounds of CDTI with 55% coverage
  - C-F: A set of scenario’s that together provide a reasonable representation of what has really happened in the APOC areas. To account for variation in the duration of CDTI, we did 4 scenario’s that differ mainly in the timing of the start of CDTI. In all scenario’s, the coverage builds up slowly until the maximum of 70% is reached in the 7th round.

- Table 9 specifies the timing and coverage of CDTI in all simulated scenario’s. Further assumptions on treatment are: treatment always takes place in January; 0.1% of the population is excluded from treatment in each round because of chronic diseases etc.; the compliance pattern is semi-systematic.

<table>
<thead>
<tr>
<th>year</th>
<th>Theoretical scenario A (IDEAL)</th>
<th>Theoretical scenario B</th>
<th>scenario C</th>
<th>scenario D</th>
<th>APOC</th>
<th>scenario E</th>
<th>scenario F</th>
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<tr>
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<td>0.55</td>
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</tr>
<tr>
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<td>0.70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- Each of the 6 treatment scenario’s A-F had to be simulated for each of the 8 combinations of: type of onchocerciasis (forest vs. savannah); endemicity (meso- or hyperendemic); and type of eye-disease (blindness or visual impairment), which comes to 6x2x2x2 = 48 series of runs.
8 Post-processing of simulation results

8.1 Overview

- Each series consisted of 100 runs. These 100 runs had exactly the same input, but simulation outcomes varied as a consequence of stochastic variability. ONCHOSIM’s function COMBINE OUTPUT FILES was used to aggregate the results of the 100 runs. The following output was of relevance for our calculations:
  - The average prevalence of mf
  - The average prevalence of blindness or visual impairment
  - The average prevalence of female adult worms

- For each stratum of the analysis – defined by onchocerciasis type, endemicity level and treatment history (only for the APOC scenario) – two series of 100 runs each were done to simulate the impact of ivermectin mass treatment on blindness and visual impairment, respectively. Via post-processing of simulation results, we obtained information on all relevant indicators of the health impact of APOC. The steps in our calculations are outlined below:

  - Step I. We aggregated the results of the 100 runs within each series, calculating the trend in the mean prevalence of mf, female adult worms, blindness, visual impairment and low vision. By subtracting the prevalence of blindness from the prevalence of visual impairment, we calculated the prevalence of low vision for each stratum of the analysis.

  - Step II. Using the methods of section 8.2, we calculated the prevalence of itch from the prevalence of female adult worms and (in the period during mass treatment) the coverage for each stratum of the analysis.

  - Step III. Available data suggest that the prevalence of blindness, low vision and itch in hypo-endemic areas is roughly 1/3 of the prevalence in meso-endemic areas. We used this rule, to calculate the prevalence of these clinical manifestations in hypo-endemic areas.

  - Step IV. We earlier estimated the number of people by stratum of our analysis (see sections 2.3 and 0). Using these numbers and the stratum-specific prevalence of infection and clinical manifestations in the relevant series of runs, we calculated the number of people with infection, blindness, low vision and itch within each stratum at each time point. We added the strata-specific numbers to obtain estimates of the numbers for APOC as a whole. All numbers are scaled to the population size of the year 2005, so that results are not biased by population growth.

  - Step V. We calculate the number of DALYs lost due to low vision at each time point as: the number of cases with low vision times a disability weight of 0.282. This disability weight accounts for the fact that the quality of life is reduced. Similarly, we calculate the number of DALYs lost due to troublesome itch, using a disability weight of 0.068. See section 3.4 for background information regarding these disability weights.

  - Step VI. In the calculation of DALYs lost due to blindness, we should not only take account of the prevalent cases, but also of the years of life lost due to the blindness. From the predicted prevalence of blindness, we made deductions about the mortality, incidence, and years of life lost, years of life lived with disability, and DALYs.
Main assumption was that all blind cases would have lived for another 16 years on average, if they did not become blind. Their remaining life expectancy is reduced by 50%, i.e. to 8 years, because of the blindness.

The mortality (i.e. the number of people who die from blindness each year) was then calculated as 1/8 times the number of prevalence cases at each time point.

The incidence (i.e. the number of new cases of blindness at year $t$) was subsequently calculated as the number of blind people at year $t$ minus 7/8 times the number of blind people in year ($t-1$).

The number of years of life lost due to blindness is calculated as the incidence times 8. The life years lost are attributed to the year in which a person becomes blind.

The years of life lived with disability due to blindness at each time point is calculated as the number of people living with blindness times a disability weight of 0.6. This disability weight accounts for the fact that the quality of life is severely reduced in the blind.

The total number of DALYs lost due to blindness at each time point is then calculated as the number of years of life lost + the years of life lived with disability.

- The DALYs lost due the different disease manifestations at each moment are added to estimate the total burden of disease that is associated with onchocerciasis in the APOC area and examine the changes in the disease burden over time.

8.2 Estimate the prevalence of itch from the predicted female worm prevalence

- Itch is not included in the output of the ONCHOSIM simulation model that was originally developed for OCP. For the current analysis, we decided to estimate the prevalence of itch in post-processing the simulation outcomes (rather than changing the programme code to include it explicitly in the ONCHOSIM model, which was not feasible in the limited time frame of the rapid HIA).

Prevalence of itch in the pre-treatment situation

- In the pre-treatment situation, we could simply relate the prevalence of itch to the prevalence of microfilariae. Empirical data are available about this relationship. But this will not be valid in the post-treatment situation. Mf will disappear immediately after treatment, but healing of the skin will probably take longer. Therefore, by relating itch to the prevalence of mf, we would most likely overestimate the impact of treatment on itch. A further problem is that the mf prevalence is not a good measure to base our calculations on, because it has too much variability in the post-treatment period.

- Recognizing that having worms is a prerequisite for having infection and a more stable measure than mf, we decided to relate the itch to the presence (or number) of adult worms in the body. We used ONCHOSIM to examine how the prevalence of itch depends on the prevalence (or mean density) of worms. This was done as follows.

- We did a series of test runs in ONCHOSIM, without simulating treatment.

- We used the known associations between mf prevalence and nodules (section 3.1) and between nodules and itch (sections 3.2 and 6.2) to estimate the itch prevalence in the simulated population.
  - The translation of mf prevalence into nodule prevalence was done as follows:
    - For mf prevalence levels 40-60%: nodule prevalence = mf prevalence – 20
    - For mf prevalence levels >60%: nodule prevalence = 4/3 * mf prevalence – 40
The translation of nodule prevalence into itch prevalence was done using the Deming regression equation that was derived in section 6.2. With this equation, we can calculate the prevalence of itch that is attributable to onchocerciasis.

We then plotted the calculated itch prevalence against the prevalence of worms and the mean number of worms. The correlations were high, as shown in the following graphs. The blue dots in this graph give for each run the itch prevalence as was calculated from the mf prevalence. The pink lines are the result of an equation that calculates the itch prevalence from respectively the prevalence of worms or the average number of worms. The curve was fitted to the data.

**Figure 11. The modelled relationship between infection and itch, whereby the prevalence of troublesome itch is linked to the average number of adult worms in a population. This model was abandoned in favour of the relationship depicted in Figure 12.**

![Graph](image1)

**Figure 12. The modelled relationship between infection and itch, whereby the prevalence of troublesome itch is linked to the prevalence of adult worms in a population.**

![Graph](image2)

Initially, we planned to use the relationship with the average number of female adult worms (Figure 11). This curve does not start in zero, which may reflect that worms are often not mated if worm numbers are low. However, when we later used this relationship to predict the trend in itch
prevalence during CDTI, we found that the itch was very rapidly cleared, which seems unrealistic. Therefore, we chose to use the relationship with female adult worm prevalence (Figure 12). Note that the simulated itch prevalence (based on Deming regression) is almost linearly related to the prevalence of adult worms, but that there were no observations about the prevalence of itch in low endemic situations. We assumed that the curve goes through the origin.

- In our final simulation, we based our calculations of the itch prevalence always on the simulated worm prevalence. That is, we did not use the relationship between mf, nodule and itch prevalence anymore.

- For situations without treatment, we calculated the itch prevalence as follows:
  - Itch prevalence = $a \times fawprv + b \times \left(1-\exp\left(-\frac{fawprv}{100}\right)^2\right)$
  - NB. Close to zero, this equation can take on negative values; in that case, we assume that the itch prevalence is zero.
  - Fawprv = prevalence of female adult worms; $a$ and $b$ are parameters of the equation.
  - $a = -0.043; b = -45.532$

- The above relationship does not work if there is mass treatment, because itch is strongly reduced in those who are treated. For the post-treatment situation we assume the following:
  - In the untreated part of the population, the itch prevalence is described by the relationship above.
  - In the treated part of the population, the calculated itch is prevalence is ‘corrected’ with the $1 – Brieger-factor$
  - The Brieger factor gives the reduction in onchocerciasis-related itch prevalence in treated individuals.

**Prevalence of itch during the CDTI programme**

- As explained in above, we related the occurrence of itch to the presence of productive female worms.

- By reducing the number of productive female worms, treatment reduces the prevalence of itch. If no more productive female are present after treatment, a person is assumed to be cured from the onchocerciasis-related itch. However, treatment also has a short-term effect on people in whom productive female remain present. This can be attributed to the effect on microfilariae.

- We based our estimates of the short-term effect of ivermectin on itch on a double-blind, placebo-controlled trial (Brieger et al. 1998). Based on the published results, we assumed that ivermectin reduces the prevalence of onchocerciasis-related itch by 60% when background itch due to other causes is taken into account. After correction for the 25% worms that die with each dose of ivermectin (see par. 3.1), a 47% short-term reduction of itch was assumed in addition to the long-term effect via the prevalence of adult female worms. This is highly debatable.

- The prevalence of onchocerciasis-related itch was calculated by first modelling the long-term effect of ivermectin (via worm prevalence) and subsequently multiplying the resulting itch-prevalence by the percentage CDTI-coverage in that year multiplied by the above factor 0.47.
9 Results: predicted trend in burden of disease

9.1 Trend in prevalence of infection and disease

- In 1995 an estimated 49% of the population in APOC areas was infected. In the APOC scenario this lowers to 36% in 2005, and reaches 7% in 2015. The IDEAL scenario, in which the whole APOC population receives CDTI with a coverage of 70%, halves the number of infections by 2005 and almost eliminates onchocerciasis by 2015. See Figure 13.

![Figure 13. Trend in the average prevalence of infection among the total APOC population over the years in the IDEAL and APOC scenarios.](image)

- The prevalence of blindness decreases from 0.43% to 0.31% in 2005 and 0.14% in 2015 in the APOC scenario (Figure 14).

- The prevalence of low vision declines at a somewhat slower rate, going down from about 1.1% to 0.95% in 2005 and 0.53% in 2015 (Figure 15).

- Most pronounced is the decline in the number of people with troublesome itch. In 1995 an estimated 15% of the population in the APOC project areas is suffering from itch. By the year 2005 the percentage has halved to 7.5%, and in 2015 only 1% of the population suffers from troublesome itch in the APOC-scenario. See Figure 16.
Figure 14. Trend in the average prevalence of blindness among the total APOC population over the years in the IDEAL and APOC scenarios.

Figure 15. Trend in the average prevalence of low vision (excluding blindness) among the total APOC population over the years in the IDEAL and APOC scenarios.
Figure 16. Trend in the average prevalence of troublesome itch among the total APOC population over the years in the IDEAL and APOC scenarios.

9.2 Trend in burden of disease in DALYs lost

- Standardised to the population numbers of 2005, about 1.7 million DALYs were lost to onchocerciasis each year in the APOC population before the start of APOC. By 2005 this burden of disease has almost been halved in the APOC scenario, and reduced by two thirds in the IDEAL scenario. In 2015 about 86% of the DALYs is averted in the APOC scenario. See Figure 17.

Figure 17. Trend in the annual DALY loss among the total APOC population over the years in the IDEAL and APOC scenarios.
10 Final considerations

10.1 Uncertainties in the results

- The presented estimates are rough estimates of APOC’s health impact. They are subject to considerable uncertainty, mainly because of data limitations. For example, only few studies have examined the relationship between mf-prevalence and the occurrence of skin- or eye-disease. Moreover, interpreting and combining these studies is difficult, because they used different definitions of infection and disease. Similarly, little information is available about the short and long term effects of mass ivermectin treatment on the severity and prevalence of skin problems. Reported coverage levels should be interpreted cautiously because the quality of reporting is uncertain. Moreover, we had no information about the number of people who never participated in mass treatment. These people are pivotal in keeping transmission going.

- Because the model-predictions are uncertain, validation of predictions against actual observations from CDTI programmes is crucial. Such data were available from APOC’s impact assessment studies in about 10 sites. For ethical reasons, skin mf counts were not assessed in these studies. This precluded direct comparison of the model predictions about infection prevalence with empirical data. Data about the nodule prevalence were available, but after a number of CDTI rounds this is no longer a useful measure of infection. The prevalence of clinical manifestations showed so much unexpected and difficult to explain variability that it is not possible to use them for model-validation.

10.2 Towards a comprehensive health impact assessment (HIA)

- A more exhaustive literature review might help to find more data about the relationship between infection and disease prevalence and about the effects of ivermectin, but will not solve the main uncertainties. We recommend the inclusion of a larger number of sentinel sites in evaluation studies of APOC. Collecting information about skin mf counts to correlate infection with clinical manifestations would be very helpful. Nevertheless, uncertainty will always remain in estimates of the health impact. A comprehensive HIA should therefore include a sensitivity analysis to test the robustness of health impact estimates to underlying assumptions.

- A comprehensive HIA should include the impact of CDTI on onchocerciasis-related disease manifestations not included in this rapid HIA (reactive skin lesions other than itch, depigmentation, epilepsy, dwarfism), and the impact of ivermectin treatment on other diseases than onchocerciasis (lymphatic filariasis, loiasis, strongyloidiasis). Side effects of ivermectin, the broader health services impact of APOC, and socio-economic impact of the control programme should also be considered in a comprehensive HIA. Also, results should not only be calculated for the total APOC region, but also for countries and projects separately.

- ONCHOSIM will have to be adapted for its use for a comprehensive HIA. The current ONCHOSIM computer program is transmission-oriented and is developed for a hyperendemic savannah population. A HIA is health-oriented, and the APOC area has savannah, mixed forest-savannah regions with different degrees of endemicity. ONCHOSIM should take this into account. Moreover, the current ONCHOSIM does not allow the linking of multiple diseases to the (cumulative) exposure to the parasite, while this is needed for simultaneous prediction of all disease manifestations. Also the computer program should be adapted such that training and transfer is simplified.
• A key-question to be addressed in further studies is whether CDTI could eventually eliminate the infection completely, which would clearly maximize its impact on future generations. When the results of the HIA are combined with the results of ongoing studies on transmission in Senegal, Mali and Guinea Bissau, ONCHOSIM could be used to develop criteria for determining the best moment to stop CDTI, and to develop surveillance strategies and criteria to decide when surveillance results are such that action is needed because of a likely recrudescence of the onchocerciasis epidemic.

10.3 Conclusion

• The APOC strategy can effectively reduce the burden of onchocerciasis-related disease.

• The overall impact of the programme by 2005 has been limited by the incomplete geographic coverage in the past. Nevertheless, the burden of onchocerciasis-related disease in DALYs has almost halved by 2005. By 2015, the burden can be reduced to less than 15% of the pre-APOC burden, if the programme continues to expand and reaches its full scale in a few more years.

• For a complete and accurate account of APOC’s health impact with proper sensitivity analysis and consideration of APOC’s impact on other onchocerciasis-related disease manifestations and other diseases than onchocerciasis, a comprehensive HIA is recommended. This comprehensive assessment will require additional data collection.
Acknowledgements

We want to thank the APOC staff, and in particular director Dr. Amazigo and Drs. Noma and Zouré, for their assistance in the work. We are highly indebted to Dr. Hans Remme, whose expert input was crucial for finalizing this project in the rather short timeframe that was available for it. We also thank drs. Murdoch and Brieger, for sharing their data with us and their willingness to answer our questions. Lastly, we like to thank the members of the Joint Action Forum and the Technical Consultative Committee for providing opportunity to present the work and discuss it with experts on the issue.
References


References to unpublished documents

[a] Source: e-mail from dr. Noma, d.d. 27-Nov-2006
[b] CDTI Data - 09 Juillet 2006.xls
[c] Growth rates 1975-2003 and 2003-2015 were obtained from UNDP
[d] Source: All Project Proposals.xls
[e] APOC HIA Overview Endemicity & treatment 061129.xls
[f] Source: Hans Remme (Filename: Remme (1990) plaatje grens savannah - forest.bmp)
[g] E-mail Dr. Noma, 27 Nov 2006
[h] The resulting database was named: All APOC REMO and CDTI villages HIA APOC.xls
[i] Results are summarized in: 20061012_mix non hypo meso hyper.doc
[j] Murdoch 1.xls & Murdoch 2.xls, which were fused into Data_Mur.sav. Codebook:
    SKINEXAM.QES
[k] Phase 1 All derma oct 2000.SAV
[l] Troublesome itch.xls
[m] And the file ‘Ocular manifestations 061123_ws.xls’.
[n] See also: Effects of ivermecin on ocular oncho 061122.doc
[o] Coverage data APOC 061005 reply 8 october 2006.doc
[p] See for additional background document on this issue:
    - Ziekte in Onchosim (SdV 20nov06).doc
    - Fits run2.xls
    - Fits run3.xls
    - Sake’s e-mail dd. 26 nov 2006 (subject: Blindheid in OCP gebied)
[q] For the input definitions, see file ‘Analyse All Scenarios (itch prv FAW)_v2corr_figsLV.xls’,
    sheet ‘Explanation of scenarios’.
ANNEXA
Annex to 3.2

This annex gives details of the analysis of the Murdoch-skin disease-data to relate the nodule prevalence in adult males to the prevalence of itch in the entire population (i.e. standardized). For all 36 villages in the database.

Data
The data come from M. Murdoch and were kindly provided for this purpose. The data were reported in:


In the Murdoch-paper, the data were aggregated by groups of villages. We used the raw data, to calculate the weighted prevalence of itch by endemicity level

Need for standardization

Information about the standard population for Sub Sahara Africa is obtained from the following source:


The current study population has a different age-composition, as can be seen from the following figure. The youngest children are underrepresented, whereas the elderly are overrepresented. This introduces a bias in the estimates of the prevalence of itch in the total population.
Prevalence of itch by age (all villages combined)

<table>
<thead>
<tr>
<th>AGEGROUP</th>
<th>no examined</th>
<th>no positive for trouble</th>
<th>absent prevalence of itch</th>
</tr>
</thead>
<tbody>
<tr>
<td>05-09</td>
<td>818</td>
<td>155</td>
<td>81.1% 18.9% 100.0%</td>
</tr>
<tr>
<td>10-14</td>
<td>1002</td>
<td>191</td>
<td>80.9% 19.1% 100.0%</td>
</tr>
<tr>
<td>15-19</td>
<td>637</td>
<td>172</td>
<td>73.0% 27.0% 100.0%</td>
</tr>
<tr>
<td>20-29</td>
<td>991</td>
<td>345</td>
<td>65.2% 34.8% 100.0%</td>
</tr>
<tr>
<td>30-39</td>
<td>861</td>
<td>321</td>
<td>62.7% 37.3% 100.0%</td>
</tr>
<tr>
<td>40-49</td>
<td>796</td>
<td>332</td>
<td>58.3% 41.7% 100.0%</td>
</tr>
<tr>
<td>50-59</td>
<td>818</td>
<td>296</td>
<td>63.8% 36.2% 100.0%</td>
</tr>
<tr>
<td>60-69</td>
<td>617</td>
<td>244</td>
<td>60.5% 39.5% 100.0%</td>
</tr>
<tr>
<td>70-hi</td>
<td>370</td>
<td>133</td>
<td>64.1% 35.9% 100.0%</td>
</tr>
<tr>
<td>Total</td>
<td>6910</td>
<td>2189</td>
<td>68.3% 31.7% 100.0%</td>
</tr>
</tbody>
</table>

In this figure, “mean itchnow2” gives the prevalence of troublesome itch as a fraction.

From this table and figure we can conclude:

- The prevalence of itch is more or less stable in adults (>= 20 years). The prevalence in this age-group is: 37.53%
- The prevalence of itch in younger age groups can be expressed as a fraction of the prevalence in people >= 20 years. The fractions are:
  - 05-09  => 18.9 / 37.53 = 0.504
  - 10-14  => 19.1 / 37.53 = 0.509
  - 15-19  => 27.0 / 37.53 = 0.719

Methods for calculation of standardized prevalence

- We calculated itch prevalence levels for adults (>= 20 years) by village.
- The standard population for sub sahara Africa for the year 2000 gives the following data for the proportion of the population in each age group:
  - 00-04  => 17.0%
  - 05-09  => 14.5%
  - 10-14  => 12.8%
  - 15-19  => 11.0%
  - 20+    => 44.7%
- We could not find data on the prevalence of itch in the youngest age group (00-04 year old) and arbitrarily assumed that this is 0.1 of the prevalence in adults.
- To calculate the prevalence in entire population from the prevalence in adults, we used the following equation (\(PI = \text{prevalence of itch}\)):

\[
PI_{\text{total}} = PI_{\text{adults}} \times (0.17 \times 0.1 + 0.145 \times 0.504 + 0.128 \times 0.509 + 0.11 \times 0.719 + 0.447 \times 1) = PI_{\text{adults}} \times 0.681
\]
Results of calculations (crude or standardized prevalence vs. nodule prevalence in adult males)

```
<table>
<thead>
<tr>
<th>uniqvil</th>
<th>crude estimate of troublesome itch</th>
<th>standardized prevalence of troublesome itch</th>
<th>nodule prevalence in adult males</th>
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</thead>
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This annex sums up the data on blindness and low vision in forest/mixed areas, and the method by which these have been standardised.

Tables of the uncorrected and corrected data on blindness and low vision:

### Original data van LV

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Site / group</th>
<th>Endemicity</th>
<th>Disease manifestation</th>
<th>Blindness (%)</th>
<th>Visual impairment</th>
<th>Nodule prev</th>
<th>CMFL</th>
<th>mf prev</th>
<th>Nodule prev</th>
</tr>
</thead>
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<td>Kumba</td>
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<td>2.9</td>
<td>N</td>
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<td></td>
</tr>
<tr>
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<td>Ngambe</td>
<td>406 10+</td>
<td>37.0</td>
<td>N</td>
<td>1.3</td>
<td>2.9</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
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<tr>
<td>3 APOC Imp/DRC</td>
<td>Lusambo</td>
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<td>63.5</td>
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<td>4.5</td>
<td>N</td>
<td>N</td>
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<tr>
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<td>abstr under Y</td>
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<td>N</td>
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<tr>
<td>9 Henry 1990DRC</td>
<td>Kinsuka/Kinshasa</td>
<td>272 5+</td>
<td>4.1</td>
<td>N</td>
<td>72.0</td>
<td>1.1</td>
<td>6.9</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Whitworth 1 Sierra L.</td>
<td>1 Placebo</td>
<td>296 5+</td>
<td>4.8</td>
<td>N</td>
<td>74.0</td>
<td>2.5</td>
<td>5.3</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Whitworth 1 Sierra L.</td>
<td>1 Taberiver</td>
<td>1625 1+</td>
<td>6.7</td>
<td>N</td>
<td>65.0</td>
<td>1.5</td>
<td>4.3</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 APOC Imp/Tanzania</td>
<td>Morogoro</td>
<td>425 10+</td>
<td>18.3</td>
<td>N</td>
<td>6.5</td>
<td>4.2</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 APOC Imp/Uganda</td>
<td>Busenyi</td>
<td>366 10+</td>
<td>11.9</td>
<td>N</td>
<td>1.0</td>
<td>3.7</td>
<td>N</td>
<td>N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Corrected data (correction steps are described below)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Site / group</th>
<th>N</th>
<th>Ages</th>
<th>Mf prev</th>
<th>blindness all ages</th>
<th>visual impairment all ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 APOC Imp/Cameroon</td>
<td>Kumba</td>
<td>437 10+</td>
<td>77</td>
<td>5+</td>
<td>0.23</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>2 APOC Imp/Cameroon</td>
<td>Ngambe</td>
<td>406 10+</td>
<td>74</td>
<td>5+</td>
<td>0.23</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>3 APOC Imp/DRC</td>
<td>Lusambo</td>
<td>374 10+</td>
<td>85</td>
<td>5+</td>
<td>0.00</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>4 Henry 1990DRC</td>
<td>Kinsuka/Kir</td>
<td>169 10+</td>
<td>50.3</td>
<td>5+</td>
<td></td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>5 Brown 1988DRC</td>
<td>Kasai</td>
<td>327 20+</td>
<td>4.1</td>
<td>5+</td>
<td>72.0</td>
<td>1.1</td>
<td>6.9</td>
</tr>
<tr>
<td>6 Kayembe DRC</td>
<td>Lusambo</td>
<td>750 10+</td>
<td>0.15</td>
<td>5+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 APOC Imp/Nigeria</td>
<td>Ikorn</td>
<td>413 10+</td>
<td>27.8</td>
<td>5+</td>
<td>27.8</td>
<td>0.9</td>
<td>6.2</td>
</tr>
<tr>
<td>8 APOC Imp/Nigeria</td>
<td>Olamaboro</td>
<td>508 10+</td>
<td>37.7</td>
<td>5+</td>
<td>37.7</td>
<td>1.6</td>
<td>9.4</td>
</tr>
<tr>
<td>9 Henry 1990DRC</td>
<td>Kinsuka/Kinshasa</td>
<td>272 5+</td>
<td>4.1</td>
<td>5+</td>
<td>72.0</td>
<td>1.1</td>
<td>6.9</td>
</tr>
<tr>
<td>10 Whitworth 1 Sierra L.</td>
<td>1 Placebo</td>
<td>296 5+</td>
<td>4.8</td>
<td>5+</td>
<td>74.0</td>
<td>2.5</td>
<td>5.3</td>
</tr>
<tr>
<td>11 Whitworth 1 Sierra L.</td>
<td>1 Taberiver</td>
<td>1625 1+</td>
<td>6.7</td>
<td>5+</td>
<td>65.0</td>
<td>1.5</td>
<td>4.3</td>
</tr>
<tr>
<td>12 APOC Imp/Tanzania</td>
<td>Morogoro</td>
<td>425 10+</td>
<td>18.3</td>
<td>5+</td>
<td></td>
<td>6.5</td>
<td>4.2</td>
</tr>
<tr>
<td>13 APOC Imp/Uganda</td>
<td>Busenyi</td>
<td>366 10+</td>
<td>11.9</td>
<td>5+</td>
<td></td>
<td>1.0</td>
<td>3.7</td>
</tr>
</tbody>
</table>

- Standardization steps:
  - The APOC impact assessment studies report nodule prevalences and not mf prevalences. This is a problem, because nodule prevalence is not part of the ONCHOSIM model. We took the following steps:
    - The studies reported nodule prevalence for males aged >= 10 years, but we needed the prevalence in adult males. Reason: the prevalence in adult males can be translated into mf prevalence levels with the curve from step 5. Therefore, WS Analysed the Murdoch-data (see also step 6) to assess the relationship between the prevalence in the group >= 10 years and >=20 years. The correction factor depended on the overall endemicity level. The estimated correction factor was 1.52 for studies with nodule prevalence levels in adult males below 50% and 1.15 for studies with nodule prevalence levels in adult males >50%.
    - We read the mf prevalence in >= 5 year olds, which belongs to the corresponding nodule prevalence, from the graph from step 5.
Three of the studies did report mf prevalences for ‘wrong’ age groups. In ONCHOSIM, we usually look at the mf prevalence in people \( \geq 5 \) years. Therefore, age-standardization was required. WS used ONCHOSIM to investigate how the mf prevalence changes if we select people \( \geq 5 \) years, \( \geq 10 \) years, or \( \geq 20 \) years, and she calculated correction factors to translate one in the other:

- The prevalence among 5+ is about 1.2 times larger than the prevalence in the whole population.
- The prevalence among 5+ is 0.84-0.86 times lower than the prevalence in 10+.
- The prevalence among 5+ is 0.74 - 0.8 times lower than the prevalence in 20+.

The different studies have also reported the blindness and low vision prevalence for different age groups, while we wanted to have the prevalence in the whole population. Further, the studies had used different methods to assess blindness. Correction was needed if peripheral vision loss was not considered. Also, the studies did not correct for the background prevalence of non-onchocerca related blindness. WS made the following assumptions and corrections:

1. Correction for age: it was assumed that the prevalence in the younger age groups (that were excluded from the studies) was negligible compared to the prevalence in the age-selected study population. We calculated age-correction factors based on a standard population for Sub-Sahara Africa. These factors were 0.685, 0.447 and 0.83, respectively, to calculate the prevalence in the whole population from the prevalence in \( \geq 10 \) year olds, \( \geq 20 \) year olds and \( \geq 5 \) year olds. No correction was done for the study that had examined all individuals aged \( \geq 1 \) year. (NB. We implicitly assumed that there was no under- or oversampling of specific age groups in the studies.)

2. If a study did not measure peripheral vision loss, the prevalence of blindness was multiplied by 4/3, to correct for the 25% of blindness that may have been missed (See ‘The global burden of onchocerciasis 1990’, Remme 2004.)

3. We then subtracted the background prevalence of non-onchocerca related blindness from the calculated prevalence of blindness. An estimate for the background prevalence was obtained from (Resnikoff et al, Bull WHO 2004). This publication estimated the prevalence of all blindness in afr-D +E at 1%, and mentioned that 4% was caused by onchocerciasis. Therefore, we used 0.96% as the background prevalence of non-onchocerca related blindness and subtracted this from the reported/corrected prevalence level. The results was put to zero %, if this calculation would yield values <0%.

- The prevalence levels of low vision were also corrected. Steps 1 and 2 were exactly the same. In step 3, we also used data from (Resnikoff et al, Bull WHO 2004), who estimated the overall prevalence of low vision at 3%. We assumed that – similar to blindness – 4% of this background prevalence was related to onchocerciasis and used a background prevalence for low vision not related to onchocerciasis of 2.88.

**Difficult points:**
- These standardization steps are somewhat tricky. They are based on many assumptions that influence the end results. In a full HIA, the various steps should be discussed in more detail with project members.
- Mf prevalence levels in APOC’s Impact Assessment studies were read from the graph, while elsewhere we used simple formulas. It would be better to standardize this, and use the same equations here.
- Estimates for the background prevalence (not related to onchocerciasis) of blindness and low vision where based on information from whole Africa, including the former OCP area were the disease had been controlled. The proportion of blindness that is caused by onchocerciasis may be higher in areas where onchocerciasis has not been brought under control! However, since we are looking at areas where the less-blinding form of onchocerciasis is most prevalent, we think that the error is not too big.
Annex to 6.1

Below is the input for the ONCHOSIM model as used for this analysis. Most parameters take the same values as in the original standard input file that was developed for Asubende. The parameters that are highlighted and written in bold print have been changed for the current analysis; their values may also differ between runs (see Table 8, section 6.5, section Error! Reference source not found.).

```plaintext
/ *** Input-file for ONCHOSIM ***
/
/ I Demography
/ ------------
/ Number of age-groups (I.1)
/ 7
/ Age group upper limits Life-table (I.3) Fertility (I.4)
/ (I.2) prob. to be dead birthrate per fem.
/ 5 0.196 0.000
/ 10 0.228 0.000
/ 15 0.240 0.109
/ 20 0.260 0.300
/ 30 0.314 0.119
/ 50 0.491 0.119
/ 90 1.000 0.000
/ Nr. of immigration moments
/ 0
/
/
/ II Exposure
/ ---------
/
/ Distance factor (relative biting rate, II.1)
/ 0.40
/ Age- and sex specific relative exposure (II.2)
/ Should this be determined by a standard function ? (1=Y;0=N)
/ 1
/ If Yes
/ Function for males:
/ Funct. no. param(s)
/ 1 0.05 0.0 1.0
/ Function for females:
/ Funct. no. param(s)
/ 1 0.035 0.0 0.7
/
/ Exposure index (II.3, continuous distribution, without mean (=1.0))
/ 0.0 0.0 20.0 4 4.237
/
/
/ III Life history and productivity of the parasite in the human host
/ ---------------------------------------------
/
/ The total lifespan of the female worm (III.1, cont. distr.)
/ Offset Min. Max. Dist. nr. Mean Other param(s)
/ 0.0 0.0 25.0 3 10.0 3.76
/
/ The prepatent period (III.2, cont. distr.)
/ Offset Min. Max. Dist. nr. Mean Other param(s)
/ 0.0 0.0 1.0 0 1.0
/
/ The age-dependent relative mf-production:
/ Number of ages for which R will be specified (III.3)
/ 3
/ Age (time since maturation,III.4) R (potential age-specific productivity, III.5)
/ 0.0 1.00
/ 5.0 1.00
/ 20.0 0.00
/ The longevity of microfilariae (III.6)
/ 9
/ The male:female ratio at inoculation (III.7)
/ 1.0
/
/ The relation between the effective parasite load and the average
```

- 71 -
skin-snip load (III.8)

Function type-param(s)
1 7.6 0.0 -1.0

Distribution of the skin-snip count (discrete distribution, without mean!)
Dist. nr-param(s)
5
5=Poisson (has no parameter)

Distribution of the impact of a productive worm on the skin-snip load (dispersal, mean = 1.0; III.10)
Offset Min. Max. Dist. nr. Param(s) (shape etc.)
0.0 0.0 5.0 2

Duration of mating-cycle Weight of male worms in view of mating (months; III.11) (III.12)
3 1.0

IV Parasite and vector

Daily survival of the fly (IV.2)
0.780

Duration of the gonotrophic cycle:
Number of possible durations (IV.3)
3

Duration (days; IV.4) Probability (IV.5)
3 0.2
4 0.6
5 0.2

Zoophily-fraction (IV.8)
0.04

Season (calendar month) specific monthly biting rates in January to December

Maximum monthly biting rate (IV.9) Nr. of immigrant Infectivity (av. nr L3)
biters (IV.10) of immigrants (IV.11)
2670 0 0.0
2350 0 0.0
1500 0 0.0
1920 0 0.0
1940 0 0.0
1690 0 0.0
2630 0 0.0
3410 0 0.0
3010 0 0.0
3290 0 0.0
3750 0 0.0
2690 0 0.0

Intake of microfilariae by the vector (nr. L1 per bite as a function of the (actual) skin-snip load; IV.12)
Function type-param(s.)
3 1.2 0.0213 0.0861
alternative function
3 0.8 0.044 0.1686

Duration of the development of the L1 to the L3 stage:
Number of possible durations (IV.14)
3

Duration (days; IV.15) Probability (IV.16)
6 0.07
7 0.79
8 0.14

Fraction L1 --> L3 Fraction release per bite (IV.17) Fraction L3 retained per cycle (IV.19)
(incl. sugar feeding)
0.85 0.65 0.90

V Force of infection as a function of L3-release

Number of successful inoculations as a function of the number of L3-larvae released per bite (V):
0.0031
### VI Disease

**Disease threshold of the cumulative relative load (continuous distribution; VI.1)**

<table>
<thead>
<tr>
<th>Offset</th>
<th>Min.</th>
<th>Max.</th>
<th>Distr.</th>
<th>Mean</th>
<th>Other distpar.(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>100000.00</td>
<td>3</td>
<td>1000.0</td>
<td>2.00</td>
</tr>
</tbody>
</table>

**Reduction in life-expectancy due to blindness (100 - %reduction; VI.2)**

<table>
<thead>
<tr>
<th>Offset</th>
<th>Min.</th>
<th>Max.</th>
<th>Distr.</th>
<th>Mean</th>
<th>Other distpar.(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
<td>1</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

### VII Monitoring and control

**Monitoring (VII.1)**

**Timing:**

| Type (VII.1.1) | 0  |

If Type = 0:

<table>
<thead>
<tr>
<th>Starting year</th>
<th>1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final year</td>
<td>2015</td>
</tr>
<tr>
<td>Interval years</td>
<td>1</td>
</tr>
<tr>
<td>Interval months</td>
<td>0</td>
</tr>
</tbody>
</table>

| Number of skin snips per person (VII.1.7) | 2 |

**Ivermectin (VII.2)**

**Timing and coverage of operations:**

<table>
<thead>
<tr>
<th>Number of moments</th>
<th>Fraction of the population excluded from treatment (chronic diseases; VII.2.2)</th>
<th>Compliance model</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

### VII.3

<table>
<thead>
<tr>
<th>year</th>
<th>month</th>
<th>total coverage (fraction; VII.2.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>2001</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>2003</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>2004</td>
<td>1</td>
<td>0.70</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2006</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2007</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2008</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2009</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2010</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2011</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2012</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2013</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>2014</td>
<td>1</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Age- and sex dependent compliance (VII.2.5)**

<table>
<thead>
<tr>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>0.80</td>
<td>0.70</td>
</tr>
<tr>
<td>0.80</td>
<td>0.74</td>
</tr>
<tr>
<td>0.70</td>
<td>0.65</td>
</tr>
<tr>
<td>0.75</td>
<td>0.70</td>
</tr>
<tr>
<td>0.80</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Instantaneous effect of the drug (reduction of the relative load; VII.2.6).** Should be specified as the percentage of the pre-treatment skin load.

<table>
<thead>
<tr>
<th>Offset</th>
<th>Min.</th>
<th>Max.</th>
<th>Distr.</th>
<th>Mean</th>
<th>Other distpar.(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

**Variability in the effect of treatment (Mean must be 1.0; VII.2.7)**

<table>
<thead>
<tr>
<th>Offset</th>
<th>Min.</th>
<th>Max.</th>
<th>Distr.</th>
<th>Mean</th>
<th>Other distpar.(s.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>20.0</td>
<td>3</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Recovery period Shape recovery Frac. malabsorption
(VII.2.8) function (VII.2.10)
(VII.2.9)  
0.875 1.483 0.05
Systematic reduction Macrofilaricidal effect: Frac. of parasites killed
(VII.2.11) 1. Frac. reduction (VII.2.12) life-expectancy (VII.2.13)
0.0 0.0 0.25

Larviciding (VII.3)

Timing:
Number of larviciding periods (VII.3.1)
1
Starting Stopping Coverage
Year Month Year Month (%)
2016 1 2017 1 100.0

VIII Miscellaneous

Starting year of the simulation (VIII.1)
1870
Stopping year of the simulation (VII.2)
2015
Initial /force of Infection
Duration (months; VIII.3) Strength (VIII.4)
90 4.0
Select a cohort? (Yes = 1, No = 0; VIII.5)
0
If yes; age from (year month) to (year month)
0 1970 1 1995 1
Sample-fraction for auto-sample (VIII.7) Max. population allowed
0.90 400
Simulation label (start in position 1; VIII.8)
Asubende_ivermectin

Initial population (VIII.9)

Males Females
3 3
4 4
2 2
2 2
3 3
5 5
3 3

Number of age-groups for the output-tables
7
Age-group upper limits
5
10
15
20
30
50
999
Standard population for the above age-groups
0 0
1769 1507
1739 1465
1085 921
1409 1738
2388 2821
1208 1237
Skin-snip count categories (enter 9 increasing classes, first is always 0)
0.5
2
4
8
16
32
64
128
/ some specifications for screen output
/ screen-output color   X-range subdiv. freq   start-
/ (1=Y;0=N)   (1=Y;0=N)   (years) X-axis (months) year
1   1   40   8   6   1970
/ plot indices (0=no, 1=yes)
/ indices: 1 = CMFL, 2 = mf-prev., 3 = mf-prev adults,
/ 4 = prev. bl. adults (x2), 5 = prev. adult female worms.
1 1 1 1 1