World Health Organization

APOC

WHO/MG/15.20

Report of the consultative meetings on

# Strategic Options and Alternative Treatment Strategies for Accelerating Onchocerciasis Elimination in Africa

**African Programme for Onchocerciasis Control**

**(APOC)**

**December 2015**

## Table of Contents

## Table of Tables and Figures

## Abbreviations and Definition of Terms

| | |
|---|---|
| ATS | Alternative Treatment strategy |
| ALB | Albendazole |
| APOC | African Programme for Onchocerciasis Control |
| a CDTI | Annual Community Directed Treatment with Ivermectin |
| A-WOL compound | Antibiotic effective against Wolbachia |
| Bi-CDTI | Biannual Community Directed Treatment with Ivermectin |
| CDD | Community drug distributors |
| CDTI | Annual Community Directed Treatment with Ivermectin |
| CMFL | Community Microfilarial Load, measure of intensity of infection of a community, calculated as the geometric mean of the number of microfilaria/snip in a cohort of >20 year old adults [1]. |
| CNTD | Center for Neglected Tropical Disease |
| aCDTM | Annual Community directed Treatment with Moxidectin |
| bCDTM | Biannual Community Directed Treatment with Moxidectin |
| DEC | Diethylcarbamazine |
| DNDi | Drug for Neglected Diseases initiative |
| DOLF | 'Death to Oncho and LF', Research project to optimize MDA for elimination of LF and onchocerciasis and to study the impact of MDA for LF on Soil Transmitted Helminths |
| CSA | Committee of Sponsoring Agency |
| CSA AGE | CSA Advisory Group on Elimination |
| IEC | Information, Education, Communication |
| JAF | Joint Action Forum |
| IVM | Ivermectin |
| LF | Lymphatic Filariasis |
| MDA | Mass Drug Administration |
| MEC | Mectizan Expert Committee |
| mf prevalence | Prevalence of people with levels of skin microfilariae detectable with skin snips (in most studies in Africa, this is determined based on 2 iliac crest skin snips taken with a 2 mm Holth punch, incubated for 24 hours in physiological saline for negative skin snips, and examined microscopically) |
| NGDO | Non-governmental Development Organisation |
| Nodule prevalence | Prevalence of people with palpable nodules |
| NTD | Neglected Tropical Diseases |

| | |
|---|---|
| OCP | Onchocerciasis Control Programme in West Africa |
| Phase 1a evaluation | Assessment of the decline towards the 'elimination breakpoint' via the prevalence of people with detectable levels of skin microfilariae and comparison of the prevalence with that predicted by ONCHOSIM for the applicable pre-endemicity levels and CDTI treatment coverage. [2] |
| Phase 1b evaluation | Confirmation that 'elimination breakpoint' has been reached and treatment can be stopped based on determination of the prevalence of people with detectable levels of skin microfilariae in survey villages along the main rivers and affluents at a distance of no more than 20-30 km between villages and vector infectivity rate determined in at least 10,000 flies collected throughout a full rainy season from a limited number of high risk locations along the principal rivers near major breeding sites of the vector. [2] |
| Provisional thresholds for stopping treatment ('elimination breakpoint') | < 5% prevalence of people with detectable levels of skin microfilariae in all surveyed villages AND<br>< 1% prevalence of people with detectable levels of skin microfilariae in 90% of surveyed villages AND<br>< 0.5 infective flies per 1000 flies. [2]<br>Provisional thresholds for stopping treatment and initiating post-treatment surveillance are based on the experiences with cessation of Onchocerciasis control in West Africa (vector control in the OCP area and CDTI in Senegal and Mali) and the methodology used (determination of prevalence of infection with 2 iliac crest skin snips obtained with a 2 mm Holth punch, incubated for 30 minutes in distilled water and an additional 24 hours in physiological saline for negative skin snips, and examined microscopically; pool screening of flies with pool size 300) [2,3]<br>(it is recognized that these do not represent 'breakpoints' in the classical sense) |
| RAPLOA | Rapid assessment of Loa loa prevalence [4]<br>RAPLOA prevalence: prevalence of eye-worm history determined via RAPLOA. |
| REMO | Rapid epidemiological mapping of onchocerciasis [5] |
| T&T | Test and Treat |
| TBS | Thick blood smear |
| TCC | Technical Consultative Committee of APOC |
| Transmission zone | A geographical area where transmission of *O. volvulus* occurs by locally breeding vectors and which can be regarded as a natural ecological and epidemiological unit for interventions [2] |
| Tx Cov | Treatment coverage, % of population which took ivermectin in a given treatment round |

| | |
|---|---|
| Year of achieving elimination | Year in which the 3-year period of surveillance following cessation of treatment ends and certification of elimination can be requested [2] |
| SAE, SAR | Serious Adverse Event, Serious Adverse Reaction (i.e. response to a drug):<br>any untoward medical occurrence that at any dose:<br>- results in death,<br>- is life-threatening,<br>- requires inpatient hospitalisation or prolongation of existing hospitalisation,<br>- results in persistent or significant disability/incapacity, or<br>- is a congenital anomaly/birth defect.<br>Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. [6] |
| WHO | World Health Organization |

# 1 Introduction

**Elimination of onchocerciasis as a public health problem in Africa.** The fight against onchocerciasis started in Africa in the 1950s with initial research and pilot programs. Significant milestones in this fight included the launch of the Onchocerciasis Control Programme in West Africa (OCP) in 1974 [7,8], the registration of ivermectin (Mectizan®) for use in onchocerciasis and Merck's decision to donate ivermectin to control onchocerciasis for as long as needed in the quantities needed in 1987 [9], and the launch of the African Programme for Onchocerciasis Control (APOC) for the countries not included in the OCP area in 1995 [10-12].

At its closure in 2002, OCP had achieved elimination of onchocerciasis as a public health problem in the majority of its programme area through larviciding based vector control, complemented later on with mass administration of ivermectin [7,8].

APOC was launched to (i) establish within a period of 12-15 years, effective and sustainable community-directed treatment with ivermectin (CDTI) with the aim to eliminate onchocerciasis as a disease of public health and socio-economic importance and (ii) eradicate the vector in selected and isolated foci.

By the end of 2013, around 100.7 million people in 132,919 communities were receiving ivermectin [13]. In 2014, the number of people receiving ivermectin had increased to around 112.5 million people, despite the fact that no treatments occurred in Liberia and Sierra Leone, due to the Ebola outbreak [14].

Onchocerciasis control in Africa faces significant challenges, which range from the large number of endemic countries and >100 million people living in meso- or hyperendemic areas in the APOC countries [15], via the remoteness of many areas to conflict interrupting control programme implementation. Despite these challenges, OCP and APOC have eliminated onchocerciasis as a public health problem in the majority of endemic areas in Africa preventing morbidity in hundreds of millions of people [16-19] and allowing to reclaim fertile lands for agriculture [20,21]. This conclusion is further supported by direct evidence obtained through an impact assessment study conducted by APOC [16] and the results of modelling studies [17,18,22].

**Shifting the goal post: from elimination of onchocerciasis as a public health problem to elimination of onchocerciasis.** A study initiated in 2005 in two hyperendemic foci in the Bakoye and Faleme foci (in Mali and Senegal) showed that 15-17 years of annual CDTI had led to elimination of onchocerciasis infection and interruption of parasite transmission [3,23]. Encouraged by these results, the Joint Action Forum (JAF) decided that APOC should take on the additional objectives of developing the evidence base to determine when and where ivermectin treatment can be stopped, and providing guidance to countries on how to prepare for, effect, and evaluate the cessation of treatment [24].

In 2010, APOC developed a 'Conceptual and Operational Framework for Onchocerciasis Elimination with Ivermectin Treatment' [2]. Between 2008 and 2015, 58 CDTI project areas underwent the 'Phase 1a' epidemiological evaluations (see 'Abbreviations and Definition of Terms', page 4) according to this framework [25,26]. In 88% of these areas, progress was as or even better than predicted by the ONCHOSIM mathematical model (see section 6), supporting the conclusion from the study in Mali and Senegal that annual CDTI can lead to interruption of *O. volvulus* transmission.

The report of the 2010 Mid-term Evaluation of APOC submitted to the 16th meeting of the Joint Action Forum (JAF16) of APOC in 2010 pointed to mounting evidence that many years of annual CDTI may have interrupted parasite transmission in many areas in Africa.[1] In 2011, the Advisory Group on Elimination to the Committee of Sponsoring Agencies (CSA) of APOC conducted a detailed analysis of pre-treatment endemicity, ivermectin treatment history and data on progress towards elimination of onchocerciasis infection and interruption of transmission in APOC project areas, where available. The results were combined with projections from modelling studies to estimate for each APOC project area the year when CDTI could be stopped. The group concluded that numerous areas in different countries are expected to have achieved elimination by 2015, but that country-wide elimination will not be achieved by 2015 in any country. However, if APOC was prolonged to 2020, 23 APOC and OCP countries were predicted to be able to stop CDTI in the last onchocerciasis endemic focus by 2017 and complete 3 years of post-treatment surveillance, i.e. have achieved elimination, by 2020. This gave the impetus for targeting elimination of onchocerciasis in APOC as well as OCP countries and inclusion of elimination of onchocerciasis in selected countries in Africa by 2020 among the WHO targets for elimination and eradication of neglected tropical diseases 2015-2020 [27]. In 2012, the Joint Action Forum of APOC set the target at elimination in 80% of African countries by 2025 [28].

**Accelerating progress towards elimination of onchocerciasis**

Since then additional data have become available which support the hypothesis that annual CDTI can eliminate onchocerciasis in large areas of Africa (see above, [14,19,29-32]).

Further support for the feasibility of elimination comes from mathematical simulation models. The modelling results highlight that the efforts required to achieve elimination depend strongly on local transmission conditions [33-35]. Scenarios and timelines for control, elimination and even eradication of onchocerciasis in Africa have been developed [36].

Elimination by 2025 requires that the criteria for stopping treatment are met latest in 2022 to allow for the confirmation of elimination three years later [2]. To achieve elimination of onchocerciasis in at least 80% of onchocerciasis endemic African countries by 2025, the reduction in transmission has to be accelerated in areas for which currently available data suggest that the criteria for stopping CDTI will not be reached by 2022.

Acceleration of the reduction in transmission can be achieved either by improving the implementation of annual CDTI, notably increasing CDTI treatment coverage, or by using alternative treatment strategies (ATS) where CDTI cannot be implemented effectively (in particular in areas co-endemic for loiasis), or CDTI effectiveness is considered sub-optimal.

## 2 Scope of this document

APOC conducted a series of consultative workshops with national control programme managers, representatives of NGDOs and other organisations involved in or supporting onchocerciasis control activities, scientists with expertise in different types of ATS currently available or under development, and experts in modelling the impact of interventions on *O. volvulus* transmission. The objective was obtain advice on the identification of areas which

[1] http://www.who.int/entity/apoc/MidtermEvaluation_29Oct2010_final_printed.pdf

require improved implementation of CDTI, areas for which country managers should consider ATS, the different types of ATS available and prerequisites for their successful implementation. The outcomes of these consultations were reviewed by TCC38 and TCC39 which strongly endorsed the conclusions. These were included in the 2015 WHO/APOC Progress report presented to the last meeting of the JAF.

This document provides additional details, the results of analyses conducted with the data which became available after the consultations and includes references to relevant information sources. It is designed to provide countries with the basis for the considerations needed to decide where and how to improve onchocerciasis control programmes to accelerate progress towards elimination of onchocerciasis.

# 3 Identification of areas requiring optimized implementation of CDTI or ATS to accelerate progress towards onchocerciasis elimination

## 3.1 Characteristics of areas requiring optimized CDTI implementation or ATS

Data acquired by APOC and the countries on pre-control endemicity levels, CDTI treatment history, as well as data on progress towards elimination from Phase 1a and Phase 1b epidemiological and entomological evaluations (see Abbreviations and Definition of Terms, page 4, where available, were reviewed. The model ONCHOSIM (see section 6) was used to estimate the year CDTI could be stopped in each APOC project area if CDTI is continued with the treatment coverage reported by the project over the last 3 years.

Based on this analysis, onchocerciasis endemic areas which require optimized CDTI or implementation of ATS to accelerate progress towards elimination, have one or more of the characteristics shown in Table 1.

**Table 1 Characteristics of onchocerciasis endemic areas that may require optimized CDTI implementation and/or ATS**

| **Area characteristics** | |
|---|---|
| **1.** | **Areas in which CDTI has not yet been initiated or was initiated only in 2014 or 2015** |
| 1a. | Hypoendemic areas in which transmission is not dependent on neighbouring meso/ hyperendemic areas |
| 1b. | Meso- or hyperendemic areas without CDTI for programmatic or non-programmatic reasons or only recently identified as needing treatment |
| **2.** | **Areas with ongoing CDTI not predicted to achieve elimination by 2025** |
| 2a. | Areas with very high vector density and/or pre-control endemicity (Nodule prevalence > 70% or CMFL > 70 mf/snip) |
| 2b. | Areas with ≤ 70% nodule prevalence or CMFL ≤ 70 mf/snip not expected by 2025 in view of year of start of CDTI and required duration of annual CDTI |
| 2c. | Areas where the average reported therapeutic coverage over the last 3 years is insufficient to achieve elimination by 2025 in view of pre-control endemicity, start of CDTI with full geographic coverage and required duration of annual CDTI |
| 2d. | Areas in which the Phase 1a and/or Phase 1b epidemiological or entomological surveys conducted by APOC and the countries indicate that in at least one area of the transmission zone the residual prevalence is higher than needed for elimination to be achieved by 2025. |

## 3.2 Areas requiring optimized CDTI implementation or ATS to accelerate progress towards elimination

For each country, onchocerciasis endemic areas meeting at least one of these characteristics are listed in Table 2. Table 3 provides an estimate of the 2015 population in these areas. It is important to note that both tables reflect current data and need to be updated as additional data become available.

**Table 2 Projects/areas not included in CDTI or with ongoing CDTI but unlikely to achieve elimination by 2025 without optimized CDTI or ATS**

| Country | Project/ District Name [1] | Population 2015 | Area classification as per Table 1[2] | |
|---|---|---|---|---|
| **Areas in which CDTI has not yet been initiated or with ongoing annual CDTI** | | | | |
| **Angola** | P5Angola | 267,844 | 1a* | Untreated hypoendemic area* |
| **Angola** | NY Benguela | 116,100 | 1b | Untreated meso/hyperendemic area |
| **Angola** | Uige | 193,601 | 1b | Untreated meso/hyperendemic area |
| **Cameroon** | P20Cameroon | 166,364 | 1b* | Untreated meso/hyperendemic area* |
| **Cameroon** | Western | 1,809,161 | 2a | Very high endemicity level |
| **Cameroon** | Littoral 1 | 309,898 | 2c | Insufficient treatment coverage |
| **Cameroon** | Centre 1 | 472,128 | 2d | Inadequate progress to elimination |
| **Cameroon** | Littoral 2 | 165,320 | 2d | Inadequate progress to elimination |
| **CAR** | P5CAR | 146,273 | 1a* | Untreated hypoendemic area* |
| **CAR** | P20CAR | 64,396 | 1b* | Untreated meso/hyperendemic area* |
| **CAR** | Region 5 | 509,165 | 2b | Treatment end date > 2022 |
| **CAR** | Region 6 East | 391,772 | 2b | Treatment end date > 2022 |
| **Congo** | P20Congo | 39,901 | 1b* | Untreated meso/hyperendemic area* |
| **Cote d`Ivoire** | Cavaly Upper Nzo | 237,793 | 2d | Inadequate progress to elimination |
| **DRC** | P5DRC | 7,755,918 | 1a* | Untreated hypoendemic area* |
| **DRC** | P20DRC | 2,439,010 | 1b* | Untreated meso/hyperendemic area* |
| **DRC** | NY Lualaba | 1,019,358 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Masisi-Walikale | 56,585 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Rutshuru-Ngoma | 8,808 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Sankuru | 486,324 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Ueles | 165,447 | 1b | Untreated meso/hyperendemic area |
| **DRC** | Ituri-Nord | 1,300,848 | 2a | Very high endemicity level |
| **DRC** | Ituri-Sud | 1,189,112 | 2a | Very high endemicity level |
| **DRC** | Katanga-Nord | 649,132 | 2a | Very high endemicity level |
| **DRC** | Katanga-Sud | 719,004 | 2a | Very high endemicity level |
| **DRC** | Masisi-Walikale | 1,085,812 | 2a | Very high endemicity level |
| **DRC** | Mongala | 1,509,864 | 2a | Very high endemicity level |
| **DRC** | Tshopo | 1,652,750 | 2a | Very high endemicity level |
| **DRC** | Ubangi-Nord | 829,146 | 2a | Very high endemicity level |
| **DRC** | Ueles | 1,631,034 | 2a | Very high endemicity level |
| **DRC** | Lualaba | 233,221 | 2b | Treatment end date > 2022 |
| **DRC** | Bas-Congo Kinshasa | 1,556,831 | 2c | Insufficient treatment coverage |
| **DRC** | Butembo-Beni | 967,353 | 2c | Insufficient treatment coverage |

| Country | Project/ District Name [1] | Population 2015 | Area classification as per Table 1[2] | |
|---|---|---|---|---|
| **DRC** | Lubutu | 346,439 | 2c | Insufficient treatment coverage |
| **DRC** | Tshuapa | 1,472,510 | 2c | Insufficient treatment coverage |
| **DRC** | Ubangi-Sud | 1,398,580 | 2c | Insufficient treatment coverage |
| **DRC** | Sankuru | 1,106,393 | 2d | Inadequate progress to elimination |
| **Gabon** | P5Gabon | 85,916 | 1a* | Untreated hypoendemic area* |
| **Nigeria** | Cross River | 1,383,685 | 2d | Inadequate progress to elimination |
| **Nigeria** | Kogi | 1,977,483 | 2d | Inadequate progress to elimination |
| **South Sudan** | P5SouthSudan | 832,477 | 1a* | Untreated hypoendemic area* |
| **South Sudan** | P20SouthSudan | 30,243 | 1b* | Untreated meso/hyperendemic area* |
| **South Sudan** | West Bahr El Ghazal | 3,255,512 | 2c | Insufficient treatment coverage |
| **South Sudan** | West Equatoria | 767,891 | 2c | Insufficient treatment coverage |
| **Tanzania** | Morogoro | 361,040 | 2d | Inadequate progress to elimination |
| **Uganda** | Phase 3 (Rukungiri, Nebbi, Arua, Mbarara) | 1,564,433 | 2a | Very high endemicity level |
| **Areas with ongoing biannual CDTI** | | | | |
| **Ethiopia** | Kamashi | 496,800 | 1b | Untreated meso/hyperendemic area |
| **Uganda** | Phase 5 (Pader, Kitgum, Lamwo) | 570,199 | 2b | Treatment end date > 2022 |

* Areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTi before decisions on any onchocerciasis control strategy to be implemented.

[1] P5: areas with a kriging predicted prevalence of 5-20% not currently covered by CDTI

[1] 20: areas with a kriging predicted prevalence of >20% not currently covered by CDTI

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

**Table 3 Population in 2015 in areas currently not included in CDTI or with ongoing CDTI but unlikely to achieve elimination by 2025 without optimized CDTI or ATS**

| | 1a* Untreated hypoendemic areas | 1b Untreated meso/hyper endemic areas | 1b* Untreated meso/hyper endemic areas[2] | 2a Very high endemicity level | 2b Treatment end date >2022 | 2c Insufficient treatment coverage | 2d Inadequate progress to elimination | Total |
|---|---|---|---|---|---|---|---|---|
| **Angola** | 267,844 | 309,701 | | | | | | **577,545** |
| **Cameroon** | | | 166,364 | 1,809,161 | | 309,898 | 637,448 | **2,922,870** |
| **CAR** | 146,273 | | 64,396 | | 900,937 | | | **1,111,606** |
| **Congo** | | | 39,901 | | | | | **39,901** |
| **Cote d`Ivoire** | | | | | | | 237,793 | **237,793** |
| **DRC** | 7,755,918 | 1,736,522 | 2,439,010 | 10,566,701 | 233,221 | 5,741,713 | 1,106,393 | **29,579,478** |
| **Ethiopia** | | 496,800 | | | | | | **496,800** |
| **Gabon** | 85,916 | | | | | | | **85,916** |
| **Nigeria** | | | | | | | 3,361,167 | **3,361,167** |
| **South Sudan** | 832,477 | | 30,243 | | | 4,023,403 | | **4,886,123** |
| **Tanzania** | | | | | | | 361,040 | **361,040** |
| **Uganda** | | | | 1,564,433 | 570,199 | | | **2,134,632** |
| **Total** | **9,088,426** | **2,543,022** | **2,739,915** | **13,940,295** | **1,704,357** | **10,075,014** | **5,703,842** | **45,794,870** |

* Areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTI before decisions on the onchocerciasis control strategy to be implemented.

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

## 3.3 Areas requiring special considerations

### 3.3.1 Hypoendemic areas excluded from CDTI when APOC pursued elimination of onchocerciasis as a public health problem

When APOC was launched, CDTI treatment areas were delineated to ensure that all areas with significant risk of onchocercal disease, i.e. with > 20% prevalence of nodules in adult males, are included in CDTI. To achieve the new objective of elimination of onchocerciasis transmission, control programmes now need to cover all areas with sustained local transmission.

#### 3.3.1.1 APOC guidance on revising ivermectin treatment boundaries

In March 2012, APOC brought together national onchocerciasis and lymphatic filariasis control programme coordinators from 10 APOC countries, onchocerciasis experts and public health officials to discuss methods for identifying areas not included in CDTI which need interventions to achieve onchocerciasis elimination. Following discussions of the resulting recommendations with the TCC in September 2012, APOC provided guidance on how to assess the need for implementation of onchocerciasis control in those areas where the nodule prevalence was <20% during the initial REMO surveys, and which are not included in ongoing CDTI projects: the 'APOC Guidelines for revising ivermectin treatment boundaries

within the context of onchocerciasis elimination'. They are provided as an Annex to this report.

#### 3.3.1.2 Results of surveys of hypoendemic areas to assess their need for treatment

APOC identified 14 countries in which the need for treatment in areas classified as hypoendemic during the initial REMO needed to be evaluated. APOC initiated these evaluations between 2013 and 2015 in all countries other than Mozambique.

Table 4 shows the results of the epidemiological evaluation via skin snips conducted in 13 different areas categorized as hypo-endemic based on the original rapid epidemiological mapping (REMO) [5,15] and not included in CDTI.

In 9 of these areas, prevalence was too low to justify the assumption that the infections are due to local transmission requiring onchocerciasis control in these areas. In one area, the prevalence was significantly higher than the available REMO data had suggested.

#### 3.3.1.3 Conclusions for decisions on need of interventions in areas characterized as hypoendemic based on the initial REMO

The analysis of the evaluation data resulted in the conclusion that current infection prevalence may be significantly higher than the original REMO surveys suggested or may be substantially lower, possibly due to the impact of CDTI on transmission in neighbouring areas.

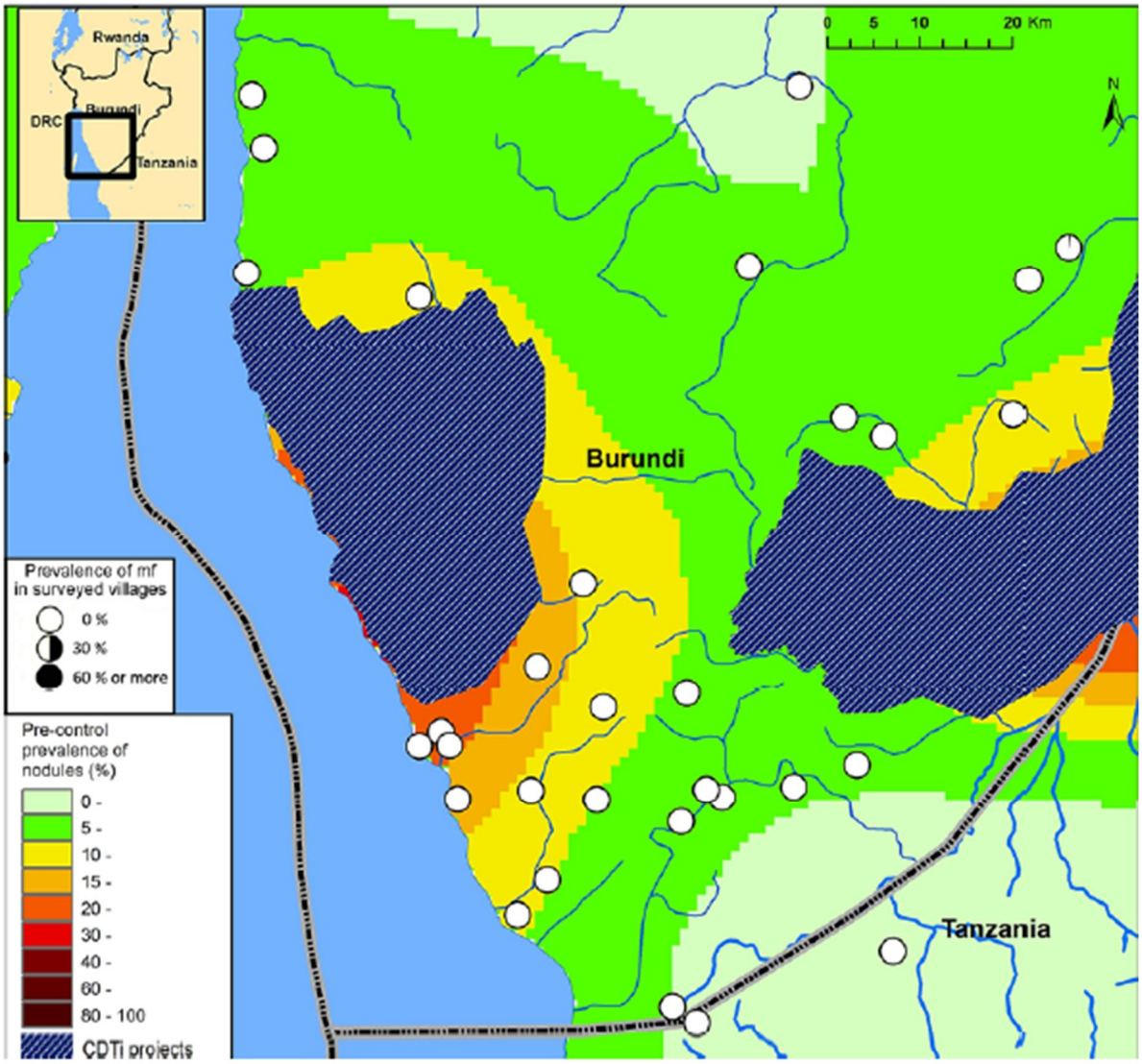
An example is provided in Figure 1 which shows the results of the surveys in Burundi. They are superimposed on the contour map of pre-control nodule prevalence and the CDTI treatment areas. Even in areas in which pre-control nodule prevalence was >10% and which were not included in CDTI, the proportion of people with detectable levels of skin microfilariae was now zero.

Consequently, decisions on whether or not to initiate control activities in areas considered hypoendemic based on the initial REMO surveys should always be informed by new epidemiological evaluations.

**Table 4 Results of epidemiological evaluation of hypoendemic areas to assess current *O. volvulus* infection prevalence**

| | Villages surveyed | Persons examined | Number mf positive | Percentage mf positive | Probability that area prevalence exceeds 1.4% | Probability that maximum sample stratum prevalence exceeds 5% | Conclusion |
|---|---|---|---|---|---|---|---|
| **Burundi and neighbouring areas in Tanzania and DRC** | 48 | 10,912 | 7 | 0.1 | 0.00 | 0.05 | No treatment needed |
| **Chad** | 32 | 9,416 | 1 | 0.0 | 0.00 | 0.00 | No treatment needed |
| **Congo North** | 15 | 1,171 | 1 | 0.1 | 0.00 | 0.01 | No treatment needed |
| **Equatorial Guinea** | 66 | 3,285 | 0 | 0.0 | 0.00 | 0.00 | No treatment needed |
| **Ethiopia North** | 10 | 1,709 | 0 | 0.0 | 0.00 | 0.00 | No treatment needed |
| **Ethiopia Gurage Shewa** | 16 | 2,723 | 4 | 0.1 | 0.00 | 0.03 | No treatment needed |
| **Ethiopia Gojam** | 15 | 2,886 | 7 | 0.2 | 0.00 | 0.02 | No treatment needed |
| **Ethiopia South** | 32 | 4,680 | 0 | 0.0 | 0.00 | 0.05 | No treatment needed |
| **DRC/Congo Bas Congo** | 12 | 1,357 | 7 | 0.5 | 0.00 | 0.36 | No treatment needed |
| **Cameroon South** | 31 | 5,469 | 108 | 2.0 | 1.00 | 1.00 | Borderline. Follow-up surveillance |
| **DRC Bandudu** | 11 | 1,630 | 103 | 6.3 | 1.00 | 1.00 | Include in Bandudu CDTi project |
| **Gabon** | 87 | 6,653 | 629 | 9.5 | 1.00 | 1.00 | Treatment needed |
| **Angola centre** | 29 | 5,733 | 757 | 13.2 | 1.00 | 1.00 | Treatment needed |

**Figure 1: Contour map of pre-control prevalence of nodules, areas covered by CDTI and results of epidemiological surveys conducted to assess the need for interventions in hypoendemic areas in Burundi**




#### 3.3.1.4 Methods for assessing prevalence of infection in hypoendemic areas

The 'APOC Guidelines for revising ivermectin treatment boundaries within the context of onchocerciasis elimination' recommend that two skin biopsies (skin snips, one from each iliac crest) are used to assess the prevalence of patent infections.

Information on other methods to assess the prevalence of infection is provided in section 4.4.5. Decisions on which method to use and in which population to use it, need to take into account the prior ivermectin treatment history and the objectives of the evaluation (post treatment surveillance or identification of areas to be treated).

### 3.3.2 *Loa loa* co-endemic areas

In *Loa loa* co-endemic areas, both the level of onchocerciasis and the level of loiasis endemicity need to be taken into account for decisions on the onchocerciasis control strategy to be implemented. CDTI is justified only where onchocerciasis is meso- or

hyperendemic due to the risk of serious adverse reactions to ivermectin in those with high intensity of infection with *Loa loa* [4,37-39]. The precautions to be taken for implementation of ivermectin treatment in loiasis co-endemic areas depend on the level of loiasis endemicity. The Technical Consultative Committee (TCC) of APOC and the Mectizan Expert Committee (MEC) have specified two different strategies to be employed: strategy 1 for areas with RAPLOA prevalence is ≥40 % (*Loa loa* microfilaria prevalence ≥20%) and strategy 2 for areas with RAPLOA prevalence <40% ((*Loa loa* microfilaria prevalence ≥20%) [4,38,39]. The TCC and MEC recommendations are provided as an Annex to this report.

Table 5 and Table 6 extract from the areas shown in Table 2 and Table 3 those areas where the krigging analysis predicted maximum RAPLOA prevalence is ≥40% [4]. Table 7 and Table 8 extract from the areas shown in Table 2 and Table 3 those areas where loiasis is endemic, but where the krigging analysis predicted maximum RAPLOA prevalence is <40% [4].

Prior to decisions on what strategy to implement, the data obtained during the RAPLOA surveys should be consulted. The Mectizan Donation Programme and the MEC require data on loiasis prevalence and details on the treatment strategy to be implemented for approval of ivermectin provision.

**Table 5 Projects/areas with krigging analysis predicted RAPLOA prevalence ≥40% unlikely to achieve elimination by 2025 without optimized CDTI or ATS**

| | Project/ District Name [1] | Population 2015 | Area classification as per Table 1[2] | |
|---|---|---|---|---|
| **Areas in which CDTI has not yet been initiated or was initiated only in 2014 or 2015** | | | | |
| **Angola** | P5Angola | 267,844 | 1a* | Untreated hypoendemic area* |
| **Angola** | Uige | 193,601 | 1b | Untreated meso/hyperendemic area |
| **Cameroon** | P20Cameroon | 166,364 | 1b* | Untreated meso/hyperendemic area* |
| **CAR** | P5CAR | 146,273 | 1a* | Untreated hypoendemic area* |
| **CAR** | P20CAR | 64,396 | 1b* | Untreated meso/hyperendemic area* |
| **DRC** | P5DRC | 7,755,918 | 1a* | Untreated hypoendemic area* |
| **DRC** | NY Ueles | 165,447 | 1b | Untreated meso/hyperendemic area |
| **DRC** | P20DRC | 2,439,010 | 1b* | Untreated meso/hyperendemic area* |
| **Gabon** | P5Gabon | 85,916 | 1a* | Untreated hypoendemic area* |
| **South Sudan** | P5SouthSudan | 832,477 | 1a* | Untreated hypoendemic area* |
| **South Sudan** | P20SouthSudan | 30,243 | 1b* | Untreated meso/hyperendemic area* |
| **Areas with CDTI initiated before 2014 which require optimized CDTI or ATS to accelerate progress towards elimination** | | | | |
| **Cameroon** | Western | 1,809,161 | 2a | Very high endemicity level |
| **Cameroon** | Littoral 1 | 309,898 | 2c | Insufficient treatment coverage |
| **Cameroon** | Centre 1 | 472,128 | 2d | Inadequate progress to elimination |
| **Cameroon** | Littoral 2 | 165,320 | 2d | Inadequate progress to elimination |
| **CAR** | Region 6 East | 391,772 | 2b | Treatment end date > 2022 |
| **DRC** | Ituri-Sud | 1,189,112 | 2a | Very high endemicity level |
| **DRC** | Masisi-Walikale | 1,085,812 | 2a | Very high endemicity level |

| | Project/ District Name [1] | Population 2015 | Area classification as per Table 1[2] | |
|---|---|---|---|---|
| **DRC** | Mongala | 1,509,864 | 2a | Very high endemicity level |
| **DRC** | Tshopo | 1,652,750 | 2a | Very high endemicity level |
| **DRC** | Ubangi-Nord | 829,146 | 2a | Very high endemicity level |
| **DRC** | Ueles | 1,631,034 | 2a | Very high endemicity level |
| **DRC** | Bas-Congo Kinshasa | 1,556,831 | 2c | Insufficient treatment coverage |
| **DRC** | Lubutu | 346,439 | 2c | Insufficient treatment coverage |
| **DRC** | Ubangi-Sud | 1,398,580 | 2c | Insufficient treatment coverage |
| **DRC** | Sankuru | 1,106,393 | 2d | Inadequate progress to elimination |
| **South Sudan** | West Equatoria | 767,891 | 2c | Insufficient treatment coverage |

* Areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTi before decisions on any onchocerciasis control strategy to be implemented.

[1] P5: areas with a kriging predicted prevalence of 5-20% not currently covered by CDTI

[1] P20: areas with a kriging predicted prevalence of >20% not currently covered by CDTI

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

**Table 6 Population in 2015 in projects/areas with krigging predicted RAPLOA prevalence ≥40%**

| | 1a* Untreated hypo-endemic areas | 1b Untreated meso/hyper endemic areas | 1b* Untreated meso/hyper endemic areas[2] | 2a Very high endemicity level | 2b Treatment end date > 2022 | 2c Insufficient treatment coverage | 2d Inadequate progress to elimination | Total |
|---|---|---|---|---|---|---|---|---|
| **Angola** | 267,844 | 193,601 | | | | | | 461,444 |
| **Cameroon** | | | 166,364 | 1,809,161 | | 309,898 | 637,448 | 2,922,870 |
| **CAR** | 146,273 | | 64,396 | | 391,772 | | | 602,441 |
| **DRC** | 7,755,918 | 165,447 | 2,439,010 | 7,897,718 | | 3,301,850 | 1,106,393 | 22,666,335 |
| **Gabon** | 85,916 | | | | | | | 85,916 |
| **South Sudan** | 832,477 | | 30,243 | | | 767,891 | | 1,630,611 |
| **Total** | 9,088,426 | 359,048 | 2,700,014 | 9,706,879 | 391,772 | 4,379,638 | 1,743,841 | 28,369,617 |

* Potential ATS areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTi before decisions on any onchocerciasis control strategy to be implemented.

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

**Table 7 Projects/areas with krigging analysis predicted maximum RAPLOA prevalence <40% unlikely to achieve elimination by 2025 without optimized CDTI or ATS**

| | Project/ District Name [1,3] | Population 2015 | Area classification as per Table 1[2] | |
|---|---|---|---|---|
| **Areas in which CDTI has not yet been initiated or was initiated only in 2014 or 2015** | | | | |
| **Congo** | P20Congo | 39,901 | 1b* | Untreated meso/hyperendemic area* |
| **DRC** | NY Lualaba | 1,019,358 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Masisi-Walikale | 56,585 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Rutshuru-Goma | 8,808 | 1b | Untreated meso/hyperendemic area |
| **DRC** | NY Sankuru | 486,324 | 1b | Untreated meso/hyperendemic area |
| **Areas with CDTI initiated before 2014 which require optimized CDTI or ATS to accelerate progress towards elimination** | | | | |
| **CAR** | Region 5 | 509,165 | 2b | Treatment end date > 2022 |
| **DRC** | Ituri-Nord | 1,300,848 | 2a | Very high endemicity level |
| **DRC** | Katanga-Nord | 649,132 | 2a | Very high endemicity level |
| **DRC** | Katanga-Sud | 719,004 | 2a | Very high endemicity level |
| **DRC** | Lualaba | 233,221 | 2b | Treatment end date > 2022 |
| **DRC** | Butembo-Beni | 967,353 | 2c | Insufficient treatment coverage |
| **DRC** | Tshuapa | 1,472,510 | 2c | Insufficient treatment coverage |
| **Nigeria** | Cross River | 1,383,685 | 2d | Inadequate progress to elimination |
| **Nigeria** | Kogi | 1,977,483 | 2d | Inadequate progress to elimination |
| **South Sudan** | West Bahr El Ghazal | 3,255,512 | 2c | Insufficient treatment coverage |
| **Uganda** | Phase 3 | 1,564,433 | 2a | Very high endemicity level |
| **Uganda** | Phase 5 | 570,199 | 2b | Treatment end date > 2022 |

* Areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTi before decisions on any onchocerciasis control strategy to be implemented.

[1] P5: areas with a kriging predicted prevalence of 5-20% not currently covered by CDTI

[1] P20: areas with a kriging predicted prevalence of >20% not currently covered by CDTI

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

[3] Since this table is based on krigging analysis predicted maximum *Loa loa* prevalence, areas included here may be areas without history of eye-worm detected during the RAPLOA surveys [4]

**Table 8 Population in 2015 in projects/areas with krigging analysis predicted maximum RAPLOA prevalence <40% unlikely to achieve elimination by 2025 without optimized CDTI or ATS**

| | 1a* Untreated hypoendemic areas | 1b Untreated meso/hyper endemic areas | 1b* Untreated meso/hyper endemic areas[2] | 2a Very high endemicity level | 2b Treatment end date > 2022 | 2c Insufficient treatment coverage | 2d Inadequate progress to elimination | Total |
|---|---|---|---|---|---|---|---|---|
| Angola | | 116,100 | | | | | | **116,100** |
| CAR | | | | | 509,165 | | | **509,165** |
| Congo | | | 39,901 | | | | | **39,901** |
| DRC | | 1,571,075 | | 2,668,983 | 233,221 | 2,439,864 | | **6,913,143** |
| Ethiopia | | 496,800 | | | | | | **496,800** |
| Nigeria | | | | | | | 3,361,167 | **3,361,167** |
| South Sudan | | | | | | 3,255,512 | | **3,255,512** |
| Uganda | | | | 1,564,433 | 570,199 | | | **2,134,632** |
| | **0** | **2,183,975** | **39,901** | **4,233,416** | **1,312,585** | **5,695,376** | **3,361,167** | **16,826,420** |

* Areas for which epidemiological surveys are needed to confirm that these areas are currently endemic for onchocerciasis and not covered by CDTi before decisions on any onchocerciasis control strategy to be implemented.

[2] 'Untreated meso/hyperendemic area' - includes areas in which CDTI was initiated only in 2014 or 2015

[3] Since this table is based on krigging analysis predicted maximum Loa loa prevalence, areas included here may be areas without history of eye-worm detected during the RAPLOA surveys. [4]

# 4 Options and considerations for accelerating progress towards elimination

This chapter presents the options available to accelerate progress towards elimination including their rationale and different facts countries need to consider before deciding on which strategy to adopt.

Numerous studies and APOC evaluations show that various strategies have resulted or may result in elimination. These strategies include annual CDTI [3,13,14,23,25,29-32,40], annual CDTI followed by biannual CDTI [41,42], and vector elimination alone or in combination with ivermectin treatment [43-45]. Disappearance of onchocerciasis without any intervention has also been reported [46]. In other areas, elimination was not achieved in spite of 15-20 years of annual CDTI [47-50].

These empirical data are insufficient to understand where well implemented annual CDTI will be sufficient and where additional interventions are required to achieve elimination. They also do not provide evidence for the relative effectiveness of various intervention strategies in reducing infection prevalence. Field studies which compare the impact of different strategies or a particular factor of a given strategy (e.g. treatment coverage) on the time to elimination, when all other factors impacting this time are equal (e.g. pre-control endemicity, distribution of villages relative to vector breeding sites, productivity of breeding sites, ...), are obviously not feasible.

In the absence of such data, mathematical models are a useful tool to systematically compare the effectiveness of different types of interventions for a range of different settings, and to help inform the most effective strategy for a given setting (for more

information see section 6). In this report, the rationale for a particular strategy is therefore frequently based on the findings from modelling.

Modelling inputs for this report have been provided by two onchocerciasis modelling groups, employing two conceptually different, but well established models: ONCHOSIM and EPIONCHO. The two groups now collaborate within the NTD Modelling Consortium (www.ntdmodelling.org). Due to the differences between the two models, the impact of onchocerciasis control interventions is described in different terms:

- ONCHOSIM provides an estimate of (a) the number of years and (b) the number of ivermectin treatment rounds to reach elimination (with 99% probability).
- EPIONCHO results included in this report are provided as estimates of (a) the microfilarial prevalence in those aged ≥5 years after 12 years of intervention and 3 years of post-intervention surveillance (i.e. 15 years in total), and (b) the percentage increase in effectiveness (based on the projected microfilarial prevalence) of the ATS evaluated relative to the effectiveness of annual CDTI.

The modelling data presented in this document are either drawn from previously published work or from simulations conducted specifically for the APOC consultations on ATS and yet to be published.

The following needs to be taken into account for decisions to implement ATS based on the modelling results presented:

- The modelling predictions presented in absolute terms (e.g. the required duration of interventions or the expected infection prevalence at a certain point in time) should be interpreted with caution, because of the uncertainties that are inherent to modelling.
- Because the outcomes of the two models are presented in different terms, they are not directly comparable. The outputs of both models do, however, demonstrate the direction and relative magnitude of differences between the impact of the different strategies on progress towards elimination of onchocerciasis.

Section 6 provides additional information about the role modelling in support of onchocerciasis control and elimination, the two models, and a more detailed discussion of the interpretation of model predictions, agreement between the two models and remaining uncertainties.

## 4.1 Optimization of annual CDTI implementation

### 4.1.1 Rationale

Implementation of the ATS presented in section 4.2 - 4.4 poses more operational challenges than annual CDTI, requires the availability of the necessary human, financial and material resources. It cannot be achieved without an even stronger commitment from all levels of the health system, NGDOs and communities than required for annual CDTI.

Consequently, where the analysis of pre-control endemicity, CDTI history and, if available, the results of epidemiological evaluations suggest that progress towards elimination has been suboptimal due to poor CDTI implementation, optimization of CDTI implementation should be the first step to accelerating progress towards elimination. Programmes which cannot successfully implement annual CDTI, cannot be expected to successfully implement any of the ATS.

This is true not only for the implementation of complementary vector control (see section 4.3) and of a 'Test and Treat' strategy (see section 4.4), but also for implementation of biannual CDTI (see section 4.2).

In view of this, TCC recommended that countries should prioritize optimal implementation of CDTI [51].

The impact of increasing annual CDTI treatment coverage to the APOC recommended 80% on time to elimination has been compared with the impact of increasing CDTI frequency with continuing treatment coverage of <80% using both ONCHOSIM and EPIONCHO. Both models predict that increasing treatment coverage during annual CDTI reduces years to elimination to an extent that is generally similar to that achieved by switching to biannual CDTI without improving treatment coverage [33,52]. Based on the experience in Ghana, the in-country costs/year for biannual treatment are approximately 50%-60% higher than those for annual treatment [53]. Since the number of years to elimination is significantly lower with biannual compared to annual CDTI, the total cost to elimination, however, was estimated to be similar for the two strategies [54].

For two levels of hyperendemicity, Table 9 and Table 10 show ONCHOSIM and EPIONCHO predictions on the impact of switching from annual CDTI at 65% coverage to either annual CDTI at 80% coverage, biannual CDTI at 65% coverage or biannual CDTI coverage at 80% coverage.

**Table 9 Number of years and ivermectin treatment rounds to elimination with annual and biannual CDTI with different treatment coverage initiated after 5 years of annual CDTI with 65% treatment coverage (ONCHOSIM predictions)**

| **Pre-control endemicity** | **Reference: continue** | **New strategy initiated after 5 years of a CDTI with 65% Tx cov** | | |
|---|---|---|---|---|
| Parameter | **a CDTI Tx cov: 65%** | **a CDTI Tx cov: 80%** | **Bi CDTI Tx cov: 65%** | **Bi CDTI Tx cov: 80%** |
| **Hyperendemic area with mf prevalence in ≥5 yrs old population: 70%, CMFL: 16 mf/skin snip** | | | | |
| Number of years to elimination after strategy switch | 7 | 5 | 4 | 3 |
| Number of CDTI rounds to elimination after strategy switch | 7 | 5 | 8 | 6 |
| **Very hyperendemic area with mf prevalence ≥5 yrs old population: 87%, CMFL: 56 mf/skin snip** | | | | |
| Number of years to elimination after strategy switch | 22 | 17 | 13.5 | 12 |
| Number of CDTI rounds to elimination after strategy switch | 22 | 17 | 27 | 24 |

a CDTI - annual CDTI, Bi CDTI - biannual CDTI, Tx cov - treatment coverage

Model assumptions: a) Percentage of systematic non-compliers (i.e. % of people who consistently do not participate in CDTI): 5%, b) % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%

**Table 10 Predicted microfilarial prevalence in ≥5-year old population after 12 years of intervention plus 3 years of surveillance and the percentage increase in effectiveness of annual CDTI at 80% coverage or biannual CDTI at the 65% or 80% coverage compared to continuing annual CDTI at 65% coverage (EPIONCHO predictions)**

| **Pre-control endemicity** | **Reference: continue** | **New strategy initiated after 5 years of a CDTI with 65% Tx cov** | | |
|---|---|---|---|---|
| Parameter | **a CDTI Tx cov: 65%** | **a CDTI Tx cov: 80%** | **Bi CDTI Tx cov: 65%** | **Bi CDTI Tx cov: 80%** |
| **Hyperendemic area with mf prevalence ≥5-yr old population: 70%, CMFL: 15 mf/skin snip** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 14.6% | 9.5% | 7.8% | 6.4% |
| Percentage increase in effectiveness* | NA | 34.7% | 46.7% | 56.2% |
| **Very hyperendemic area with mf prevalence ≥5-yr old population: 87%, CMFL: 53 mf/skin snip** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 48.7% | 42.0% | 35.7% | 31.8% |
| Percentage increase in effectiveness* | NA | 13.9% | 26.9% | 34.7% |

a CDTI - annual CDTI, Bi CDTI - biannual CDTI, Tx cov - treatment coverage, NA - not applicable
Model assumptions: a) Percentage of systematic non-compliers (i.e. % of people who consistently do not participate in CDTI): 5%, b) % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%. * effectiveness is calculated relative to microfilarial prevalence after 12 years of annual CDTI at 65% coverage plus 3 years of surveillance (i.e. 15 years in total).

The relative advantage of annual CDTI with APOC recommended 80% treatment coverage relative to biannual CDTI with low treatment coverage also applies in areas without prior CDTI. A possible exception are the rare areas where pre-treatment prevalence exceeds 90% [35].

Both models support the TCC recommendation that optimization of CDTI implementation should be the first step to accelerating progress towards elimination. In areas in which CDTI cannot be successfully implemented, it cannot be expected that the much more demanding ATS can be effectively implemented.

### 4.1.2 Optimization of the CDTI process

The key elements of CDTI implementation should be reviewed and improved, including

- the strength of the health system,
- the human and financial resources assigned to CDTI,
- the performance of programme management (including drug ordering and distribution system),
- the quality of the partnership between the health system, NGDOs and the communities,
- the training of health care workers and community drug distributors (CDDs),
- the suitability of the Information, Education and Communication (IEC) materials,
- the community mobilization and ownership,
- the CDD motivation, work overload and attrition,
- the self-monitoring of CDTI by the communities and
- the monitoring by programme management.

Appropriate feedback should be provided to the communities. Quality of reporting at all levels – from the CDD via the district to the country levels - should be strengthened to ensure that coverage data reported reflect the actual achievements. The development of simple reporting tools should be prioritized to allow the CDDs and frontline health workers to generate reports in a timely manner so that measures to improve performance can be implemented in time for the next treatment round.

The training material developed by APOC for faculties of medicine and health sciences [55,56] should be used by programme managers at the national and district level when preparing plans for optimizing programme performance. The advice on improvement of CDTI performance provided by TCC to each annual report for each APOC project area provides further guidance on actions to be taken by the national control programmes and the project coordinators.

Since multiple reasons may contribute to persistent high prevalence and intensity of infection, a thorough analysis of all performance determining parameters of each project may be required. The benefit of such an analysis was recently demonstrated: APOC requested a team of experts in Nigeria and Cameroon to conduct such a thorough analysis for each underperforming project to identify the reasons for persistent high prevalence and make recommendations on how to accelerate progress towards elimination. In both countries, the evaluation teams concluded that numerous elements of the CDTI process have to be improved from the national to the community level.

### 4.1.3 Optimizing community mobilization and ownership

The success of CDTI depends on the investment made by the country and project teams to engage communities in all aspects of the project. Community awareness, conducted through community-level gatherings and use of local structures (such as religious groupings, women's groups, youth groups) is a critical step in informing the communities about the project and facilitating the selection of CDDs to be involved in the project.

The ownership of CDTI by the community is assessed by the involvement of the community members in mobilization as well as initiation of activities (collection of ivermectin and other commodities at the health center), selection of CDDs and incentivizing of the CDDs.

A critical element of ownership introduced in the course of implementing CDTI is Community Self-Monitoring (CSM). In many instances community mobilization and implementation of CSM was found to be insufficient.

Studies conducted on factors that influence community involvement have established that conducting programmes without supporting the growth of CDDs and reinforcing education of communities could lead to a decrease in treatment coverage [57]. CDD attrition has been associated to the inability of communities to compensate them.

Any revision of the treatment schedule should be communicated to and agreed upon with the communities since it has implications on the timing and workload for the various community level structures involved in CDTI.

The concerns raised by TCC on review of the annual reports by projects submitted to APOC and TCC and the TCC recommendations on how to optimize community mobilization and ownership should be consulted by the countries and programme teams. APOC has provided guidance on community self-monitoring [58].

### 4.1.4 Addressing systematic-noncompliance

In a study including 8480 villagers from 101 villages in Cameroon and Nigeria which had undergone 8 years of CDTI, the percentage of those who had never, only once or only twice taken ivermectin were 5.9%, 8.5% and 12.3%, respectively [59].

Efforts to optimize treatment coverage need to include identification and motivation of those people who have been 'systematic non-compliers' (i.e. people who consistently did not participate in CDTI in the past) as well as those who participated rarely in CDTI. The percentage of systematic non-compliers has a pronounced impact on the effectiveness of CDTI and the time to (and, depending on the magnitude of systematic non-compliance, the feasibility of) elimination [22,34,35,54].

Table 11 compares the impact of the percentage of systematic non-compliers on the effectiveness of various CDTI strategies as modelled by EPIONCHO.

A number of studies have examined factors impacting compliance with CDTI (e.g. [59-68]). As CDTI reduces the percentage of those suffering from symptoms, the health benefits recognized [69,70] will decrease. This may increase the percentage of systematic non-compliers. The approach to community mobilization thus needs to be adapted to the specific epidemiological situation of a community. Operational research, informed by prior experience [59-68,71-79] may have to be conducted to understand the reasons for low population participation so that appropriate strategies can be developed to increase therapeutic coverage.

Where applicable, special strategies need to be developed and resourced for migratory populations and internally displaced populations. These could include mobile teams and outreach approaches. Mobile teams were used by the OCP when ivermectin treatment was introduced. The logistic cost was extremely high. For this reason, mobile teams cannot be recommended to be used nation-wide but can be considered for special settings.

**Table 11 Predicted microfilarial prevalence in ≥5-year old population after 12 years of intervention plus 3 years of surveillance and the percentage increase in effectiveness of annual CDTI at 80% coverage or biannual CDTI at 65% or 80% coverage compared to continuing annual CDTI at 65% coverage with 5% compared to 0% systematic non-compliers (EPIONCHO predictions)**

| **Pre-control endemicity**<br>***Percentage of systematic non-compliers*** | **Reference: continue** | **New strategy initiated after 5 years of a CDTI with 65% Tx cov** | | |
|---|---|---|---|---|
| Parameter | **a CDTI Tx cov: 65%** | **a CDTI Tx cov: 80%** | **Bi CDTI Tx cov: 65%** | **Bi CDTI Tx cov: 80%** |
| **Hyperendemic area with mf prevalence ≥5 yrs old population: 70%, CMFL: 15 mf/skin snip** | | | | |
| ***Percentage of systematic non-compliers: 5%*** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 14.6% | 9.5% | 7.8% | 6.4% |
| Percentage increase in effectiveness* | NA | 34.7% | 46.7% | 56.2% |
| ***Percentage of systematic non-compliers: 0%*** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 5.1% | 0.01% | 0.00% | 0.00% |
| Percentage increase in effectiveness * | NA* | 83.5% | 91.7% | 99.3% |
| **Very hyperendemic area with mf prevalence ≥5 yrs old population: 87%, CMFL: 53 mf/skin snip** | | | | |
| ***Percentage of systematic non-compliers: 5%*** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 48.7% | 42.0% | 35.7% | 31.8% |
| Percentage increase in effectiveness* | NA* | 13.9% | 26.9% | 34.7% |
| ***Percentage of systematic non-compliers: %*** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 40.9% | 23.2% | 12.7% | 3.0% |
| Percentage increase in effectiveness* | NA* | 43.2% | 69.1% | 92.6% |

a CDTI - annual CDTI, Bi CDTI - biannual CDTI, Tx cov - treatment coverage, NA - not applicable
Model assumptions: % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%
* effectiveness is calculated relative to microfilarial prevalence after 12 years of annual CDTI at 65% coverage plus 3 years of post-treatment surveillance (i.e. 15 years in total)

### 4.1.5 Special consideration for optimizing CDTI in *Loa loa* co-endemic areas

Where poor CDTI treatment coverage in meso- or hyperendemic areas is attributed to the fear of populations of adverse reactions to ivermectin treatment in people heavily co-infected with *Loa loa*, and CDTI has been decided upon as the strategy to continue, reflections are needed to develop improved IEC material for the affected communities.

Research may be needed to better understand the knowledge about and the perceptions of these adverse reactions in the affected populations since very little detailed information is available.

Furthermore, it needs to be ensured that all those measures are implemented which were specified by the MEC and TCC for CDTI in onchocerciasis meso- and hyperendemic areas which are *Loa loa* co-endemic [38].

The central review of all projects reports by APOC management and the TCC and the advice provided to each project after this review, allowed each project to benefit from the lessons learnt in all other projects. In the absence of APOC, countries with *Loa loa* co-endemic areas should develop collaborations that allow them to share their experiences and best practices.

### 4.1.6 Optimizing the timing of CDTI in areas with seasonal transmission

#### 4.1.6.1 Rationale

In the majority of onchocerciasis endemic areas, the intensity of transmission varies over the course of a year in relation to the availability of blackfly breeding sites (determining vector density and biting rates) and vector survival (determining parous rates and ultimately infection and infectivity rates). In some areas, notably the Sahel zone, transmission occurs (nearly) exclusively during the few months of the rainy season (i.e. seasonal transmission). In other areas, transmission occurs throughout the year (i.e. perennial transmission), but with a defined peak transmission period, and in still others there may be two peak transmission periods.

After ivermectin treatment, skin microfilarial density decreases quickly and remains suppressed at a low level for around two to three months. This is due to a combination of the microfilaricidal effect of ivermectin and the effect of the drug on the production of microfilariae by adult female worms [80]. From around that time onward, the female macrofilariae resume production of microfilariae. The skin becomes slowly repopulated with microfilariae which are available for transmission to the vector. The impact of CDTI on transmission from humans to vectors is consequently maximal when CDTI occurs just before the peak biting season, so that skin microfilarial densities are minimal when the number of vectors is maximal. In contrast, when CDTI occurs after the peak biting season, skin microfilarial loads may be maximal when the number of vectors is maximal, resulting in an avoidable degree of transmission.

Modelling of the impact of the timing of CDTI relative to peak biting/transmission season for two different patterns of seasonal transmission with the model EPIONCHO suggests that optimal timing of CDTI can significantly reduce the number of years to elimination in areas with highly seasonal transmission. For a setting in which 60% of the adult population was infected pre-control and transmission occurred during only 5 months of the year, the number of years to reach the epidemiological thresholds for stopping treatment defined in the APOC 'Conceptual and Operational Framework of Onchocerciasis Elimination with Ivermectin Treatment' [2] was estimated to be 40% lower with optimal than 'worst possible' timing of CDTI. For a setting with the same pre-control endemicity but high levels of transmission during a five month long rainy season and continuing low level during the rest of the year, the number of years was estimated to be 20% lower with optimal than 'worst possible' timing of CDTI. [54]

Similar results were obtained with ONCHOSIM simulations for areas with perennial transmission but with a high and a low transmission season where optimal timing of CDTI was estimated to reduce the number of years to elimination by up to two years in areas with high transmission (pre-control CMFL 70 mf/skin snip) (unpublished data).

#### 4.1.6.2 Process

One of the basic principles of CDTI is that the populations themselves determine the time of ivermectin distribution. In practice the choice of timing by the communities is subject to the constraints imposed by preparatory activities by the health system such as the release of funds or delivery of ivermectin. In recent years, integration of onchocerciasis control and lymphatic filariasis (LF) control has in some cases resulted in CDTI being delayed because albendazole was not available on time.

As a first step, information on the seasonality of vector density in the project area should be compared with the timing of CDTI reported in the project technical reports provided to APOC. Information about the seasonality of vector density is available in the scientific literature (e.g. [81,82]) and sometimes in the APOC project technical reports. The entomologists who worked with APOC on mapping vector species and breeding sites were also gathering this information. Furthermore, the local population can provide information on when they suffer most from blackfly bites.

In areas with highly seasonal transmission and where CDTI timing is not optimal, project managers should explain to the populations why CDTI just before the period of highest vector density is advantageous to them. In some regions in Burkina Faso, the populations are well aware of this and demand ivermectin delivery in time for them to organise CDTI just before the season of high transmission. These populations could help to develop the effective IEC material explaining the rationale for distributing ivermectin at a given time of the year.

Subsequently, programme managers need to ensure that all prerequisites for CDTI are put in place for CDTI to occur at the time agreed upon with the population.

## 4.2 Biannual community directed treatment with ivermectin

### 4.2.1 Rationale

The Onchocerciasis Elimination Program for the Americas (OEPA), used 6-monthly (and in hyperendemic villages 3-monthly) ivermectin mass treatment in the 13 foci of 6 Central and South American countries [83-85]. In these countries an estimated 0.56 million people lived in an estimated 1939 communities of which 63%. 25% and 12% were hypo-, meso- and hyperendemic, respectively. Biannual ivermectin treatment rapidly suppressed transmission of the parasite [86,87]. Between 17-25 rounds of semi-annual treatment with ivermectin, complemented in 138 hyperendemic communities for several years with additional two treatment rounds/year, have resulted or are likely to have resulted in interruption of transmission in 11 foci [88-93].

In Africa, 16 years of biannual CDTI have eliminated onchocerciasis transmission in the River Gambia focus where pre-control infection prevalence was at least 60% in 9 of 21 villages for which data are available [3,23].

Modelling suggests that biannual CDTI will reduce the number of years to elimination compared to annual CDTI even in the highly endemic areas present in many APOC countries [33,52]. Table 9 and Table 10 above illustrate this for two different levels of hyperendemicity based on ONCHOSIM and EPIONCHO simulations, respectively.

Shorter and more intensive mass treatment programmes could minimize the risk of interruption of control activities, e.g. due to conflict, and increasing prevalence of parasites with low susceptibility to ivermectin.

### 4.2.2 Process

The processes for implementing biannual CDTI are the same as those for annual CDTI. The advice given in section 4.1 on optimization of implementation of CDTI should be taken into account.

Based on the experience in Ghana, the annual in-country costs for biannual CDTI are approximately 50-60% higher than the annual in-country costs for annual CDTI [53].

Consequently, support of all levels within the health system needs to be ensured before the decision to implement biannual CDTI.

Appropriate IEC material needs to be generated to ensure that the communities understand the rationale for the change in strategy and the importance of everybody participating in each treatment round so that high treatment coverage is achieved in both treatment rounds.

### 4.2.3 Implications

Modelling studies suggest several implications that countries need to consider for a decision to move from an annual to a biannual CDTI strategy and for implementation of the strategy:

- The extent to which biannual CDTI will decrease time to elimination of transmission depends on the treatment coverage achieved [33]. This is shown for two scenarios in Table 9 and Table 10.
- The total number of treatment rounds to elimination will be higher with biannual CDTI than annual CDTI (Table 9).
- Increasing treatment coverage during annual CDTI may reduce the number of years to elimination to an extent similar to that achieved through implementation of biannual CDTI without improved treatment coverage, but without the additional number of treatment rounds to elimination which biannual CDTI requires [33] (Table 9 and Table 10).
- One rationale for biannual CDTI proposed is that it will increase the number of people who will receive at least one treatment/year since those who for some reason were not able to participate in one round, may be able to participate in the second round in that year. It is noteworthy that the treatment coverage assumed in the modelling applies to each treatment round.
- An increase in the percentage of people receiving ivermectin in at least one of the two biannual CDTI treatment rounds is unlikely to affect the percentage of 'systematic non-compliers' (i.e. people who consistently do not participate in CDTI). The percentage of systematic non-compliers has a significant impact on the time to (and, depending on their proportion in the population and their microfilarial load, also the feasibility of) elimination not only with annual, but equally with biannual CDTI (Table 11). Consequently, the advice provided in section 4.1.4 is also applicable for biannual CDTI.
- The level of endemicity before introduction of annual CDTI, as well as the prevalence of infection at the time of switching from an annual to a biannual CDTI strategy will impact the difference in years to elimination between continuation of an annual CDTI strategy and switching to a biannual CDTI strategy [52].
- In areas with highly seasonal transmission, the number of years to elimination with CDTI will depend on the time of CDTI relative to vector biting rate. CDTI will be most effective when performed at a time that results in minimal skin microfilariae levels in the population when biting rates are highest (see section 4.1.6, [54]). Consequently, in areas with highly seasonal transmission, a second treatment round outside the transmission season will not be as effective as the treatment prior to the peak transmission season.

## 4.3 Complementary Vector control

### 4.3.1 Rationale

Vector control is directed against *Simulium* larvae using WHO approved and environmentally safe insecticides. Vector control through larviciding aimed at eliminating the vector was the first and principal strategy of the OCP [8,94,95].

In APOC countries, vector elimination was the principal onchocerciasis elimination strategy only in selected areas (Bioko (Equatorial Guinea) [45], Tukuyu (Tanzania), Itwara and Mpamba-Nkusi (Uganda) [44,96,97]) based on the isolation of the area or the transmission effectiveness of the local vector.

In other areas of APOC countries, vector control was not considered operationally or financially feasible as the principal control strategy. In selected areas in APOC countries, vector control could, however, be used to complement CDTI to rapidly reduce human-fly-contact and accelerate elimination of onchocerciasis.

Complementing CDTI with vector control is advantageous particularly in areas where vector density is very high resulting in significant transmission even when the skin microfilariae density in the population is low. Table 12 provides the number of years to elimination and the number of CDTI rounds and Table 13 the relative effectiveness of CDTI without and with vector control based on ONCHOSIM and EPIONCHO modelling, respectively.

The cost of vector control activities can, however, be very high, depending on a number of factors including e.g. the size (and volume) of the rivers, the number of breeding sites, the frequency of larviciding required, the productivity of the breeding sites, and their accessibility to larviciding. Furthermore, implementation of vector control requires significant preparatory work (see section 4.3.3).

**Table 12 Number of years and ivermectin treatment rounds to elimination with annual and biannual CDTI with different treatment coverage and complementary vector control initiated after 5 years of annual CDTI with 65% treatment coverage (ONCHOSIM predictions)**

| **Pre-control endemicity** | **Reference: continue** | **New strategy initiated after 5 years of a CDTI with 65% Tx cov** | | |
|---|---|---|---|---|
| Parameter | **a CDTI Tx cov: 65%** | **a CDTI Tx cov: 80%** | **Bi CDTI Tx cov: 65%** | **Bi CDTI Tx cov: 80%** |
| **Mesoendemic area with mf prevalence total population: 57%, mf prevalence >5 yrs old population: 70%, CMFL: 16 mf/skin snip** | | | | |
| **No complementary vector control** | | | | |
| Number of years to elimination after strategy switch | 7 | 5 | 4 | 3 |
| Number of CDTI rounds to elimination after strategy switch | 7 | 5 | 8 | 6 |
| **Complementary vector control reducing biting rates by 50%** | | | | |
| Number of years to elimination after strategy switch | 5 | 4 | 3.5 | 3 |
| Number of CDTI rounds to elimination after strategy switch | 5 | 4 | 7 | 6 |
| **Complementary vector control reducing biting rates by 75%** | | | | |
| Number of years to elimination after strategy switch | 4 | 4 | 3 | 3 |
| Number of CDTI rounds to elimination after strategy switch | 4 | 4 | 6 | 6 |
| **Complementary vector control reducing biting rates by 100%** | | | | |
| Number of years to elimination after strategy switch | 4 | 4 | 3 | 2.5 |
| Number of CDTI rounds to elimination after strategy switch | 4 | 4 | 6 | 5 |
| **Hyperendemic area with mf prevalence total population:72%, mf prevalence >5 yrs old population: 87%, CMFL: 56 mf/skin snip** | | | | |
| **No complementary vector control** | | | | |
| Number of years to elimination after strategy switch | 22 | 17 | 13.5 | 12 |
| Number of CDTI rounds to elimination after strategy switch | 22 | 17 | 27 | 24 |
| **Complementary vector control reducing biting rates by 50%** | | | | |
| Number of years to elimination after strategy switch | 13 | 12 | 10.5 | 9 |
| Number of CDTI rounds to elimination after strategy switch | 13 | 12 | 21 | 18 |
| **Complementary vector control reducing biting rates by 75%** | | | | |
| Number of years to elimination after strategy switch | 10 | 9 | 9 | 8.5 |
| Number of CDTI rounds to elimination after strategy switch | 10 | 9 | 18 | 17 |
| **Complementary vector control reducing biting rates by 100%** | | | | |
| Number of years to elimination after strategy switch | 8 | 8 | 7.5 | 7.5 |
| Number of CDTI rounds to elimination after strategy switch | 8 | 8 | 15 | 15 |

Model assumptions: a) Percentage of systematic non-compliers (i.e. % of people who consistently do not participate in CDTI): 5%, b) % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%

**Table 13 Predicted microfilarial prevalence in ≥5-year old population after 12 years of intervention plus 3 years of surveillance and the percentage increase in effectiveness of annual CDTI at 80% coverage or biannual CDTI at 65% or 80% coverage with complementary vector control compared to continuing annual CDTI at 65% coverage without vector control (EPIONCHO predictions)**

| **Pre-control endemicity** | **Reference: continue** | **New strategy initiated after 5 years of a CDTI with 65% Tx cov** | | |
|---|---|---|---|---|
| Parameter | **a CDTI Tx cov: 65%** | **a CDTI Tx cov: 80%** | **Bi CDTI Tx cov: 65%** | **Bi CDTI Tx cov: 80%** |
| **Hyperendemic area with mf prevalence ≥5-yr old population: 70%, CMFL: 15 mf/skin snip** | | | | |
| **No complementary vector control** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 14.6% | 9.5% | 7.8% | 6.4% |
| Percentage increase in effectiveness* | NA | 34.7% | 46.7% | 56.2% |
| **Complementary vector control reducing biting rates by 50%** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 9.8% | 6.4% | 5.6% | 4.8% |
| Percentage increase in effectiveness* | 32.5% | 56.2% | 61.4% | 67.0% |
| **Complementary vector control reducing biting rates by 75%** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 7.4% | 4.8% | 4.6% | 4.0% |
| Percentage increase in effectiveness* | 49.1% | 66.9% | 68.6% | 72.4% |
| **Complementary vector control reducing biting rates by 100%** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 5.1% | 3.3% | 3.6% | 3.3% |
| Percentage increase in effectiveness* | 65.1% | 77.1% | 75.6% | 77.6% |
| **Very hyperendemic area with mf prevalence ≥5 yrs old population: 87%, CMFL: 53 mf/skin snip** | | | | |
| **No complementary vector control** | | | | |
| Microfilarial prevalence in ≥5-yr old population after 15 years* | 48.7% | 42.0% | 35.7% | 31.8% |
| Percentage increase in effectiveness* | NA | 13.9% | 26.9% | 34.7% |
| **Complementary vector control reducing biting rates by 50%** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 43.4% | 36.1% | 31.1% | 27.7% |
| Percentage increase in effectiveness* | 11.0% | 26.0% | 36.3% | 43.1% |
| **Complementary vector control reducing biting rates by 75%** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 37.2% | 29.9% | 26.5% | 23.9% |
| Percentage increase in effectiveness* | 23.8% | 38.6% | 45.6% | 51.0% |
| **Complementary vector control reducing biting rates by 100%** | | | | |
| Microfilarial prevalence in ≥5 yrs old population after 15 years* | 22.0% | 17.5% | 18.0% | 17.2% |
| Percentage increase in effectiveness* | 54.9% | 64.1% | 63.1% | 64.7% |

a CDTI - annual CDTI, Bi CDTI - biannual CDTI, Tx cov - treatment coverage, NA - not applicable
Model assumptions: % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%
Model assumptions: a) Percentage of systematic non-compliers (i.e. % of people who consistently do not participate in CDTI): 5%, b) % reduction in reproductive capacity of female macrofilariae per round of treatment: 35%. * effectiveness is calculated relative to microfilarial prevalence after 12 years of annual CDTI at 65% coverage plus 3 years of surveillance (i.e. 15 years in total), without vector control.

### 4.3.2 Options and requirements for decision making

Vector control can be implemented with two different objectives:

1) Local elimination of the vector, which may be feasible in selected isolated foci [44,45,96,97].

2) Reduction of vector density and thus biting rates in other areas through larviciding timed so that the maximum reduction is achieved at the time biting rates and thus transmission of the parasite would be highest.

The decision to implement vector control and the choice of the vector control objective require a large amount of information including, but not limited to the following:

- Maps of the river systems
- Maps of potential breeding sites.
- Information on rainfall pattern in the area.
- Data on vector species and their characteristics.
- Data on the effectiveness of potentially suitable larvicides obtained through experimental larviciding treatment to optimize the approach to vector control.
- Vector control capacity available in the national health services.
- Data for the calculation of the cost (including capacity building) as well as cost-effectiveness of different vector control strategies.

### 4.3.3 Guide for countries

A 'Guide for decision making and implementation of vector control as Alternative Treatment Strategies for elimination of onchocerciasis' for countries has been generated and is available in an Annex to this report.

## 4.4 Test and Treat strategies

A 'Test and Treat' (T&T) strategy is defined as 'any strategy that requires diagnosis for infection and/or contra-indications to treatment before a decision on whom to treat with what regimen' is made.

This strategy deviates from APOC's community-directed intervention approach in several ways:

- It is not mass-drug administration based
- Some diagnostic tests cannot be administered by CDDs and require at a minimum extensive training of community health workers while others will require administration by health care workers or personnel with specific skills and experience.
- The drugs used may have a safety profile not consistent with distribution by CDDs and require involvement of personnel with specific skills and experience.
- For drug regimens with >1 dose per treatment round, monitoring of therapeutic coverage and compliance may require more resources than monitoring of compliance with CDTI .
- More than one type of treatment may be used within a community depending on the strategy chosen. This also requires extensive training to ensure that specific treatments are given to those for whom they are indicated and not to those for whom they are contra-indicated.

For the design of T&T strategies, a series of questions needs to be answered before implementation is decided upon:

1. Who needs to be tested?
2. Which infection or which infections are to be tested for?
3. Which contra-indications other than infections need to be tested for?
4. Which tests are to be used?
5. Who can conduct these tests?
6. Who will be treated?
7. What drug regimen is the most suitable for which subpopulation?
8. What resources are required for successful implementation (including level of personnel for applying the test and for providing the drug)?

All of these requirements imply that prerequisites for successful implementation of T&T include and go significantly beyond those for successful implementation of biannual CDTI outlined in section 4.2. Prior to implementation of a T&T strategy, the feasibility of implementation needs to be examined, operational research to determine critical factors for successful implementation needs to be conducted, commitment at all levels of the health system and of the communities needs to be obtained and the timely availability of all required financial, material and human resources needs to be assured. Detailed guidelines and Standard Operating Procedures as well as specific Information, Education and Communication (IEC) material for the population need to be developed. The IEC material should differ for populations used to CDTI and those in which the T&T strategy is the first onchocerciasis control strategy implemented.

### 4.4.1 Rationale

#### 4.4.1.1 T&T in loiasis-endemic areas

In *Loa loa* endemic areas in which onchocerciasis is meso- or hyperendemic, CDTI can be implemented with the two modified strategies specified in the TCC and MEC guidelines[2] because the probability and extent of benefit of ivermectin treatment (reduction in and progression of onchocerciasis signs and symptoms) is considered to exceed the risk of serious adverse reactions. In contrast, in onchocerciasis hypoendemic areas which are *Loa loa* co-endemic, no matter how low the level of loiasis endemicity, the proportion of the population benefitting from ivermectin is very low. Consequently, the benefit from CDTI is too low relative to the risk of serious adverse reactions to ivermectin in those with high level of infection with *Loa loa* for CDTI to be justified.

Similarly, in areas co-endemic for LF, at any level of endemicity, and *Loa loa* but not onchocerciasis meso- or hyperendemic, mass drug administration (MDA) of ivermectin and albendazole is not justifiable: individuals with LF will not receive any direct benefit from the reduction in blood microfilariae levels (which reduces transmission, but does not reduce their symptoms which are due to the adult worms). In 2012, WHO recommended twice

[2] http://www.who.int/apoc/publications/recommendations/en/) http://www.mectizan.org/resources/mec-tcc-guidelines-for-use-of-mectizan-in-loa-endemic-areas

yearly albendazole treatment, combined with vector control activities, as the provisional strategy for interruption of LF transmission in loiasis co-endemic areas without onchocerciasis [98]. The preliminary results obtained in the Republic of the Congo (DOLF project) suggest that this strategy will be effective [99].

A T&T strategy with diagnosis for *Loa loa* infection allows to exclude individuals with a level of *Loa loa* infection above that considered to put them at unacceptable risk of serious adverse reactions to ivermectin.

#### 4.4.1.2 T&T in loiasis-endemic areas

A T&T strategy can also be considered for areas which are not *Loa loa* endemic, i.e. where the proportion of the infected population and the level of transmission is expected to be very low. In that case, elimination of transmission could be achieved faster by identifying those infected and treating them once with a course of a macrofilaricide (combined with ivermectin if the macrofilaricide has no effect on microfilariae) than to continue CDTI for many years (or MDA with ivermectin and albendazole).

A T&T strategy can be equally applied to other situations where a specific subgroup of the population should be excluded from MDA with the chosen drug since it puts them at unacceptable risk (e.g. a pregnancy test for women because the drug chosen has reproductive toxicity).

### 4.4.2 T&T strategies for onchocerciasis hypoendemic areas co-endemic for *Loa loa*

As outlined above, CDTI cannot be implemented in onchocerciasis hypoendemic areas co-endemic for *Loa loa,* indicating a T&T strategy. Onchocerciasis is considered hypo-endemic when nodule prevalence in adults is < 20%, which, in ivermectin treatment naive areas, corresponds to 20-60% of the population with microfilariae (mf) in their skin [100].

In areas in which the prevalence of *Loa loa* microfilaraemia exceeds 20% (corresponding to a RAPLOA prevalence of 40% [4,101]), the proportion of adults with > 30,000 *Loa loa* mf/ml blood and thus at risk of severe neurological adverse reactions to ivermectin is around 2-3% and the proportion of adults with > 8000 *Loa loa* mf/ml blood and thus at risk of marked reaction with functional impairment for several days is around 6-7% [37,39,102]. These prevalences need to be taken into account to determine the best T&T strategy.

Two different T&T strategies are possible:

1) a strategy in which, as a first step, *Loa loa* infected individuals at risk of severe adverse reactions are identified to be excluded from treatment with ivermectin (LOA FIRST).

2) a strategy in which, as a first step, *O. volvulus* infected individuals to be targeted for treatment are identified (ONCHO FIRST).

#### 4.4.2.1 Test to exclude highly *Loa loa* infected individuals from ivermectin treatment (LOA FIRST)

In this strategy, all residents are systematically tested to determine the level of *Loa loa* microfilaraemia in each individual (see section 4.4.4).

*Loa loa* infected individuals excluded from ivermectin treatment can subsequently be tested for infection with *O. volvulus* and, if found to be infected, can be treated with drugs which affect the *O. volvulus* macrofilariae, but have no effect on the microfilariae and thus do not induce *Loa*-related serious adverse reactions. Considering (a) the prevalence of

onchocerciasis in hypoendemic areas (b) the relationship between the prevalence of *Loa loa* infection and infection intensity [39], and assuming (c) that the threshold for exclusion from ivermectin treatment is set to 30,000 *Loa loa* mf/ml [37], the percentage of the population who should not receive ivermectin treatment but will need individualized treatment with another drug is estimated not to exceed 1%.

#### 4.4.2.2 Test for *O. volvulus* infection to select individuals for treatment against *O. volvulus* (ONCHO FIRST)

In this strategy, all residents are systematically tested for active infection with *O. volvulus* (see section 4.4.5) to identify those in need of treatment.

If the chosen treatment is known or suspected to be microfilaricidal, individuals found to be infected with *O. volvulus* need to be tested further for *Loa loa* microfilarial density to exclude those at risk of severe and/or serious adverse reactions from the microfilaricidal treatment and treat them with a macrofilaricide which is not microfilaricidal.

### 4.4.3 T&T strategies for onchocerciasis endemic areas not co-endemic for *Loa loa*

The epidemiological evaluations by APOC and the countries in areas with long term CDTI [13,14,25,26,29-32,40,51,103] have shown that in many areas the prevalences of patent infection (as determined by skin snip) have been reduced to very low levels, including in some areas to levels that meet the provisional criteria for stopping CDTI [2]. In some areas none of the individuals tested was skin snip positive.

In areas with particularly high pre-CDTI endemicity, the prevalence of infected individuals was often still higher than 10% despite > 20 years of CDTI. In such a situation, it needs to be evaluated whether continuation of CDTI is cost-effective considering that CDTI does not include measures to determine the extent to which those still infected, and hence in need of treatment, are or are not participating in CDTI (see section 4.1.4).

An alternative is a T&T strategy in which the total population is tested for patent *O. volvulus* infection (via skin snips or the DEC patch test (see section 4.4.5, [23,104]) and those found to be infected are treated.

### 4.4.4 Tools to test for infection with *Loa loa*

The current gold standard for *Loa loa* diagnosis is examination for mf of Giemsa stained calibrated (usually 50 or 70 µl) thick blood smears (TBS) prepared from blood sampled between 10:00 h and 16:00 h [39]. This method requires significant laboratory capacity and personnel. A well trained technician is estimated to be able to read up to 30-50 TBS per hour, depending on the mean *Loa loa* microfilarial density on the TBS. In addition, this is not a point-of-care method to detect at-risk individuals

Two main alternative methods are being developed:

- Determination of the amount of *Loa loa* DNA in the blood which correlates with the level of microfilaremia [105]. This method requires a well equipped central laboratory and hence results are not immediately available for decision making.
- Determination of *Loa loa* microfilaremia with the "Cellscope Loa", also called "LoaScope" [106]. Seven 5-second videos are obtained from a blood sample in a capillary, inserted into a special magnifying device, coupled with a smartphone. The *Loa* mf which displace the red blood cells are counted by the image analysis software

loaded into the smartphone. The number of mf/ml blood is shown on the smartphone screen within one minute, and the test has thus the huge advantage of being a point-of-care diagnostic test [106]. This device was tested in August-October 2015 in Cameroon in an area where a significant number of serious adverse reactions, including fatal ones, occurred in 1999. Some 15,000 individuals were tested, corresponding to a coverage of almost 60% of the total population. This participation rate shows that the extensive community information and education conducted had achieved a high level of confidence, despite the history of post-ivermectin adverse reactions 15 years ago. Among those tested, only 2.2% were excluded from ivermectin treatment because of their high *Loa* microfilaraemia, whereas the others were treated with ivermectin. No case of serious adverse reaction occurred among them. Further studies are ongoing to assess the perception and the cost-effectiveness of the strategy.

Either of these methods allows identification of individuals infected with *Loa loa* who are at risk of severe and/or serious adverse reactions to ivermectin and their exclusion from the ivermectin treatment provided to all other individuals.

### 4.4.5 Tools to test for infection with *O. volvulus*

The current gold standard for diagnosing infection with *O. volvulus* is the skin biopsy (skin snip) method which requires the use of costly sclerectomy punches (Holth- or Walser-type), sterilization of the punches between use on different subjects, well-trained technicians and is labor intensive. The method is relatively invasive which may result in low population acceptance for diagnosing *O. volvulus* infection in hypoendemic areas where people are very unlikely to suffer from symptoms or in meso- or hyperendemic areas where CDTI has eliminated onchocerciasis morbidity.

A field suitable test for human antibodies against the *O. volvulus* antigen OV16 is now commercially available to detect *O. volvulus* infection from Standard Diagnostics, Inc. (http://www.standardia.com/en/home/product/rapid/infectious-disease/Anti-Onchocerciasis_IgG4.html). Currently, it is not known for how many years OV16 antibodies remain in circulation after the last *O. volvulus* macrofilariae in an individual has died. Studies conducted in areas where onchocerciasis transmission was interrupted suggest that this might be up to 10 years. Therefore, the test may result in false positive diagnosis of *O. volvulus* infection in areas where transmission and thus infection prevalence was reduced due to long term CDTI. Large scale studies comparing the sensitivity and specificity of OV16 detected with ELISA, the OV16 field suitable test and the skin snip method are currently ongoing.

The OCP had initiated use of the DEC patch. The DEC patch detects patent *O. volvulus* infection through the localized skin reaction that appears when skin microfilariae are exposed to diethylcarbamazine applied to a small area of skin via a patch [107-109]. A manual for field workers on the use of the ad-hoc prepared patch usingusing DEC diluted in Nivea cream (referred to as the OCP DEC patch) is available on the APOC website[3]. A ready-to-use DEC patch manufactured according to Good Manufacturing Practices which utilizes modern transdermal delivery technology (LTS-2 patch) has now been developed. Clinical evaluation of the LTS-2 patch resulted in the conclusion that the ability to detect active

[3] http://www.who.int/apoc/publications/guidefortraindec_patch/fr/, http://www.who.int/apoc/publications/guidefortraindec_patch/en/

infections is comparable to that of the DEC patch used by OCP and that the safety profile is suitable for large scale evaluation [23,104]. Large scale evaluation of the LTS-2 patch sensitivity and specificity is planned in a study that will simultaneously evaluate other available tools for the diagnosis of onchocerciasis. The specificity of the LTS-2 patch in *Loa loa* co-endemic areas also needs to be evaluated. A study of the OCP DEC patch in a forest area of Cameroon where *Loa loa* is co-endemic showed that the proportion of positive results was higher in children infected with *Loa loa* than in those who were amicrofilaraemic (20% vs. 5.3%), but that only 9.5% of those with *Loa loa* microfilaraemia developed a grade 2 [108,110]. The LTS-2 patch is not commercially available. Lohmann Therapie Systeme, (LTS, Andernach, Germany), the company which developed it at no cost at the request of WHO, will manufacture batches at the request of WHO and provide them to WHO at cost. Countries can request patches from WHO.

## 4.5 Treatments

### 4.5.1 Drugs registered for use in onchocerciasis

Ivermectin is currently the only drug registered (i.e. approved by regulatory authorities) for use in *O. volvulus* infections and is included among the antifilarials in the 2013 WHO Model list of Essential Medicines.[4]

### 4.5.2 Drugs registered for human use for other indications

Clinical studies with the tetracycline antibiotic doxycycline (daily administration for 4-6 weeks [111]) have provided proof-of-concept that depleting *O. volvulus* of its symbiotic bacterium *Wolbachia pipientis* results in permanent sterilization of the parasite (200 mg/d for 4 weeks or 100 mg/d for 5 weeks) and can also exert a macrofilaricidal effect (6 weeks 200 mg/d) [112,113]. Doxycycline has not kill the microfilariae but it reduces their ability to develop into infective stages within the blackfly vectors [114]. Because doxycycline is not microfilaricidal, it does not give rise to the type of adverse reactions in *Loa loa* infected individuals seen after ivermectin treatment.

Meta-analytical modelling of all available doxycycline clinical trial data to date suggests that there is no statistically significant difference between the effect of the different dose levels (100 vs. 200 md/d) or different treatment durations (4, 5, and 6 weeks) evaluated. The modelling further suggested that the macrofilaricidal effect is due to a shortening of the lifespan of the macrofilariae by 70-80% from an average of 10 years to 2-3 years [111].

Doxycycline is approved in many countries for the treatment or prevention of specified infectious diseases. The indications for which use is approved may differ between countries. Doxycycline is included in the 2013 WHO Model list of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/) as an antibiotic and antimalarial. The warnings/precautions (including pregnancy and age <8 years) for use of doxycycline need to be taken into account for doxycycline-based treatment strategies, including set up of an appropriate pharmacovigilance system.

Applications to include antibiotics found to be safe and effective for use in *O. volvulus* among the antifilarials in the WHO Model List of Essential Medicines are being considered (A. Hoerauf, personal communication).

[4] http://www.who.int/medicines/publications/essentialmedicines/en/

### 4.5.3 Drugs in clinical development

Research for drugs with higher effect on the parasite is ongoing. The amount of data on the safety and efficacy of these drugs, how they could potentially be used by control programmes and when they may become available for use differs between the different drugs. This section provides an overview based on currently available information. Countries may want to keep a 'watching brief' on the progress being made.

#### 4.5.3.1 Moxidectin

Moxidectin is an anthelminthic used in veterinary medicines. The UNICEFF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), evaluated, with support from OCP and APOC, the potential of moxidectin for onchocerciasis control and elimination. WHO has licensed all data it has to the Australian Not-for-Profit organisation Medicines Development for Global Health (MDGH[5]). MDGH intends to register moxidectin for onchocerciasis with funds provided by the Global Health Investment Fund (GHIF[6]). MDGH also intends to develop moxidectin for LF and scabies.

In the first study conducted in *O. volvulus* infected people in Ghana by TDR [115], a single dose of 8 mg moxidectin resulted in skin microfilariae levels which were for 12 months lower than the lowest levels achieved after treatment (at 2 months) with the standard dose of ivermectin. The superiority of 8 mg moxidectin over ivermectin was confirmed in a larger study conducted in Ghana, Liberia and DRC in adolescents ≥ 12 years and adults. The safety data suggest that moxidectin is suitable for mass drug administration [51]. A large scale community study to evaluate the effect of multiple annual and biannual treatments, as well as a study to determine a safe dose for children 4-11 years old are being planned.

Modelling with EPIONCHO was conducted to compare the time and in-country costs to reach the provisional operational thresholds for stopping ivermectin treatment with annual community directed treatment with 8 mg moxidectin (aCDTM), biannual CDTI and annual CDTI. The modelling suggested that these thresholds are reached after a similar number of years with aCDTM and biannual CDTI. Since a second treatment/year increases in-country costs, reaching elimination would be cheaper for countries with an aCDTM strategy, provided moxidectin is donated to countries [54].

There are no data on the effect of moxidectin on *Loa loa* microfilariae. Given moxidectin's effect on *O. volvulus* microfilariae, it is likely that moxidectin will result in adverse reactions in people with high levels of *Loa loa* infection similar to those seen after ivermectin treatment(see section 4.4). While data on the effect of moxidectin on *Loa loa* microfilariae remain unavailable, it has to be assumed that moxidectin could be used in *Loa loa* co-endemic areas only within a 'Test and Treat' strategy.

#### 4.5.3.2 Anti-*wolbachia* compounds

The University of Bonn is part of the 'A-WOL consortium'[7], funded by the Bill and Melinda Gates Foundation[8] and the Global Health Innovative Technology fund.[9] Together with their

[5] http://www.medicinesdevelopment.com/

[6] www.ghif.com, http://ghif.com/us10-million-investment-into-the-registration-of-moxidectin/, www.who.int/tdr/news/2015/moxi-treatmt-funding/en/index.html

[7] http://www.a-wol.com/; http://www.a-wol.com/our-consortium/

[8] http://www.gatesfoundation.org/

partners from Kwame Nkrumah University of Science and Technology (KNUST), Ghana, they are conducting clinical studies to assess the effect of antibiotics registered for non-filarial indications and which have shown anti-wolbachial efficacy in *in-vitro* and *in-vivo* laboratory assays. The objective of these studies is to develop treatment regimens for onchocerciasis and lymphatic filariasis with < 7 days duration ([116], for ongoing study see ISRCTN43697583). The results from these studies will show whether these treatment regimen are effective and whether the safety profile and treatment regimen are compatible with mass drug administration or whether these antibiotic regimens are candidates for treatments within a T&T strategy.

The publications resulting from this work are available on the consoritum website.[10]

### 4.5.4 Drugs in discovery and pre-clinical testing

#### 4.5.4.1 Flubendazole

Flubendazole is a drug used in veterinary medicine and also approved in a number of countries for treatment of human intestinal parasites [117].

A clinical study of injectable (intra-muscular) flubendazole conducted in people with onchocerciasis in Mexico suggested that the macrofilariae are killed while the microfilariae are not affected [118,119]. Further studies were not conducted because of inflammatory reactions at the injection site [118]. New oral formulations of flubendazole providing high systemic bioavailability have now been developed [120]. Additional studies in animal models have been conducted which support the initial efficacy data. Pre-clinical safety testing is currently ongoing [121-123]. The first study of the tablets in people could be initiated in 2016 or 2017 (C.D. Mackenzie, T. Geary, personal communication). It is currently not known when all studies required for registration of oral flubendazole will be completed. It is also not known whether flubendazole will be safe across all ages and both sexes.

Currently available data in animal models and humans do not suggest that flubendazole kills microfilariae. Therefore, flubendazole is a very promising candidate for mass drug administration in *Loa loa* co-endemic areas, even if its safety profile should require 'selective MDA' e.g. based on sex and/or age due to reproductive toxicity [123].

#### 4.5.4.2 Emodepside

Emodepside is a compound approved in combination with praziquantel (Profender®) for the treatment of gastrointestinal nematodes in animals (tablets for dogs, spot-on solution for cats). Studies sponsored by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) showed that emodepside has activity in laboratory models of human filarial parasites, as well as on *O. volvulus* macrofilariae (Townson S., Awadzi, K. Progress Report to TDR on project A50391, 25.5.2006 to 30.12.2007). Emodepside has been suggested as a candidate for development for human filarial infections [124].

The Not-for-profit organisation Drugs for Neglected Diseases Initiative (DNDi) is conducting pre-clinical research to determine the safety profile of emodepside in the laboratory and in

[9] http://www.ghitfund.org
[10] http://www.a-wol.com/outputs/publications/

animal models.[11] DNDi announced that emodespide will enter healthy volunteer studies in 2015 (DNDi E-news December 2015 - Scientific Update, R&D status November 2015: DND*i* Filarial Diseases programme, November 2015, accessed 13 December 2015).

#### 4.5.4.3 Anti-*wolbachia* compounds

The AWOL consortium is also conducting research to discover new compounds which could ultimately be transitioned into pre-clinical safety testing and ultimately clinical trials to determine whether they are safe and efficacious against *O. volvulus* with regimens of only a few days [125].

# 5 Considerations for onchocerciasis - LF co-endemic areas

In areas in which onchocerciasis is co-endemic with Lymphatic Filariasis (LF), decisions on strategies for onchocerciasis elimination should be made in the context of ongoing or planned efforts for the elimination of LF. Global elimination of LF is targeted for 2020. The strategy is preventive chemotherapy through annual mass drug administration (MDA) with albendazole plus ivermectin (in countries where onchocerciasis is endemic) or diethylcarbamazine (in other countries) for ≥ 5 years. Progress towards achieving this goal in Africa is less than originally planned due to the fact that mapping of LF prevalence has not been completed in all countries. Recent data on the lack of specificity relative to *Loa loa* of the Immunochromatographic Card Test (ICT) used to map LF endemic areas [126-128], indicate that in loiasis-endemic areas the presence of LF needs to be re-evaluated before cost-effective control strategies can be decided upon.

In LF endemic areas which are loiasis co-endemic, the community benefit of MDA with ivermectin does not justify the individual risk of serious adverse reactions to ivermectin that can occur in *Loa loa* infected people [129]. In 2012, WHO recommended twice yearly albendazole treatment, combined with vector control activities, as the provisional alternative treatment strategy for interruption of LF transmission in loiasis co-endemic areas without onchocerciasis [98]. Albendazole is not microfilaricidal and therefore does not induce the type of adverse reactions in *Loa loa* infected individuals seen after ivermectin treatment. The ongoing studies conducted in the Republic of Congo and in DRC (DOLF studies) on the impact of 3 years of semi-annual albendazole treatment will provide further data on the efficacy of the proposed regimen.

# 6 The role of modelling in onchocerciasis control and the strengths and limitations of modelling

## 6.1 Rationale for the use of modelling

Ambitious targets have been set for the elimination of onchocerciasis in Africa. Mathematical models provide the opportunity to predict and compare the population-level effect of different types of interventions. They can thus help to identify the most effective interventions according for different epidemiological settings.

There is a paucity of empirical data comparing the impact of different types of interventions on trends in infection prevalence and achievement of elimination in Africa. Available data are usually not directly comparable because of underlying differences in pre-control

[11] http://www.dndi.org/diseases-projects/portfolio/emodepside.html

endemicity, distance from breeding sites, productivity of breeding sites, compliance, and other factors that influence the impact of interventions. Since it is impossible to compare possible strategies under controlled circumstances, mathematical models are the only available means to assess the relative efficacy of different interventions, where the targets can be achieved with current interventions, where strategy adjustments may be needed, and how the progress to elimination can be accelerated most effectively.

## 6.2 History of modelling in support of onchocerciasis control

Modelling has played a significant role in informing onchocerciasis control activities since the early stages of the OCP, helping to determine: (i) the threshold biting rates of the savannah members of the *S. damnosum s.l.* complex, below which endemic onchocerciasis would not be able to persist [130]; (ii) the dynamics of recolonization by blackflies of breeding sites after spraying of the larvicides [130,131], and (iii) the duration of vector control that would be necessary to interrupt transmission and prevent recrudescence [132]. Early modelling projections using ONCHOSIM indicated that 14 years of full-scale vector control would be required to reduce the risk of recrudescence to less than 1% [132]. These projections were later confirmed by the epidemiological trends presented by Hougard et al. [133].

When ivermectin MDA emerged as a new intervention strategy during the late 1980s and early 1990s, ONCHOSIM was used to model the effectiveness of combined vector control and MDA, predicting that 12 years of combined interventions would be sufficient to reduce the risk of recrudescence to less than 1%, even in the most severely affected areas, assuming an ivermectin treatment coverage of at least 65% [134].

The ONCHOSIM model was later also applied to assess prospects of achieving elimination with ivermectin mass treatment as the only intervention [33,135]. A similar analysis was done with the more recently developed model EPIONCHO [34]. Both models have also been used to assess the public health impact of onchocerciasis control in the APOC countries [17,22,136].

Since the inclusion of onchocerciasis elimination in Africa among the APOC objectives, both ONCHOSIM and EPIONCHO have been increasingly used to evaluate the effectiveness, cost-effectiveness as well as the feasibility of and relative time to achieving elimination for a variety of intervention strategies: annual or biannual CDTI [33,52,54,135], complementary vector control (for this report, Section 4.3.1) and emerging treatments such as moxidectin [54] (Section 4.5.3.1) or doxycycline [137] (Section 4.5.2). Model simulations have also highlighted the importance of treatment coverage and compliance with CDTI, indicating that only a relatively small proportion of systematically non-compliant individuals is enough to sustain transmission despite ongoing interventions ([35], Section 4.1.4).

## 6.3 Comparison of ONCHOSIM and EPIONCHO

Modelling results referenced or provided in this report were derived from two different models:

- ONCHOSIM: originally developed by researchers from Erasmus MC (Rotterdam, the Netherlands) in collaboration with OCP and later refined in collaboration with APOC;
- EPIONCHO: developed by researchers from Imperial College London (London, UK).

Both are well-established models developed for the same purpose: to evaluate hypotheses regarding the transmission dynamics of onchocerciasis and to serve as a tool for planning and evaluation of interventions. Good information about the processes involved in onchocerciasis transmission was obtained by analysing data from the Onchocerciasis Control Programme and data from studies done in areas where savanna-type of infection occurs. This information was incorporated in the models [33,35,52,138]. Both models have been applied in many previously published modelling studies (see section 6.2).

There are many similarities between the models, but there are also differences, e.g. with respect to the modelling approach, the extent to which the models account for heterogeneities in the human population (e.g. in exposure to blackfly bites), and assumptions regarding density dependence in various processes in the transmission cycle. A first comparison of the models and their predictions for a number of relevant scenarios was recently published [35].

Both models agree that annual CDTI may be sufficient to bring mf prevalence below a critical threshold in meso-endemic areas and estimates of the required duration of interventions are comparable. For hyperendemic areas, the models gave more deviating results, with ONCHOSIM being more 'optimistic' regarding the feasibility of elimination and required duration of interventions than EPIONCHO. Both models do agree that annual or biannual CDTI is insufficient to achieve elimination in very highly hyperendemic areas.

Although the models' predictions regarding the required duration of interventions for achieving elimination sometimes differ, in general the model predictions regarding the relative effectiveness of alternative interventions are comparable.

A more detailed comparison of the two models and previously published predictions is in preparation (Basanez et al. River blindness: mathematical models for control and elimination) [35].

## 6.4 Interpretation of modelling results: robustness and uncertainties

There is renewed focus on validating model predictions against longitudinal epidemiological data collected during both research studies and routine programmatic monitoring and evaluation activities. This is a crucial task because many components of both ONCHOSIM and EPIONCHO are parameterized primarily using pre-control data and key population and transmission processes do not necessarily hold through long-term intervention [139]. In this endeavour, APOC has been an important partner in agreeing to share relevant epidemiological and programmatic data which will ultimately improve the accuracy of model predictions.

Even with further validation using these and other data, some modelling assumptions will inevitably be difficult or sometimes impossible to validate directly. It is also not feasible to validate models unequivocally across the highly heterogeneous demographic, ecological and demographic settings among onchocerciasis foci in Africa. Some key uncertainties can be expressed in model outputs. However, it is rarely feasible to undertake comprehensive structural and parametric uncertainty analysis while maintaining interpretable output which is useful to support and inform decisions on intervention strategies. Hence, while models provide an excellent tool to help decisions on interventions strategies—and indicate likely required durations of interventions—ultimately the attainment of elimination goals must be

verified by data collected during appropriately designed long-term, longitudinal monitoring and evaluation followed by surveillance activities.

# 7 List of Annexes

- APOC Guidelines for revising ivermectin treatment boundaries within the context of onchocerciasis elimination
- Guide for decision making and implementation of vector control as Alternative Treatment Strategies for elimination of onchocerciasis
- Recommendations for the treatment of Onchocerciasis with Mectizan® in areas co-endemic for Onchocerciasis and Loiasis of the Mectizan® Expert Committee and the Technical Consultative Committee of APOC
- List of participants in APOC consultative meetings on alternative treatment strategies.

# 8 References

Reference List


1. Remme J, Ba O, Dadzie KY, Karam M: **A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area.** *Bull World Health Organ* 1986, **64:** 667-681.

2. African Programme for Onchocerciasis Control (APOC): **Conceptual and Operational Framework of Onchocerciasis Elimination with Ivermectin Treatment.** WHO/APOC/MG/10.1 edition. Edited by African Programme for Onchocerciasis Control. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control; [www.who.int/apoc/oncho_elimination_report_english.pdf]; 2010.

3. Diawara L, Traore MO, Badji A, Bissan Y, Doumbia K, Goita SF *et al.*: **Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal.** *PLoS Negl Trop Dis* 2009, **3:** e497.

4. Zoure HG, Wanji S, Noma M, Amazigo UV, Diggle PJ, Tekle AH *et al.*: **The geographic distribution of Loa loa in Africa: results of large-scale implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA).** *PLoS Negl Trop Dis* 2011, **5:** e1210.

5. Noma M, Nwoke BE, Nutall I, Tambala PA, Enyong P, Namsenmo A *et al.*: **Rapid epidemiological mapping of onchocerciasis (REMO): its application by the African Programme for Onchocerciasis Control (APOC).** *Ann Trop Med Parasitol* 2002, **96 Suppl 1:** S29-S39.

6. ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use): *Guideline for Good Clinical Practice, E6, R1, 1996*. www.ich.org; 1996.

7. Benton B, Dadzie Y, Boatin B: **[The onchocerciasis control program in West Africa (OCP): essential characteristics].** *Sante* 1998, **8:** 26.

8. Boatin B: **The Onchocerciasis Control Programme in West Africa (OCP).** *Ann Trop Med Parasitol* 2008, **102 Suppl 1:** 13-17.

9. Campbell WC: **History of avermectin and ivermectin, with notes on the history of other macrocyclic lactone antiparasitic agents.** *Curr Pharm Biotechnol* 2012, **13:** 853-865.

10. Fobi G, Yameogo L, Noma M, Aholou Y, Koroma JB, Zoure HM *et al.*: **Managing the Fight against Onchocerciasis in Africa: APOC Experience.** *PLoS Negl Trop Dis* 2015, **9:** e0003542.

11. Roungou JB, Yameogo L, Mwikisa C, Boakye DA, Bundy DA: **40 Years of the APOC Partnership.** *PLoS Negl Trop Dis* 2015, **9:** e0003562.

12. Seketeli A, Adeoye G, Eyamba A, Nnoruka E, Drameh P, Amazigo UV *et al.*: **The achievements and challenges of the African Programme for Onchocerciasis Control (APOC).** *Ann Trop Med Parasitol* 2002, **96 Suppl 1:** S15-S28.

13. African Programme for Onchocerciasis Control (APOC): *2014 Progress Report*. World Health Organization/African Programme for Onchocerciasis Control; 2014.

14. African Programme for Onchocerciasis Control (APOC): *2015 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control; 2015.

15. Noma M, Zoure HG, Tekle AH, Enyong PA, Nwoke BE, Remme JH: **The geographic distribution of Onchocerciasis in the 20 participating countries of the African programme for Onchocerciasis control: (1) priority areas for ivermectin treatment.** *Parasit Vectors* 2014, **7:** 325.

16. Ozoh GA, Murdoch ME, Bissek AC, Hagan M, Ogbuagu K, Shamad M *et al.*: **The African Programme for Onchocerciasis Control: impact on onchocercal skin disease.** *Trop Med Int Health* 2011.

17. Coffeng LE, Stolk WA, Zoure HG, Veerman JL, Agblewonu KB, Murdoch ME *et al.*: **African Programme For Onchocerciasis Control 1995-2015: model-estimated health impact and cost.** *PLoS Negl Trop Dis* 2013, **7:** e2032.

18. Coffeng LE, Stolk WA, Zoure HG, Veerman JL, Agblewonu KB, Murdoch ME *et al.*: **African programme for onchocerciasis control 1995-2015: updated health impact estimates based on new disability weights.** *PLoS Negl Trop Dis* 2014, **8:** e2759.

19. African Programme for Onchocerciasis Control (APOC): *2014 Progress Report*. World Health Organization/African Programme for Onchocerciasis Control; 2014.

20. McMillan DE, Painter T, Scudder T: **Settlement and development in the River blindness control zone.** *World Bank Technical Paper* 1992, **No WTP 192**.

21. Benton B: **Economic impact of onchocerciasis control through the African Programme for Onchocerciasis Control: an overview.** *Ann Trop Med Parasitol* 1998, **92 Suppl 1:** S33-S39.

22. Turner HC, Walker M, Churcher TS, Basanez MG: **Modelling the impact of ivermectin on River Blindness and its burden of morbidity and mortality in African Savannah: EpiOncho projections.** *Parasit Vectors* 2014, **7:** 241.

23. Traore MO, Sarr MD, Badji A, Bissan Y, Diawara L, Doumbia K *et al.*: **Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal.** *PLoS Negl Trop Dis* 2012, **6:** e1825.

24. African Programme for Onchocerciasis Control (APOC): *Final Communiqué of the 16th session of the Joint Action Forum (JAF16) of APOC*. http://www.who.int/apoc/about/structure/jaf/en/; 2010.

25. Tekle AH, Elhassan E, Isiyaku S, Amazigo UV, Bush S, Noma M *et al.*: **Impact of long-term treatment of onchocerciasis with ivermectin in Kaduna State, Nigeria: first evidence of the potential for elimination in the operational area of the African Programme for Onchocerciasis Control.** *Parasit Vectors* 2012, **5:** 28.

26. African Programme for Onchocerciasis Control (APOC): **Report of the 39th session of the technical consultative committee (TCC), September 2014.** Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control [http://www.who.int/apoc/about/structure/tcc/en/]; 2014.

27. World Health Organization: *Accelerating work to overcome the global impact of neglected tropical diseases. A roadmap for implementation (WHO/HTM/NTD/2012.1)*. Geneva: World Health Organization (http://whqlibdoc.who.int/hq/2012/WHO_HTM_NTD_2012.1_eng.pdf); 2012.

28. African Programme for Onchocerciasis Control (APOC): *Final Communiqué, Eighteenth Session of the Joint Action Forum 11-13 December 2012*. [http://www.who.int/apoc/publications/recommendations/en/index.html]; 2012.

29. African Programme for Onchocerciasis Control (APOC): *2010 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control (http://www.who.int/entity/apoc/publications/APR_2010_EN_28Oct2010_Progress_report_final_printed_version.pdf); 2010.

30. African Programme for Onchocerciasis Control (APOC): *2011 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control (http://www.who.int/entity/apoc/publications/JZF17_OK_EN_APOC_ProgressReport2011.pdf); 2011.

31. African Programme for Onchocerciasis Control (APOC): *2012 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control (http://www.who.int/entity/apoc/publications/ENAPOCPR2012_ProgressReport2012.pdf); 2012.

32. African Programme for Onchocerciasis Control (APOC): *2013 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control; 2013.

33. Coffeng LE, Stolk WA, Hoerauf A, Habbema D, Bakker R, Hopkins AD *et al.*: **Elimination of African onchocerciasis: modeling the impact of increasing the frequency of ivermectin mass treatment.** *PLoS ONE* 2014, **9:** e115886.

34. Turner HC, Churcher TS, Walker M, Osei-Atweneboana MY, Prichard RK, Basanez MG: **Uncertainty surrounding projections of the long-term impact of ivermectin treatment on human onchocerciasis.** *PLoS Negl Trop Dis* 2013, **7:** e2169.

35. Stolk WA, Walker M, Coffeng LE, Basanez MG, de Vlas SJ: **Required duration of mass ivermectin treatment for onchocerciasis elimination in Africa: a comparative modelling analysis.** *Parasit Vectors* 2015, **8:** 552.

36. Kim YE, Remme JH, Steinmann P, Stolk WA, Roungou JB, Tediosi F: **Control, elimination, and eradication of river blindness: scenarios, timelines, and ivermectin treatment needs in Africa.** *PLoS Negl Trop Dis* 2015, **9:** e0003664.

37. Gardon J, Gardon-Wendel N, Demanga N, Kamgno J, Chippaux JP, Boussinesq M: **Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection.** *Lancet* 1997, **350:** 18-22.

38. Mectizan Expert Committee and APOC Technical Consultative Committee: **Recommendations for the treatment of onchocerciasis with Mectizan in areas co-endemic for onchocerciasis and Loiasis.** http://www.who.int/apoc/publications/recommendations/en/index.html; http://www.mectizan.org/key-mectizan-expert-committee-recommendations; 2004.

39. Boussinesq M, Gardon J, Kamgno J, Pion SD, Gardon-Wendel N, Chippaux JP: **Relationships between the prevalence and intensity of Loa loa infection in the Central province of Cameroon.** *Ann Trop Med Parasitol* 2001, **95:** 495-507.

40. African Programme for Onchocerciasis Control (APOC): *2009 Progress Report*. Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control; 2009.

41. Higazi TB, Zarroug IM, Mohamed HA, Elmubarak WA, Deran TC, Aziz N *et al.*: **Interruption of Onchocerca volvulus Transmission in the Abu Hamed Focus, Sudan.** *Am J Trop Med Hyg* 2013.

42. Katabarwa MN, Walsh F, Habomugisha P, Lakwo TL, Agunyo S, Oguttu DW *et al.*: **Transmission of onchocerciasis in wadelai focus of northwestern Uganda has been interrupted and the disease eliminated.** *J Parasitol Res* 2012, **2012:** 748540.

43. Katabarwa M, Lakwo T, Habomugisha P, Agunyo S, Byamukama E, Oguttu D *et al.*: **Transmission of Onchocerca volvulus by Simulium neavei in Mount Elgon focus of Eastern Uganda has been interrupted.** *Am J Trop Med Hyg* 2014, **90:** 1159-1166.

44. Lakwo TL, Garms R, Rubaale T, Katabarwa M, Walsh F, Habomugisha P *et al.*: **The disappearance of onchocerciasis from the Itwara focus, western Uganda after elimination of the vector Simulium neavei and 19 years of annual ivermectin treatments.** *Acta Trop* 2013, **126:** 218-221.

45. Traore S, Wilson MD, Sima A, Barro T, Diallo A, Ake A *et al.*: **The elimination of the onchocerciasis vector from the island of Bioko as a result of larviciding by the WHO African Programme for Onchocerciasis Control.** *Acta Trop* 2009, **111:** 211-218.

46. Katabarwa MN, Endeshaw T, Taye A, Tadesse Z, Frank RO: **The disappearance of onchocerciasis without intervention in Tigray Region in Northwest Ethiopia.** *Pathog Glob Health* 2014, **108:** 123.

47. Katabarwa MN, Eyamba A, Nwane P, Enyong P, Yaya S, Baldiagai J *et al.*: **Seventeen years of annual distribution of ivermectin has not interrupted onchocerciasis transmission in North Region, Cameroon.** *Am J Trop Med Hyg* 2011, **85:** 1041-1049.

48. Katabarwa MN, Eyamba A, Nwane P, Enyong P, Kamgno J, Kuete T *et al.*: **Fifteen years of annual mass treatment of onchocerciasis with ivermectin have not interrupted transmission in the west region of cameroon.** *J Parasitol Res* 2013, **2013:** 420928.

49. Katabarwa MN, Lakwo T, Habomugisha P, Agunyo S, Byamukama E, Oguttu D *et al.*: **Transmission of Onchocerca volvulus Continues in Nyagak-Bondo Focus of Northwestern Uganda after 18 Years of a Single Dose of Annual Treatment with Ivermectin.** *Am J Trop Med Hyg* 2013.

50. Yaya G, Kobangue L, Kemata B, Galle D, Gresenguet G: **[Elimination or control of the onchocerciasis in Africa? Case of Gami village in Central African Republic.].** *Bull Soc Pathol Exot* 2014.

51. African Programme for Onchocerciasis Control (APOC): **Report of the thirty-sixth session of the technical consultative committee (TCC), Ouagadougou, 11-15 March 2013.** Ouagadougou: World Health Organization/African Programme for Onchocerciasis Control (http://www.who.int/apoc/about/structure/tcc/TCC36_Final_Report_170513.pdf); 2013.

52. Turner HC, Walker M, Churcher TS, Osei-Atweneboana MY, Biritwum NK, Hopkins A *et al.*: **Reaching the London Declaration on Neglected Tropical Diseases Goals for**

**Onchocerciasis: An Economic Evaluation of Increasing the Frequency of Ivermectin Treatment in Africa.** *Clin Infect Dis* 2014.

53. Turner HC, Osei-Atweneboana MY, Walker M, Tettevi EJ, Churcher TS, Asiedu O *et al.*: **The cost of annual versus biannual community-directed treatment of onchocerciasis with ivermectin: Ghana as a case study.** *PLoS Negl Trop Dis* 2013, **7:** e2452.

54. Turner HC, Walker M, Attah SK, Opoku NO, Awadzi K, Kuesel AC *et al.*: **The potential impact of moxidectin on onchocerciasis elimination in Africa: an economic evaluation based on the Phase II clinical trial data.** *Parasit Vectors* 2015, **8:** 167.

55. African Programme for Onchocerciasis Control (APOC): *Curriculum and training module on the community-directed intervention (CDI) strategy for faculties of medicine and health sciences (2nd edition)*. Ouagadougou: WHO/African Programme for Onchocerciasis Control (http://www.who.int/apoc/publications/cdi_manual_final/en/); 2012.

56. African Programme for Onchocerciasis Control (APOC): *Curriculum and training module on the community-directed intervention (CDI) strategy for faculties of medicine and health sciences - Trainers' handbook (2nd edition)*. Ouagadougou: WHO/African Programme for Onchocerciasis Control (http://www.who.int/apoc/publications/APOC_Handbook_CDI_EN/en/); 2012.

57. York KJ, Kabole I, Mrisho M, Berry DM, Schmidt E: **Affecting Community Participation in the CDTI Program in Morogoro, Tanzania.** *Journal of Nursing Scholarship* 2014, **47**.

58. African Programme for Onchocerciasis Control (APOC): *Community self-monitoring of ivermectin treatment: a facilitator's guide*. Ouagadougou: WHO/African Programme for Onchocerciasis Control (http://www.who.int/apoc/publications/selfmonitoring/en/); 1999.

59. Brieger WR, Okeibunor JC, Abiose AO, Wanji S, Elhassan E, Ndyomugyenyi R *et al.*: **Compliance with eight years of annual ivermectin treatment of onchocerciasis in Cameroon and Nigeria.** *Parasit Vectors* 2011, **4:** 152.

60. Lakwo TL, Gasarasi DB: **Non-adherence to community directed treatment with ivermectin for onchocerciasis control in Rungwe district, southwest Tanzania.** *East Afr Med J* 2006, **83:** 326-332.

61. Yirga D, Deribe K, Woldemichael K, Wondafrash M, Kassahun W: **Factors associated with compliance with community directed treatment with ivermectin for onchocerciasis control in Southwestern Ethiopia.** *Parasit Vectors* 2010, **3:** 48.

62. Brieger WR, Okeibunor JC, Abiose AO, Ndyomugyenyi R, Kisoka W, Wanji S *et al.*: **Feasibility of measuring compliance to annual ivermectin treatment in the African Programme for Onchocerciasis Control.** *Trop Med Int Health* 2007, **12:** 260-268.

63. Brieger WR, Otusanya SA, Oke GA, Oshiname FO, Adeniyi JD: **Factors associated with coverage in community-directed treatment with ivermectin for onchocerciasis control in Oyo State, Nigeria.** *Trop Med Int Health* 2002, **7:** 11-18.

64. Endale A, Erko B, Weldegebreal F, Legesse M: **Predictors of compliance with community-directed treatment with ivermectin for onchocerciasis control in Kabo area, southwestern Ethiopia.** *Parasit Vectors* 2015, **8:** 695.

65. Nuwaha F, Okware J, Ndyomugyenyi R: **Predictors of compliance with community-directed ivermectin treatment in Uganda: quantitative results.** *Trop Med Int Health* 2005, **10:** 659-667.

66. Nuwaha F, Okware J, Ndyomugyenyi R: **Predictors for compliance with community directed ivermectin treatment in Bushenyi district of Uganda: qualitative results.** *East Afr Med J* 2004, **81:** 92-96.

67. Oyibo WA, Fagbenro-Beyioku AF: **Community response to repeated annual ivermectin treatment of onchocerciasis in Nigeria.** *Parasitol Res* 2002, **88:** 704-707.

68. Oyibo WA, Fagbenro-Beyiku AF: **Evaluation of community compliance with annual ivermectin treatment of onchocerciasis in Patigi, Nigeria.** *East Afr Med J* 1998, **75:** 237-242.

69. Okeibunor JC, muyunzu-Nyamongo M, Onyeneho NG, Tchounkeu YF, Manianga C, Kabali AT *et al*.: **Where would I be without ivermectin? Capturing the benefits of community-directed treatment with ivermectin in Africa.** *Trop Med Int Health* 2011.

70. Amuyunzu-Nyamongo M, Tchounkeu YF, Oyugi RA, Kabali AT, Okeibunor JC, Manianga C *et al*.: **Drawing and interpreting data: Children's impressions of onchocerciasis and community-directed treatment with ivermectin (CDTI) in four onchocerciasis endemic countries in Africa.** *Int J Qual Stud Health Well -being* 2011, **6**.

71. Akogun OB, Audu Z, Weiss MG, Adelakun AO, Akoh JI, Akogun MK *et al*.: **Community-directed treatment of onchocerciasis with ivermectin in Takum, Nigeria.** *Trop Med Int Health* 2001, **6:** 232-243.

72. Clemmons L, Amazigo UV, Bissek AC, Noma M, Oyene U, Ekpo U *et al*.: **Gender issues in the community-directed treatment with ivermectin (CDTI) of the African Programme for Onchocerciasis Control (APOC).** *Ann Trop Med Parasitol* 2002, **96 Suppl 1:** S59-S74.

73. Guillet P, Seketeli A, Alley ES, Agoua H, Boatin BA, Bissan Y *et al*.: **Impact of combined large-scale ivermectin distribution and vector control on transmission of Onchocerca volvulus in the Niger basin, Guinea.** *Bull World Health Organ* 1995, **73:** 199-205.

74. Newell ED: **Effect of mass treatments with ivermectin, with only partial compliance, on prevalence and intensity of O. volvulus infection in adults and in untreated 4 and 5 year-old children in Burundi.** *Trop Med Int Health* 1997, **2:** 912-916.

75. Oladepo O, Okunade A, Brieger WR, Oshiname FO, Ajuwon AJ: **Outcome of two patient education methods on recruitment and compliance with ivermectin in the treatment of onchocerciasis.** *Patient Educ Couns* 1996, **29:** 237-245.

76. Pacque M, Munoz B, Greene BM, White AT, Dukuly Z, Taylor HR: **Safety of and compliance with community-based ivermectin therapy.** *Lancet* 1990, **335:** 1377-1380.

77. Shu EN, Onwujekwe EO, Lokili P, Okonkwo PO: **A health club for a community school in south-eastern Nigeria: influence on adult perception of onchocerciasis and compliance with community-based ivermectin therapy.** *Trop Med Int Health* 2000, **5:** 222-226.

78. Whitworth JA, Alexander ND, Seed P, Thomas W, Abiose A, Jones BR: **Maintaining compliance to ivermectin in communities in two West African countries.** *Health Policy Plan* 1996, **11:** 299-307.

79. Whitworth JA, Downham MD, Lahai G, Maude GH: **A community trial of ivermectin for onchocerciasis in Sierra Leone: compliance and parasitological profiles after three and a half years of intervention.** *Trop Med Int Health* 1996, **1:** 52-58.

80. Basanez MG, Pion SD, Boakes E, Filipe JA, Churcher TS, Boussinesq M: **Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis.** *Lancet Infect Dis* 2008, **8:** 310-322.

81. Lamberton P, Cheke RA, Walker M, Winskill P, Osei-Atweneboana MY, Tirados I *et al.*: **Onchocerciasis transmission in Ghana: biting and parous rates of host-seeking sibling species of the Simulium damnosum complex.** *Parasit Vectors* 2014, **7:** 511.

82. Lamberton PH, Cheke RA, Winskill P, Tirados I, Walker M, Osei-Atweneboana MY *et al.*: **Onchocerciasis transmission in Ghana: persistence under different control strategies and the role of the simuliid vectors.** *PLoS Negl Trop Dis* 2015, **9:** e0003688.

83. Sauerbrey M: **The Onchocerciasis Elimination Program for the Americas (OEPA).** *Ann Trop Med Parasitol* 2008, **102 Suppl 1:** 25-29.

84. Cupp EW, Sauerbrey M, Richards F: **Elimination of human onchocerciasis: history of progress and current feasibility using ivermectin (Mectizan((R))) monotherapy.** *Acta Trop* 2011, **120 Suppl 1:** S100-S108.

85. Katabarwa M, Richards F: **Twice-yearly ivermectin for onchocerciasis: the time is now.** *Lancet Infect Dis* 2014, **14:** 373-374.

86. Rodriguez-Perez MA, Lutzow-Steiner MA, Segura-Cabrera A, Lizarazo-Ortega C, Dominguez-Vazquez A, Sauerbrey M *et al.*: **Rapid suppression of Onchocerca**

**volvulus transmission in two communities of the Southern Chiapas focus, Mexico, achieved by quarterly treatments with Mectizan.** *Am J Trop Med Hyg* 2008, **79:** 239-244.

87. Rodriguez-Perez MA, Lizarazo-Ortega C, Hassan HK, Dominguez-Vasquez A, Mendez-Galvan J, Lugo-Moreno P *et al.*: **Evidence for suppression of Onchocerca volvulus transmission in the Oaxaca focus in Mexico.** *Am J Trop Med Hyg* 2008, **78:** 147-152.

88. Eberhard M: **Progress toward elimination of onchocerciasis in the americas - 1993-2012.** *MMWR Morb Mortal Wkly Rep* 2013, **62:** 405-408.

89. Convit J, Schuler H, Borges R, Olivero V, Dominguez-Vazquez A, Frontado H *et al.*: **Interruption of Onchocerca volvulus transmission in Northern Venezuela.** *Parasit Vectors* 2013, **6:** 289.

90. **Progress towards eliminating onchocerciasis in the WHO Region of the Americas: verification by WHO of elimination of transmission in Colombia.** *Wkly Epidemiol Rec* 2013, **88:** 381-385.

91. West S, Munoz B, Sommer A: **River blindness eliminated in Colombia.** *Ophthalmic Epidemiol* 2013, **20:** 258-259.

92. Lovato R, Guevara A, Guderian R, Proano R, Unnasch T, Criollo H *et al.*: **Interruption of infection transmission in the onchocerciasis focus of Ecuador leading to the cessation of ivermectin distribution.** *PLoS Negl Trop Dis* 2014, **8:** e2821.

93. Rodriguez-Perez MA, Fernandez-Santos NA, Orozco-Algarra ME, Rodriguez-Atanacio JA, Dominguez-Vazquez A, Rodriguez-Morales KB *et al.*: **Elimination of Onchocerciasis from Mexico.** *PLoS Negl Trop Dis* 2015, **9:** e0003922.

94. Hougard JM, Yameogo L, Seketeli A, Boatin B, Dadzie KY: **Twenty-two years of blackfly control in the onchocerciasis control programme in West Africa.** *Parasitol Today* 1997, **13:** 425-431.

95. Hougard JM, Poudiougo P, Guillet P, Back C, Akpoboua LK, Quillevere D: **Criteria for the selection of larvicides by the Onchocerciasis Control Programme in west Africa.** *Ann Trop Med Parasitol* 1993, **87:** 435-442.

96. Garms R, Lakwo TL, Ndyomugyenyi R, Kipp W, Rubaale T, Tukesiga E *et al.*: **The elimination of the vector *Simulium neavei* from the Itwara onchocerciasis focus in Uganda by ground larviciding.** *Acta Trop* 2009, **111:** 203-210.

97. Lakwo TL, Ndyomugyenyi R, Onapa AW, Twebaze C: **Transmission of Onchocerca volvulus and prospects for the elimination of its vector, the blackfly Simulium neavei in the Mpamba-Nkusi focus in Western Uganda.** *Med Vet Entomol* 2006, **20:** 93-101.

98. World Health Organization: **Provisional strategy for interruption lymphatic filariasis transmission in loiasis-endemic countries. Report of the meeting on lymphatic**

**filariasis, malaria and integrated vector management, Accra, Ghana, March 2012.** http://www.who.int/iris/bitstream/10665/75139/3/WHO_HTM_NTD_PCT_2012.6_eng.pdf?u; 2012.

99. Pion SD, Chesnais CB, Bopda J, Louya F, Fischer PU, Majewski AC *et al.*: **The Impact of Two Semiannual Treatments with Albendazole Alone on Lymphatic Filariasis and Soil-Transmitted Helminth Infections: A Community-Based Study in the Republic of Congo.** *Am J Trop Med Hyg* 2015.

100. Coffeng LE, Pion SD, O'Hanlon S, Cousens S, Abiose AO, Fischer PU *et al.*: **Onchocerciasis: the pre-control association between prevalence of palpable nodules and skin microfilariae.** *PLoS Negl Trop Dis* 2013, **7:** e2168.

101. Takougang I, Meremikwu M, Wandji S, Yenshu EV, Aripko B, Lamlenn SB *et al.*: **Rapid assessment method for prevalence and intensity of Loa loa infection.** *Bull World Health Organ* 2002, **80:** 852-858.

102. Wanji S, Mremikwu M, Takougang I, Enyong P, Vubo E.Y., Tendongfor N *et al.*: *Rapid assessment procedures for loiasis. Report of a multi-centre study*. Geneva: UNDP/World Bank/ WHO Special Programme for Research and Training in Tropical Diseases (Rapid Assessment Procedures for Loiasis, Report of a multi-centre study, 2001, who.int/tdr/publications/documents/loiasis.pdf); 2001.

103. African Programme for Onchocerciasis Control (APOC): **Report of the 38th session of the technical consultative committee (TCC), March 2014.** http://www.who.int/entity/apoc/about/structure/tcc/tcc38_final_report_130814.pdf?ua=1; 2014.

104. Awadzi K, Opoku NO, Attah SK, Lazdins-Helds JK, Kuesel AC: **Diagnosis of O. volvulus infection via skin exposure to diethylcarbamazine: clinical evaluation of a transdermal delivery technology-based patch.** *Parasit Vectors* 2015, **8:** 515.

105. Fink DL, Kamgno J, Nutman TB: **Rapid molecular assays for specific detection and quantitation of Loa loa microfilaremia.** *PLoS Negl Trop Dis* 2011, **5:** e1299.

106. D'Ambrosio MV, Bakalar M, Bennuru S, Reber C, Skandarajah A, Nilsson L *et al.*: **Point-of-care quantification of blood-borne filarial parasites with a mobile phone microscope.** *Sci Transl Med* 2015, **7:** 286re4.

107. Toe L, Adjami AG, Boatin BA, Back C, Alley ES, Dembele N *et al.*: **Topical application of diethylcarbamazine to detect onchocerciasis recrudescence in west Africa.** *Trans R Soc Trop Med Hyg* 2000, **94:** 519-525.

108. Ozoh G, Boussinesq M, Bissek AC, Kobangue L, Kombila M, Mbina JR *et al.*: **Evaluation of the diethylcarbamazine patch to evaluate onchocerciasis endemicity in Central Africa.** *Trop Med Int Health* 2007, **12:** 123-129.

109. Boatin BA, Toe L, Alley ES, Nagelkerke NJ, Borsboom G, Habbema JD: **Detection of Onchocerca volvulus infection in low prevalence areas: a comparison of three diagnostic methods.** *Parasitology* 2002, **125:** 545-552.

110. Boussinesq M, Kamgno J, Eloundou Onoma P, Befidi R, Gardon J: *Evaluation du patch DEC chez les sujets infectés par Loa loa.* Yaounde, Cameroon: Document du Laboratoire mixte CPC/ORSTROM d'Epidémiologie et de Santé publique no 98-16, Centre Pasteur; 1998.

111. Walker M, Specht S, Churcher TS, Hoerauf A, Taylor MJ, Basanez MG: **Therapeutic efficacy and macrofilaricidal activity of doxycycline for the treatment of river blindness.** *Clin Infect Dis* 2015, **60:** 1199-1207.

112. Taylor MJ, Hoerauf A, Bockarie M: **Lymphatic filariasis and onchocerciasis.** *Lancet* 2010, **376:** 1175-1185.

113. Hoerauf A: **Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis.** *Curr Opin Infect Dis* 2008, **21:** 673-681.

114. Albers A, Esum ME, Tendongfor N, Enyong P, Klarmann U, Wanji S *et al.*: **Retarded Onchocerca volvulus L1 to L3 larval development in the Simulium damnosum vector after anti-wolbachial treatment of the human host.** *Parasit Vectors* 2012, **5:** 12.

115. Awadzi K, Opoku NO, Attah SK, Lazdins-Helds J, Kuesel AC: **A Randomized, Single-Ascending-Dose, Ivermectin-Controlled, Double-Blind Study of Moxidectin in Onchocerca volvulus Infection.** *PLoS Negl Trop Dis* 2014, **8:** e2953.

116. Hoerauf A, Marfo-Debrekyei Y, Buttner M, Debrah AY, Konadu P, Mand S *et al.*: **Effects of 6-week azithromycin treatment on the Wolbachia endobacteria of Onchocerca volvulus.** *Parasitol Res* 2008, **103:** 279-286.

117. Horton RJ: **Benzimidazoles in a wormy world.** *Parasitol Today* 1990, **6:** 106.

118. Dominguez-Vazquez A, Taylor HR, Greene BM, Ruvalcaba-Macias AM, Rivas-Alcala AR, Murphy RP *et al.*: **Comparison of flubendazole and diethylcarbamazine in treatment of onchocerciasis.** *Lancet* 1983, **1:** 139-143.

119. Mackenzie CD, Geary TG: **Flubendazole: a candidate macrofilaricide for lymphatic filariasis and onchocerciasis field programs.** *Expert Rev Anti Infect Ther* 2011, **9:** 497-501.

120. Ceballos L, Mackenzie C, Geary T, Alvarez L, Lanusse C: **Exploring the potential of flubendazole in filariasis control: evaluation of the systemic exposure for different pharmaceutical preparations.** *PLoS Negl Trop Dis* 2014, **8:** e2838.

121. Tweats DJ, Johnson GE, Scandale I, Whitwell J, Evans DB: **Genotoxicity of flubendazole and its metabolites in vitro and the impact of a new formulation on in vivo aneugenicity.** *Mutagenesis* 2015.

122. O'Neill M, Geary JF, Agnew DW, Mackenzie CD, Geary TG: **In vitro flubendazole-induced damage to vital tissues in adult females of the filarial nematode Brugia malayi.** *Int J Parasitol Drugs Drug Resist* 2015, **5:** 135-140.

123. Longo M, Zanoncelli S, Messina M, Scandale I, Mackenzie C, Geary T *et al.*: **In vivo preliminary investigations of the effects of the benzimidazole anthelmintic drug flubendazole on rat embryos and fetuses.** *Reprod Toxicol* 2014, **49C:** 33-42.

124. Olliaro P, Seiler J, Kuesel A, Horton J, Clark JN, Don R *et al.*: **Potential drug development candidates for human soil-transmitted helminthiases.** *PLoS Negl Trop Dis* 2011, **5:** e1138.

125. Taylor MJ, Hoerauf A, Townson S, Slatko BE, Ward SA: **Anti-Wolbachia drug discovery and development: safe macrofilaricides for onchocerciasis and lymphatic filariasis.** *Parasitology* 2014, **141:** 119-127.

126. Bakajika DK, Nigo MM, Lotsima JP, Masikini GA, Fischer K, Lloyd MM *et al.*: **Filarial antigenemia and Loa loa night blood microfilaremia in an area without bancroftian filariasis in the Democratic Republic of Congo.** *Am J Trop Med Hyg* 2014, **91:** 1142-1148.

127. Pion S, Montavon C., Chesnais C.J., Kamgno J, Wanji S, Boussinesq M: **Correlation between high Loa loa microfilaremia and levels of circulating filarial antigens used to detect Wuchereria Bancrofti infections.** *Journal of the American Society for Tropical Medicine and Hygiene* 2014, **91 (Supplement):** 177-178.

128. Wanji S, Amvongo-Adjia N, Koudou B, Njouendou AJ, Chounna Ndongmo PW, Kengne-Ouafo JA *et al.*: **Cross-Reactivity of Filariais ICT Cards in Areas of Contrasting Endemicity of Loa loa and Mansonella perstans in Cameroon: Implications for Shrinking of the Lymphatic Filariasis Map in the Central African Region.** *PLoS Negl Trop Dis* 2015, **9:** e0004184.

129. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux JP: **Clinical picture, epidemiology and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon.** *Filaria J* 2003, **2 Suppl 1:** S4.

130. Birley MH, Walsh JF: **Development of a model for Simmulium damnosum s.l. recolonization dynamics at a breeding site in the Onchocerciasis Control programme area when control is interrupted.** *J Appl Ecol* 1983, **20:** 507-519.

131. Dietz K: **The population dynamics of onchocerciasis.** In *Population Dynamics of Infectious Diseases*. Edited by Anderson RM. London: Chapman & Hall; 1982:209-241.

132. Plaisier AP, van Oortmarssen GJ, Remme J, Alley ES, Habbema JD: **The risk and dynamics of onchocerciasis recrudescence after cessation of vector control.** *Bull World Health Organ* 1991, **69:** 169-178.

133. Hougard JM, Alley ES, Yameogo L, Dadzie KY, Boatin BA: **Eliminating onchocerciasis after 14 years of vector control: a proved strategy.** *J Infect Dis* 2001, **184:** 497-503.

134. Plaisier AP, Alley ES, van Oortmarssen GJ, Boatin BA, Habbema JD: **Required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in west Africa.** *Bull World Health Organ* 1997, **75:** 237-245.

135. Winnen M, Plaisier AP, Alley ES, Nagelkerke NJ, van OG, Boatin BA *et al.*: **Can ivermectin mass treatments eliminate onchocerciasis in Africa?** *Bull World Health Organ* 2002, **80:** 384-391.

136. Krotneva SP, Coffeng LE, Noma M, Zoure HG, Bakone L, Amazigo UV *et al.*: **African Program for Onchocerciasis Control 1995-2010: Impact of Annual Ivermectin Mass Treatment on Off-Target Infectious Diseases.** *PLoS Negl Trop Dis* 2015, **9:** e0004051.

137. Alley WS, van Oortmarssen GJ, Boatin BA, Nagelkerke NJ, Plaisier AP, Remme JH *et al.*: **Macrofilaricides and onchocerciasis control, mathematical modelling of the prospects for elimination.** *BMC Public Health* 2001, **1:** 12.

138. Filipe JA, Boussinesq M, Renz A, Collins RC, Vivas-Martinez S, Grillet ME *et al.*: **Human infection patterns and heterogeneous exposure in river blindness.** *Proc Natl Acad Sci U S A* 2005, **102:** 15265-15270.

139. Basanez MG, French MD, Walker M, Churcher TS: **Paradigm lost: how parasite control may alter pattern and process in human helminthiases.** *Trends Parasitol* 2012, **28:** 161-171.