INFORMAL CONSULTATION ON ELIMINATION OF ONCHOCERCIASIS TRANSMISSION WITH CURRENT TOOLS IN AFRICA – "SHRINKING THE MAP"

OUAGADOUGOU, BURKINA FASO

25 – 27 FEBRUARY 2009

Executive summary

The African Programme for Onchocerciasis Control (APOC) was initiated in 1995 with the objective "to establish effective and self-sustainable, community-directed ivermectin treatment throughout the endemic areas in the geographic scope of the Programme, and, if possible, in selected and isolated foci to eradicate the vector by using environmentally safe methods". The attainment of this objective is expected to contribute towards the elimination of onchocerciasis as a disease of public health and socio-economic importance throughout Africa and to improving the welfare of its people.

APOC's objective reflects expectations of the effectiveness of available control strategies. Since vector eradication was not thought to be feasible, except in some selected and isolated foci, ivermectin mass treatment has been defined as the primary control strategy in most of the Programme area. Ivermectin effectively kills the microfilariae that cause the severe manifestations of the disease, but has limited impact on adult worms. Regular re-treatment is therefore required during the life span of adult worms. Consequently, annual mass treatment with ivermectin reduces but does not halt transmission during the first years of intervention. It was therefore concluded that mass treatment needed to be continued for a very long time. APOC/TDR supported research showed Community Directed Treatment with Ivermectin (CDTI) to be a feasible and effective mechanism for sustained ivermectin delivery.

The question of whether transmission of the parasite could eventually be eliminated and mass ivermectin treatment be stopped remained unanswered. However, recently evidence became available from Senegal and Mali, showing that it is possible to eliminate the disease in some settings in Africa. This led APOC to adopt as one of the new objectives for the phasing out period (2008-2015) "to determine when and where ivermectin treatment can be safely stopped and to provide guidance to countries on preparing to stop ivermectin treatment where feasible".

To refine APOC's strategy in moving towards the elimination of onchocerciasis, an informal consultation of experts in various onchocerciasis related fields were invited to a meeting in Ouagadougou titled "INFORMAL CONSULTATION ON ELIMINATION OF ONCHOCERCIASIS TRANSMISSION WITH CURRENT TOOLS IN AFRICA". This meeting was organised by the African Programme for Onchocerciasis Control (APOC), in collaboration with The Bill & Melinda Gates Foundation and Mectizan Donation Programme.

The objectives of the meeting were:
1. To review the state-of-the-art of elimination of onchocerciasis transmission with current tools in Africa, and to predict the feasibility of elimination in different parts of the continent.
2. To identify critical issues for the feasibility and optimal strategies of elimination in different epidemiological settings.
3. To identify research needs and priorities to answer key challenges related to elimination of onchocerciasis

Elimination was defined as the reduction of infection and transmission to the extent that interventions can be stopped, but post intervention surveillance is still necessary.

The meeting concluded that the Mali / Senegal study has provided convincing evidence that elimination of onchocerciasis is possible in Africa with current tools, which is supported by promising results from other countries. However, evidence is still insufficient to define the precise circumstances under which elimination is or is not feasible and the interventions required to achieve this goal. In particular, there is still a lack of information from forest areas, a major part of APOC's target zone.

The feasibility of elimination and efforts required to achieve this goal depend on the following factors:

1. Local circumstances: seasonal transmission, extent of hyperendemic areas and maximum endemicity level before the start of interventions, extent of transmission zones, level of onchocerciasis transmission in surrounding areas (including currently untreated low-endemic areas), vectorial capacity, immigrating flies, human migration, and accessibility.
2. Operational factors: geographic coverage, therapeutic coverage, years of ivermectin distribution, number of treatment rounds provided per year.
3. Local obstacles to treatment: Political instability / conflict, *Loa loa* co-endemicity

A framework to assess the potential for elimination in different parts of the continent was agreed.

The meeting concluded that it will be difficult to achieve elimination in the whole of Africa. Therefore, APOC should proceed gradually, targeting elimination where it is considered feasible. A critical evaluation of the epidemiological and operational situation in countries is required, before adopting the goal of elimination. This is particularly important, because a shift in strategy may require programmatic changes that can have far reaching implications for communities who play a leading role in the control programme.

Action points for moving forward to elimination include:

1. Generation of more empirical evidence on the feasibility of elimination and required interventions under different circumstances
2. Development of guidelines for countries on what has to be done to achieve, prove and maintain elimination of onchocerciasis infection and transmission.
3. Reviewing target areas for mass treatment and delineation of transmission zones.
4. Defining what has been accomplished in project areas to date and preparing projects for elimination where feasible.
5. Continue investments in development of better tools for onchocerciasis elimination, including:
    a. tools to kill or sterilize viable adult worms;
    b. diagnostic tools for measuring the presence and number of parasites in the human host, particularly viable adult worms.
6. Examination of the opportunities of linking with LF elimination programmes.

Based on this list, research needs and priorities were defined. They are listed in this report.

Introduction and rationale

The African Programme for Onchocerciasis Control (APOC) was initiated in 1995 with the objective "to establish effective and self-sustainable, community-directed ivermectin treatment throughout the endemic areas in the geographic scope of the Programme, and, if possible, in selected and isolated foci to eradicate the vector by using environmentally safe methods". The attainment of this objective is expected to contribute towards the elimination of onchocerciasis as a disease of public health and socio-economic importance throughout Africa and to improving the welfare of its people.

APOC's objective reflects expectations of the effectiveness of available control strategies. Since vector eradication was not thought to be feasible or cost-effective, except in some selected and isolated foci, ivermectin mass treatment has been chosen as the primary control strategy in most of the Programme area. Ivermectin effectively kills the microfilariae that cause the severe manifestations of the disease, but has limited impact on adult worms. Regular re-treatment is therefore required during the life span of adult worms to clear the infection entirely. Consequently, annual mass treatment with ivermectin reduces but does not halt transmission during the first years of intervention. It was therefore concluded that mass treatment needed to be continued for a very long time. APOC's research showed Community Directed Treatment with Ivermectin (CDTI) to be a feasible and effective mechanism for sustained ivermectin delivery.

Whether transmission of the parasite could eventually be eliminated and mass ivermectin treatment stopped was not known.

At a conference on the eradicability of onchocerciasis in Atlanta in 2002, it was concluded that onchocerciasis is not eradicable worldwide using current tools due to the major barriers in Africa (Dadzie *et al.* 2003). However, in most, if not all, of the Americas, and possibly Yemen and some sites in Africa, elimination of onchocerciasis transmission was thought to be feasible using current tools. Since then, the Pan American Health Organisation has resolved to eliminate onchocerciasis in the Americas and the Onchocerciasis Elimination programme of the Americas (OEPA) was established in 1992 to undertake this. OEPA has made steady progress and in several sites onchocerciasis transmission appears to have been stopped (Sauerbrey 2008). In 2008, PAHO adopted a new resolution calling for elimination of morbidity from onchocerciasis and interruption of transmission by the year 2012.

Evidence that it is possible to eliminate the disease in some settings in Africa with ivermectin treatment alone has recently emerged from Senegal and Mali (Diawara *et al*. 2009), and is supported by promising findings from Guinea Bissau and Kaduna State in Nigeria. This led APOC to include an additional objective, namely to develop the evidence base on when and where ivermectin treatment can be stopped, and provide guidance to countries on how to prepare for and evaluate cessation of treatment where feasible (APOC 2008). This was approved by APOC's governing body, the Joint Action Forum, in December 2008.

To shape APOC's strategy in moving towards the elimination of onchocerciasis, an informal consultation of experts in various onchocerciasis related fields were invited to the meeting, on which we report here, titled "INFORMAL CONSULTATION ON ELIMINATION OF ONCHOCERCIASIS TRANSMISSION WITH CURRENT TOOLS IN AFRICA" (Ouagadougou, Burkina Faso, 25-27 February 2009). This meeting was organised by the African Programme for Onchocerciasis Control (APOC), in collaboration with The Bill & Melinda Gates Foundation and Mectizan Donation Programme. The agenda of the meeting and list of participants are included as appendices.

The objectives of the meeting were:
1. To review the state-of-the-art of elimination of onchocerciasis transmission with current

tools in Africa, and to predict the feasibility of elimination in different parts of the continent.

2. To identify critical issues for the feasibility and optimal strategies of elimination in different epidemiological settings.

3. To identify research needs and priorities to answer key challenges related to elimination of onchocerciasis.

Opening

The meeting started with nostalgic reminiscing about the history of onchocerciasis control and initiation of APOC. Many of the meeting participants played a significant role in these efforts, defining strategy, implementing the activities and evaluating progress. There have been debates about the path to follow, but the innovative approach of CDTI as pioneered by APOC has proven to be successful. The important role of Merck & Co. Inc. in this success, with their unprecedented drug donation and commitment, is acknowledged, as is the emerging role of the Bill and Melinda Gates Foundation in defining a way forward.

Recent studies in Mali and Senegal now show that the CDTi approach can even lead to elimination in specific foci. These successes need to be celebrated and built on. With the renewed focus on neglected tropical diseases as well as significant funding and goodwill, there is now a unique opportunity to take these advances forward and explore new tools and strategies. The main challenge for the future is to "shrink the map" of onchocerciasis prevalence in Africa, by eliminating onchocerciasis transmission where possible. Participants were invited to explore the options available to advance control and eliminate onchocerciasis in an open, scientific discussion.

Definitions

The APOC Governing Body, the Joint Action Forum, during its meeting in December 2008, requested that the informal consultation clearly define what is meant by elimination. The participants therefore discussed this question at length and arrived at the following definition of onchocerciasis elimination.

Elimination of onchocerciasis:

Short definition:
Reduction of *O. volvulus* infection and transmission to the extent that interventions can be stopped, but post intervention surveillance is still necessary

Operational definition:
Defining when interventions can be stopped is a challenge, and in practice the stop-decision always needs to be evaluated afterwards. Therefore, operationally, elimination requires achieving the following steps:

- **Interventions have reduced *O. volvulus* infection and transmission below the point where the parasite population is believed to be irreversibly moving to its demise/extinction in a defined geographical area;**
- **Interventions have been stopped;**
- **Post intervention surveillance for an appropriate period has demonstrated no recrudescence of transmission to a level suggesting recovery of the *O. volvulus* population;**
- **Additional surveillance is still necessary for timely detection of recurrent infection, if a risk of reintroduction of infection from other areas remains.**

Theoretical basis for these definitions:
In the above definitions, the term intervention refers to the active measures implemented to reduce the parasite population in previously endemic areas. For APOC, this currently includes (annual) mass ivermectin treatment and, in isolated foci, vector control. The term surveillance is used to describe the activities to ensure that the infection transmission has stopped and that there are no new infections.
Both definitions are based on the ideas of the International Taskforce for Disease Eradication (ITFDE) and Dahlem Workshop on the Eradication of Infectious Diseases in 1997, which defined elimination

of infection theoretically as "a reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required" (Dowdle & Hopkins 1998). The continued need for measures to prevent reestablishment relates to the local nature of the concept: there remains a risk of reintroduction of infection from outside.
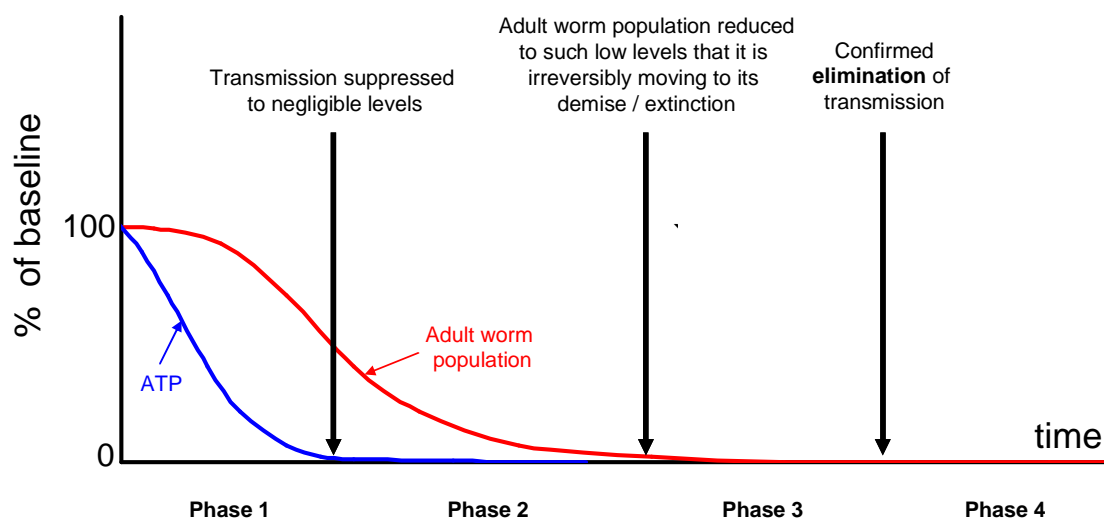
The operational definition of onchocerciasis elimination reflects current thinking about the impact of interventions, as illustrated in Figure 1. Basically, we distinguish 4 phases in elimination programmes, which differ with respect to transmission and needs for interventions / surveillance.

- Phase 1 - Interventions lead to a reduction in transmission and parasite numbers, but transmission still continues. If interventions are continued successfully, both measures will decline and at some point remaining transmission may be zero or negligible (1st arrow). This achievement is conditional on continued interventions.

- Phase 2 - Transmission in this phase is negligible or zero, as long as interventions are continued. In this phase, the adult worm parasite population shows an accelerated decrease due to natural or treatment-induced death of old worms without replenishment. This phase ends if the adult worm population is reduced to such low levels that it will move irreversibly to its demise / extinction, even without further interventions (2nd arrow). In modelling terms: the parasite density is brought below its *breakpoint*.

- Phase 3 - Parasite numbers are now so low that any residual transmission is insufficient for the parasite population to survive: possibly remaining parasites have too low a chance of successful reproduction and eventually the parasite population becomes extinct. Intervention measures have been stopped. Post-intervention surveillance is required, to check that the parasite population and transmission do not recover after stopping the interventions. If post-intervention surveillance confirms the continued absence of transmission, we say that elimination is achieved (3rd arrow). The WHO guidelines suggested using a period of at least 3 years (WHO. 2001).

- Phase 4 - After achieving elimination, a routine surveillance system should be established for timely detection of the possible reintroduction of infection from other areas where the infection still occurs. Theoretically, this phase continues until global eradication is achieved.

We deliberately attributed no time scale to the different phases, acknowledging that their duration depends on chosen control strategies (vector control, mass treatment, or a combination) and local circumstances.

Figure 1. Schematic representation of the phases in programmes for elimination of onchocerciasis transmission, in relation to the theoretical fall-off of the adult worm population and annual transmission potential (ATP). Arrows mark major achievements, which indicate the transition between phases and changes in required interventions or surveillance activities as described.

	Phase 1	Phase 2	Phase 3	Phase 4
Transmission:	Ongoing	Negligible, conditional on continued intervention	(Irreversibly approaching) zero due to insufficient or absent adult worms	Zero
Intervention:	Active intervention, aimed at reducing worm burden or transmission (mass treatment and/or vector control)		None	None
Surveillance:	Monitoring & evaluation of progress		Active surveillance to proof elimination	Surveillance for timely detection of a possible reintroduction of infection

Transmission zone

A geographical area, where transmission of *O. volvulus* occurs by locally breeding vectors. This zone can be regarded as a natural ecological and epidemiological unit for interventions.

A transmission zone can be 'open' or 'closed', depending on whether there is migration of (possibly infected) flies or humans to and from neighbouring areas. Complete closure may rarely occur in real life. For practical purposes, we define closed transmission zones as those where in- or out-migration of infected humans or flies is a relatively rare event that normally has little impact on the transmission dynamics.

To achieve elimination in closed transmission zones, interventions can be restricted to the transmission zone itself. However, post-intervention surveillance is still necessary if there is a risk of reintroduction of infection from outside. To eliminate onchocerciasis from open transmission zones, interventions are also needed in the source-areas of infected flies and humans. It will therefore be important to define transmission zones and determine whether these are closed or open systems.

Session 1: Elimination with ivermectin: state of the art

Elimination in the Americas, current evidence / critical issues – Frank Richards

– The Onchocerciasis Elimination Programme of the Americas (OEPA) aims to eliminate onchocerciasis from the Americas by ivermectin mass treatment given twice per year with a goal of reaching >85% eligible population coverage.
– It is thought that onchocerciasis was taken to the Americas from Africa. Yet, the epidemiology of onchocerciasis in the Americas has some unique features: it is limited to specific foci, relatively static and most of the American vectors are not as efficient as those in Africa.
– If elimination is to occur, interventions (such as treatment coverage) need to be sufficient over a specified time period
– OEPA uses a 2x per year ivermectin treatment regimen, because this is thought to keep transmission at negligible levels throughout the whole year and to reduce the adult worm lifespan.
– Epidemiological and entomological data should be monitored in sentinel areas:
  o Population based surveys are important
  o Transmission should be measured by looking at infection rates in children
  o ATP thresholds are important (Breakpoint / R_0 concept)
– OEPA's criteria for certification of elimination are based on those published by WHO in 2001 (2001), but the OEPA steering committee made some modifications based on operational, statistical, cost and programmatic considerations. These criteria distinguish between elimination of morbidity and transmission.
  o Elimination of morbidity:
    ▪ Prevalence of microfilariae (mf) in the cornea or anterior eye chamber <1%
  o Elimination of transmission:
    ▪ OCP standard of L3 in flies <0.05% (0.1% in parous flies);
    ▪ ATP lower than 5-20 L3 per season;
    ▪ Absence of detectable infection in school children and antibody prevalence of <0.1%.
– Based on current guidelines, a sufficiently long post treatment surveillance period (at least 3 years by WHO guidelines (2001)) is required to declare elimination.
– Progress towards elimination of onchocerciasis in the Americas is traced by documenting how many of the 13 foci have reached phase 2, 3 and 4 in the elimination process (see Figure 1): 6 are in phase 3 ("interruption of transmission") and 1 other has partially met the criteria for this phase; 1 has reached phase 2 ("suppression of transmission") and the remaining 5 foci are still in phase 1. The "problem" clusters are located in Venezuela and Brazil. These results can be summarized in a tabular form, sorting the foci by phase and using colour codes for the achieved phases ("Onchocerciasis flag"). This categorization or "flag" is now also being used in the Ugandan programme for elimination.
– NB. WHO certifies country not 'foci' for elimination. Following progress in foci is an important step towards elimination, but certification of elimination can only occur at the national level when all foci have been eliminated. External technical assistance is usually required.
– WHO guidelines should be used 'in principle' but may have to be modified. They are useful for guiding the declaration of elimination, but must be constantly re-evaluated given country and programmatic requirements / realities.
– The new PAHO resolution about onchocerciasis elimination, which was adopted in 2008, now explicitly includes a timeframe for elimination: elimination of (new) ocular morbidity and interruption of transmission is to be achieved by 2012.

The feasibility of using entomological measures such as ATP for monitoring & evaluation and for certifying elimination was discussed because of the problems in catching and counting flies. Current methods, based on landing catches, are expensive and have increasing ethical concerns. There is a

need for a new efficient trap to capture flies that will solve the ethical dilemma of using current methods.

Elimination in Africa, current evidence/critical issues - Hans Remme

– The Onchocerciasis Control Program in West Africa (OCP) has successfully eliminated onchocerciasis by vector control from most of the original OCP area, and this achievement has been well-documented. An important publication in a French language journal (Agoua *et al*. 1995) gave the results of epidemiological and entomological studies after 14 years of vector control. In 18 catching points pre-control infectivity rates that ranged from 60 – 90 per 1000 parous females had decreased to less than 1 per 1000; levels at which recrudescence was thought to be most unlikely. These results validated the cessation of larviciding at the time.

– When OCP stopped vector control, prevalence of infection and transmission were not 0, but transmission was below threshold levels required to stop transmission of disease. This shows that it is not necessary to bring transmission down to zero.

– Whilst the criteria used by OCP were generally validated, recrudescence of infection along the River Bougouriba at the time demonstrated a situation where evaluations had failed to detect residual transmission along an affluent where a new dam had created new breeding sites.

– The example of OCP showed that (local) elimination is feasible in Africa by vector control. Whether this can be achieved by ivermectin treatment remained uncertain. It was therefore agreed to carry out a study to test the feasibility of elimination in 3 foci in Mali and Senegal, where ivermectin mass treatment was started in the late eighties and remained the only control strategy. Two foci had annual treatment; the other had 6-monthly treatment.

– The results from this study showed that whilst prevalence varied it had been above 70% in many villages prior to the intervention:
  o After 15 to 17 years of ivermectin treatment, the infection and transmission levels were below postulated thresholds for elimination (Prevalence of mf < 1% in 90% of villages and < 5% in all villages; Rate of flies with L3 in the head < 0.5 per 1000 flies)
  o Treatment was therefore stopped in test areas of 5 to 8 villages in each focus.
  o Evaluations 1.5 to 2 years after the last treatment showed no infected persons and no infected blackflies in the test areas
  Hence the study provided the first empirical evidence that elimination of onchocerciasis with ivermectin treatment is feasible in endemic foci in Africa.

– In Guinea Bissau, civil conflict interrupted the MDA program and provided a natural experiment in which the impact of just 6 annual ivermectin treatments could be evaluated. Epidemiological and entomological evaluations undertaken 12 years after the last treatment round in the River Geba focus showed that onchocerciasis had been eliminated. It is not clear if this was a result of ivermectin alone or whether other factors also played a role as the area was only hypoendemic before the start of control, and the epidemiological situation may have been unstable.

– **In summary, there is now evidence from Senegal, Mali and Guinea Bissau that elimination is possible within defined geographical areas.**

– In addition, there are promising data from two foci in Kaduna State in Nigeria, which were meso endemic before the start of control and in which, after 16-19 years of ivermectin treatment the prevalence of mf has reduced to zero.

– Based on the positive findings from the above studies, the Joint Action Forum has adopted a new objective for APOC, namely to determine when and where ivermectin treatment can be stopped and to provide guidance to countries on preparing to stop ivermectin treatment where feasible (APOC 2008).

– Issues remaining to be addressed are:
  o Elimination thresholds – stopping criteria
    ▪ Does infection/transmission need to be 0 to stop treatment?

- If not, what level is acceptable in what epidemiological situation, considering the risk of recrudescence?
- How do we measure the relevant level of infection (indicators, tools, strategies; cross-sectional or trends)?
  - o Recrudescence
    - What is the risk of recrudescence for different indicator levels?
    - How many years after stopping treatment is recrudescence still possible?
    - What are the dynamics of recrudescence?
    - How to detect recrudescence in time (tools, practical surveillance strategies / early warning)?
  - o Other endemic areas in Africa:
    - What is the feasibility, timeframe for other vector parasite complexes / endemicity levels?
    - To what extent are elimination prospects influenced by spatial factors (vector reinvasion, distance factors, coverage patterns, human migration, etc.)
  - o Alternative intervention strategies:
    - Treatment frequencies, 6-monthly vs. yearly treatment
    - Vector control
    - Endpoint strategies

Some of these issues were discussed in later sessions, focusing on the question: how confident are we that elimination strategies working in one area will also work in others?
- Besides the successes shown in OCP, there was also the temporary setback in Bougouriba. Targeted studies in this area showed that new breeding sites had developed there, causing the recrudescence, which was successfully addressed before the closure of OCP. This highlighted the need for continued environmental evaluations so that opportunities for re-infestation can be identified and controlled.
- For ivermectin mass treatment programmes it is also important to understand whether few remaining infected individuals after mass treatment can pose a threat to elimination. Are there "super spreaders" for onchocerciasis?

Session 2: Predictors of elimination with ivermectin

Long term impact of ivermectin treatment on survival and reproductivity of the parasite – Kwablah Awadzi
- Ivermectin is a powerful microfilaricidal drug. It is also thought to affect adult worms in two ways:
  - o Effects on vitality of adult female worms;
  - o Effects on reproductive activity of the parasite.
- In general, ivermectin is considered very effective. However, some findings suggest that ivermectin is not always that effective, for example:
  - o Persistent microfilaridermias despite multiple treatments;
  - o Suboptimal response of adult female worms:
    - Non status embryostaticus;
    - Non serial embryostaticus.
  - o Putative development of resistance;
  - o Putative loss of ability to sequestrate mf *in utero*.
  There were lengthy discussions on possible explanations for these observations.
- Based on his studies, Dr. Awadzi categorized the female worm responses to ivermectin as follows:

- o Category 1: Female worm fully responsive;
- o Category 2: Female worm response partial or incomplete;
- o Category 3: Female worm is not responsive.
- – In conclusion: there is general agreement on the complete microfilaricidal effects of ivermectin. There is also an effect on longevity or fertility of (female) adult worms. Some studies suggest that some adult worms are not responsive or only partially responsive to treatment, but there was debate regarding the explanation for such findings.

The discussion highlighted two issues. Firstly, further evidence of poor response to ivermectin treatment needs to be collected. Implications for elimination need to be assessed and plans for how to respond need to be defined. Secondly, the search for other drugs with good macrofilaricidal effects should continue.

Long term impact of ivermectin treatment on survival and reproductivity of the parasite – Ed Cupp

- – This presentation summarized the results of several clinical trials, done in the Americas to investigate how treatment frequency affects its impact (Cupp & Cupp 2005).
- – These trials compared the following three treatment regimens:
  - o monthly treatment for a period of 4, 8 or 12 months
  - o single dose vs. 4 6-monthly doses
  - o 3-monthly treatment

- – Other evaluations concerned the impact of repetitive community-wide ivermectin treatment in Guatemala (Cupp *et al.* 2004)
- – Main conclusions from these studies:
  - o Ivermectin has activity against the adult worm when used sequentially (e.g. 2 or 4x per year), reducing the number of both male and female worms found in nodules;
  - o Exposure to 2x/yr ivermectin treatment over a 6 year period (1995-2001) significantly reduced the numbers of males per nodule (p<0.0001) compared to historical controls and significantly altered reproductive status in surviving females producing microfilariae (p<0.0001).
- – An important consideration for using multiple treatments per year is to suppress transmission, so that new L3 larvae are not formed and incidence of new infections is prevented. The increased effect on male and female adult worms also benefits elimination efforts.
- – The above unpublished studies suggest that the effect of 5 years of 6-monthly ivermectin treatment is greater than that of 12-13 years interrupted transmission by vector control.

There was some debate about the interpretation of data and the added effect on adult worms. The data from Duke may still be available at John Hopkins University for reanalysis. There are no studies that explicitly compare the effect of once yearly vs. twice yearly treatment.

Model predictions of elimination: strategies, assessment and critical factors – Hans Peter Duerr & Wilma Stolk

- – Dr. Duerr explained theoretical thinking about elimination vs. persistence of onchocerciasis infection and discussed some important concepts. See also (Duerr *et al.* 2005)
  - o A persistence curve shows how the parasite density (e.g. measured by ATP, CFML, mf prevalence, number of adult worms) depends on the annual biting rate of the black fly vector and what happens under the influence of interventions.
  - o With a constant biting rate, the parasite density will (move to, or) remain in a stable equilibrium, which depends on the biting rate. In general, a higher biting rate will result in a

higher equilibrium level, but tends to a maximum.

- o Vector control reduces the biting rate. If the annual biting rate is brought below a threshold, called the <u>threshold biting rate</u>, parasites cannot effectively reproduce because there are too few flies to transmit infection from one person to another. If annual biting rates remain below this threshold, the parasite population will decline and eventually move towards extinction.
- o Repeated ivermectin mass treatment reduces the parasite density in humans (e.g. measured by CMFL, mf prevalence, number of adult worms), and therefore the density in flies (e.g. measured by the ATP), and number of new infections. Below a threshold parasite density, called the <u>breakpoint</u>, the mating probability and chance of successful reproduction become too low: the number of new infections introduced into the human population is too low to maintain the worm population. Without any further intervention, the parasite population will move to extinction. The breakpoint density depends on the annual biting rate (ABR): the higher the ABR, the lower the breakpoint.
- Mass ivermectin treatment can lead to elimination if the parasite density is brought below the breakpoint. This theory explains why it is not necessary to reduce the parasite density to zero to achieve elimination: it is sufficient to bring it below its breakpoints. If control stops before the breakpoint is reached, recrudescence occurs and the parasite density will move back towards its equilibrium level.
- The breakpoint level depends on the ABR: the higher the ABR, the lower the breakpoint. In areas with high ABR, longer or more intensive interventions will be required, because the initial parasite density is higher and reproductive capacity at low parasite density is also higher. In areas with very high biting rates, the standard mass treatment approach may not be sufficient to reach the breakpoint. Additional measures may be required, such as extra efforts to increase the coverage, more frequent mass treatment, or addition of vector control.
- Challenges for APOC:
  - o Identify adequate and feasible diagnostics for monitoring parasite density, infection intensity, and prevalence.
  - o Determining the breakpoint curve.
  - o Defining setting-specific control requirements (e.g. additional vector control in areas with very high ABR)

- Dr. Stolk mentioned that the modelling groups in Rotterdam, Tuebingen and Imperial College London are all working on estimating breakpoints. This presentation summarized results obtained with the ONCHOSIM simulation model (Plaisier *et al.* 1990).
- Estimates of the coverage and number of treatment rounds required to achieve elimination in different settings have already been published (Winnen *et al.* 2002). In summary:
  - o 10 rounds of annual ivermectin mass treatment with 65% coverage are usually not sufficient to achieve elimination in a village with pre-control CMFL = 30. The elimination probability is about 5%.
  - o The elimination probability increases with increasing duration of the mass treatment programme, but >20 annual treatments are required for >= 90% probability of elimination
  - o Factors that determine the required duration of mass treatment are:
    - ▪ Local transmission conditions, including the
      - • Pre-control endemicity level (which mainly depends on fly density / ABR)
      - • Heterogeneity in exposure between individuals (leading to variability in the parasite densities)
    - ▪ Programmatic factors, including coverage, extent of systematic non-compliance, frequency of treatment (NB. the required duration of mass treatment is about halved, when treatment is given 6-monthly instead of annually)
- Efforts are ongoing to estimate "breakpoints" (see above) and define criteria for determining when to stop mass ivermectin treatment in different situations.
  - o ONCHOSIM determines the outcomes of a mass treatment programme by chance processes.

The same intervention applied in areas with similar transmission conditions may sometimes lead to elimination and sometimes to recrudescence.

o The probability of elimination can be related to the remaining parasite density after the last treatment round, here measured by CMFL or mf prevalence. The table shows rough estimates of the levels to which CMLF and mf prevalence must be reduced to achieve ≥90% probability of elimination:

	CMFL	Mf prev
Meso-endemic areas (simulated with the following mean pre-control values: CMFL 30 mf/s, mf prevalence 52%)	0.2 mf/s	8%
Hyper-endemic areas (simulated with the following mean pre-control values: cmfl about 70 mf/s, mf prevalence 75%)	0.1 mf/s	3%

o Note that the 'breakpoint' levels depend on the pre-control endemicity (influenced by biting rate, exposure heterogeneity, and other local factors) and the risk of failure that is still considered acceptable.

– All estimates presented are subject to uncertainties, e.g. about:
   ▪ Effects of ivermectin
   ▪ Density dependence in different processes of the transmission cycle
   ▪ Heterogeneity in exposure

– Model predictions remain to be validated, using the available data on trends in infection prevalence / CMFL during (and preferably after!) long term ivermectin treatment.

Key issues raised in discussion:
– Breakpoints should be determined for different indicators of parasite density in human or vector populations, e.g. measured by ATP, CFML, mf prevalence, number of adult worms. This is particularly important, because skin snipping is no longer popular and is increasingly considered to be unethical.
– We need to understand the correlations between different infection indicators in situations close to elimination.
– There is already substantial data available that can be used for model validation and there may be opportunities to collect new data.
– Statistical approaches (instead of mathematical modelling) can also help to determine how the infection prevalence / CMFL after treatment depends on programmatic factors. This requires the availability of many data. It could be useful to bring all available data together.

Session 3: Spatial issues in Elimination

Vector migration and vector / parasite complexes, human migration issues – Frank Walsh

– Before OCP, the entomologists knew that *S. damnosum* flies were migrating. Yet the extent of the problem was not anticipated.
– Major problems occurred in the Leraba and White Volta basin, where infection recommenced with the start of the rainy season. After many studies, entomologists were convinced that the programme was working well, but that the flies were coming from outside (mainly from the southwest). When vector control was extended in a southwestern direction, the problems in the core areas disappeared.
– Lesson learned: for control measures to be effective, the source areas of migrating flies need to be included in the intervention zone.
– Vector migration may explain the fact that the severest onchocerciasis foci were not on

permanent rivers, but on the temporary ones. When there are many immigrant (older) flies, the parous rates in an invaded area are higher. Normally around 50%, but in invaded areas it can be 70 to 80%. If infected in source area, they arrive with mature L3 larvae (higher infectivity rate).

– We now know that individual flies can move distances of 300-600 km. This is common in savanna flies (*Simulium damnosum* s.s., *S. savannum*), but not in forest flies (which live in a favourable ecological environment and have no reason to move).

– This has implications for APOC:
  o In northern savanna areas, APOC would need to work on a large scale concurrently, because of immigrant flies: treatments are needed both in the areas where the flies come from and those where they fly to.
  o It would be beneficial to start in the source area of flies and to provide mass treatment just prior to the migration period. This has large benefits for the areas where the flies go to, in particular where treatment is given only yearly. But this may not be feasible in practice, because other factors co-determine when communities provide treatment.

– APOC also operates in isolated transmission zones.
  o *Simulium neavei* must be considered separately. These flies live and breed in pockets of forest. They don't have the tendency to move up to air streams for travelling long distances. They are really isolated. In areas like this we do not have to worry about control in surrounding areas (as was necessary in the northern savannas). *S. neavei* flies are very effective vectors: they are extremely anthropophilic flies with a long lifespan, and obligatorily breed on certain species of crabs. For elimination, vector control would be very cost-effective in this type of area.
  o Isolated *S. damnosum* foci are generally large. There have been foci in which the vector was eliminated by vector control, even in areas with *S. damnosum* s.s. as the main vector.

– Conclusion: if elimination is the objective, it is important to consider whether the "transmission zone" (see definitions) is open or closed.

Key points from discussion:
– Reflecting on the success regarding *S. neavei* elimination: must we always go for vector elimination or would a period of vector control be sufficient for onchocerciasis elimination? Is there a need for vector control in APOC's elimination efforts?

What is the impact of fly and human migration between Nigeria and Benin? We have fly movement, maybe dispersion of flies from Nigeria to Benin in July-Sept every year. This has been reported by people from the Kara basin and is currently under investigation by APOC/MDSC.

Vector migration and vector / parasite complexes, human migration issues – Daniel Boakye
– Migration is an important issue for transmission and elimination. We need to understand:
  o infectivity of migrant flies
  o distances covered and establishment of viable colonies
    ▪ vector species and their distribution
    ▪ availability of suitable breeding sites
  o Bi-directional migrations due to seasonal changes.
– Migration patterns of major savanna subspecies are understood, e.g.
  o *S. damnosum* distribution in rainy and dry season; during the dry season, flies are found much further south
  o *S. sirbanum* - in the rainy season flies move up north; in the dry season they are found much further south.
– Breeding sites may often contain several species. The vectorial capacity of these species can differ. In isolated transmission zones, vector control attempts focus on removing the main vector, but other minor vectors (with different breeding sites and behaviour) may remain and become more important in transmission.

– Although savanna vectors are better at transmitting savanna parasites, they can also transmit forest parasites and *vice versa*. Unpublished results of feeding experiments, carried out with *S. sanctipauli*, were presented.

Key points from discussion:
– Model predictions suggest that imported infections (e.g. via migrating flies) are an important factor for the success of elimination predictions.
– We have many data on transmission from OCP and OEPA, but few from APOC, because APOC was originally set up as a morbidity control programme. However, when considering elimination we have different data requirements, which need to be listed and will include data on vector migration.
– Project areas are not strictly based on (closed) transmission zones. Sometimes only part of a transmission zone may be covered by a project, while another part is not covered, (e.g. because it is in another country). This is problematic for achieving interruption of transmission.
– Remote sensing could help to identify breeding sites and dispersion areas for different vector species.
– When APOC succeeds in introducing treatment in all areas, then the importance of migrating flies is limited, because immigrant flies will no longer be heavily infected. However, maintaining high treatment coverage is not always possible (e.g. in conflict areas). Moreover, even low infection rates in immigrant flies may threaten elimination.

Target areas/ populations for ivermectin treatment and non-treatment areas – Mounkaila Noma, Hans Remme and Frank Richards
– At the beginning of the APOC programme, the key questions were;
  o What is the magnitude and distribution of the disease?
  o Where is ivermectin mass treatment needed?
  o Who is in need of ivermectin mass treatment?
– Data was not available at the time to answer these questions in APOC areas. Therefore a WHO Expert Committee on Onchocerciasis Control was set up to make estimates.
– It was then decided to do Rapid Epidemiological Mapping for Onchocerciasis (REMO) rather than using techniques such as skin snips for practical and ethical reasons.
– The principles of REMO (outlined in Noma *et al.* 2000) are:
  o Division of the country into zones
  o Selection of communities to be surveyed by zones
  o Rapid epidemiological assessment of endemicity in the selected communities (by nodule palpation of 50 adult males)
– REMO was used to delineate the population at high risk of contracting onchocerciasis, where ivermectin would be needed. It also gives some indication of pre-control prevalence and intensity of infection, which can be related to other infection indicators (e.g. blindness, low vision, itch) to get estimates of the pre-control burden of disease and potential impact of APOC.

- Dr. Remme's presentation focussed on the question of whether treatment zones need to be expanded to include hypo-endemic zones.
- REMO aimed to delineate hyper- and meso-endemic areas, where treatment would be required. Hypo-endemic areas would in principle not be mass treated, but passive treatment should be stimulated. If hypo-endemic villages were surrounded by villages with higher endemicity, they were also included in the target area for mass treatment. In practice, the boundaries of treatment target areas were not always clear and administrative boundaries also played a role in defining them.
- In discussing whether treatment is required in currently untreated hypo-endemic zones, it is useful to distinguish two types of hypo-endemicity:
  o First, we can have hypo-endemic tails of transmission zones: in most transmission zones, the

infection is greatest at the river and declines with increasing distance from the river. Hypo-endemic areas here represent the "tail" of the transmission zone. The hyper- or meso-endemic core area is already included in the treatment programme. It is hypothesized that hypo-endemic tail areas only exist because of incoming infections from the core-area and that infection would disappear from this area once the infection in the core is successfully controlled.

    o Second, there may be independent hypo-endemic areas that are self-perpetuating and will not disappear unless control happens in that specific area.

- Dr. Richards observed that the rationale for not treating in "true" hypo-endemic areas will have to be re-visited for an elimination strategy (the current policy of passive treatment is not widely implemented). To prevent re-introduction of infection into treatment areas from hypo-endemic areas, the latter would also have to be treated. Thus, a new transmission map for Africa is needed including hypo-endemic areas in target areas for treatment.

Group discussions focussed on the following issues:
- The term "hypo-endemicity" was introduced because of its operational consequence: there was no need for mass treatment in low-endemic areas for morbidity control programmes. In the context of elimination programmes, the term does not function anymore, because it has no operational consequence. There was a consensus at this meeting to abandon the term.
- In elimination the term **transmission zone** becomes more relevant than a distinction between hyper- meso- and hypo-endemic areas. The challenge is to define the geographical area needed to move from control to elimination; *i.e.* is this equivalent to that for control or is it more? If it is more, by how much?
- The methods to define and delineate transmission zones are not clear. This is an operational research issue. The delineation will be difficult as there is little data outside the treatment areas to guide the expansion. REMO data will probably be of limited use, because of the high risk of false-positivity in low endemic areas and limited sensitivity to detect low intensity infections.
- The issue of *Loa loa* presence in hypo-endemic areas and the risk/benefits of treating with ivermectin need to be kept in view.

Session 4: Assessing infection and transmission

Onchocerciasis: old and new diagnostic procedures – Tom Unnasch
– An ideal test for monitoring for elimination needs to have the following characteristics.
    o High specificity
    o High sensitivity
    o High throughput
    o Inexpensive
    o Field based (i.e. no cold chain etc)
– One complicating factor that needs to be kept in view is the existence of *O. ochengi*: a very similar cattle parasite, transmitted by the same vector, often impossible to distinguish morphologically and whose presence can cause false estimates. In areas where these coincide, an assay must be able to distinguish these two *Onchocerca* species.

- *O. volvulus* only exists in 2 hosts – in humans and black flies – and there are advantages and disadvantages of monitoring in either:

	Advantages	Disadvantages
Humans	- Sentinel population will potentially sample thousands of vectors per year - monitoring methods are simple, inexpensive and well documented	- Infection process is inefficient - Long pre-patent period
Flies	- Immediate indication of transmission levels	- In areas under control infected flies are often rare - Large numbers of flies need to be screened to detect transmission

The importance of <u>high specificity</u> cannot be stressed enough: in low-prevalence situations, it is extremely important to have high specificity in detecting rare events. Low specificity implies many false-positives, particularly in low-prevalence situations.
- Not only the choice of test, but also <u>sampling methods</u> are critical in certifying elimination.
  - The more negative observations accumulated, the stronger the conclusion of an absence of transmission will be => negative results are valuable
  - Sampling CANNOT be confined to a single time frame or single area if one seeks to prove absence;
  - Always calculate confidence intervals: all sampling is associated with sampling errors and that must always be considered!

Diagnostic tools, evaluation and post treatment surveillance strategies – Laurent Toe

- Many diagnostic tools have been developed for onchocerciasis:

Test	
Epidemiological tools for measuring infection levels in humans & early detection of infection in humans:	
Parasitology	Skin Biopsy
	Nodule Palpation
Serology (antibody detection)	Tricock 1
	Tricock 2
	C27
	OV 16
	Ov 3.6 Ov 9.4
DNA Tests	O-150 PCR
	Scratch PCR
DEC skin patch test	« OCP TEST »
	LTS
Entomological tools for measuring transmission levels & early detection of recrudescence of infection:	
Parasitology	Fly dissection
	Fly pool screening

The methods used to evaluate the impact of vector control on infection and transmission in the OCP were:
- skin snip surveys undertaken every three years in sentinel villages in order to assess the

incidence and trends in prevalence of mf
- fly collection at selected catching points near major breeding sites in each river, and the dissection of the flies for parasites in order to estimate vector density and transmission indicators, i.e. annual biting rates, annual transmission potentials and vector infectivity rates

- For post intervention surveillance, the following strategy may be considered:
  - Entomological surveillance: detection of areas at risk of recrudescence of transmission
    • Method: pool screening
    • Periodicity: every 3 years in surveillance sites
    • Indicator: infectivity rate
  - Epidemiological surveillance: detection of new infections
    • Methods:
      - Skin biopsy
      - DEC patch test
    • Periodicity: every 3 years in surveillance sites
    • Indicator: prevalence and incidence

Comparison of available diagnostic techniques

Test	Specificity	Sensitivity	*ochengi* interferes	Throughput	Cost	Application
skin snip	→100%	low	no	low	low	field
Nodule palpation	moderate	low	no	high	low	field
snip PCR	→100%	→100%	no	low	high	lab
scratch PCR	→100%	→100%	no	low	high	lab
DEC patch	variable	variable	no	low	low	field
Ov16 ELISA	→100%	± 60%	????	high	medium	lab
fly dissection	Low	low	yes	low	medium	field
pool screen PCR	→100%	→100%	no	high	varies	lab

Key points from discussion
- High specificity is really crucial for surveillance, because even with 99% specificity, we will pick up many false positives in our surveillance exercise. This is posing large problems for lymphatic filariasis elimination programmes. By (separately!) applying two different types of tests, we may be able to improve the specificity, if we require both tests to be positive for taking action.

- There was discussion about the recommendation to implement pool screening, because there have been large problems in the past:
  o Fly density is often low, making it difficult to catch sufficient fly numbers for reliable estimation of infectivity rates. In such situations, vector infectivity is also not a good indicator of transmission intensity. The Pool Screen software, developed for analyzing pool screen data, has been adjusted to better deal with such situations: it does not only calculate infectivity rates, but also the ABR and ATP. The latter is a better indicator of transmission than infectivity rate alone: a high infectivity rate is not problematic as long as the ATP is low.
  o There were practical problems with respect to transportation of flies and lab capacity, but these have been overcome or can be overcome with additional investments.
  o Fly catching (still based on human landing) continues to pose a problem. There is a need for an efficient trap. A trap should probably have the following characteristics: CO_2 can be used as a first attractant; when the fly is close, a visual attractant is needed to bring the fly towards the trap; a biochemical attractant is needed to elicit a landing response. In the past, there were problems with identifying attractants, but biochemical methods have improved and trap development might succeed now.
- Another question related to the use of pool screening concerns the stage of infection that should be detected: should we aim for detection of L3 or is it better to detect any stage of infection?

Because infection rates are usually much higher than infectivity rates, the sensitivity of the tests improves when you examine flies for any infection stage.

- There was also discussion about the possible use of the OV16 antibody test in the African context. OV16 is successfully used in OEPA. It is expected that the test will also work for the African species of onchocerciasis, although there is some uncertainty about the specificity (in particular for distinguishing *O. volvulus* and *O. ochengi* exposure).
- There have been experiments with a card format test, which can be easily used in the field without requiring ELISA. An unpublished validation study with the card test conducted in 2001 showed:
  o sensitivity 80% in mf positives;
  o 7% of OCP personnel were positive;
  o In uncontrolled areas, children are frequently found positive; however, positivity either does not occur or is infrequent in this age group after interruption of transmission;
  o The correlation between mf prevalence and the OV16 card test positive is not too bad.
- Some practical problems remain:
  o problems with expiry dates;
  o components are still patented;
  o the card test was never marketed, because of uncertain benefits. Significant investments would be required to (re)develop a card test for large scale use in APOC.
  Experience with the card test for antigen detection of LF is not promising.

- There was discussion about recommendations for the type of diagnostic test to be used in post-treatment surveillance. There are a number of candidate tests each of which has it advantages and disadvantages. An assessment is necessary of what needs to be done to bring these tests into practice. This should include:
  o Further validation of the DEC patch test;
  o Development of traps for fly catching, to enable large-scale implementation of pool screening with PCR;
  o Development of a rapid format card test for detection of OV16 antibody, with sufficient sensitivity and specificity.

Session 5: Twice yearly vs. annual treatment with ivermectin

Shifting the focus from control to elimination may have programmatic and strategic consequences. An important issue is the frequency of treatment: will yearly treatment be sufficient to achieve elimination? OEPA, which from the start aimed for elimination, has chosen to provide treatment 6-monthly. The Mali/Senegal study (see session 1) shows that elimination can be achieved by yearly mass treatment if continued for a long time. Results from Kaduna also support this, but the strategy may not be optimal. Data from Cameroon and Uganda suggest that a once yearly treatment regimen over 10 - 12 years will fail to disrupt transmission (Katabarwa *et al.* 2008). Histological evaluation of nodules in worms between 1993 and 2005 showed an initial ivermectin effect – but the live female worms persisted. Better effects may be achieved by twice yearly treatment.

Advantages and disadvantages of shifting to twice yearly treatment are listed below.

Advantages of twice yearly treatment:
1. Leads to a more sustained reduction in skin mf densities in treated individuals
2. Multiple treatments per year will result in a stronger reduction in live and reproductive adult worms in nodules
3. May help to increase the proportion of people that is treated at least once per year
4. May speed up the achievement of the point at which transmission is negligible or zero, as long

as the intervention continues (see definition section: "suppression of transmission")
5. May reduce time needed to achieve elimination, therefore easier to proclaim an endpoint and proclaim success in elimination. Heightens programme focus on shifting to elimination
6. May reduce the risk of resistance spreading in the worm-population

Disadvantages:
1. Will lead to a change in the CDTI philosophy in which communities decide when to treat
2. Distribution times will be necessarily more controlled from central level
3. When transmission intensity reaches low levels after several years of mass treatment, the extra benefit of twice yearly treatment may be limited
4. Extra costs involved
5. May put extra strains on communities and volunteers
6. Retraining of community volunteers and others involved
7. Logistics in country
8. More ivermectin needed

Discussion
– There is general agreement that the time needed for elimination is shorter with six monthly treatment, although it is not certain whether a 2x higher frequency of treatment results in 2x shorter required duration. Some argued that it may reduce the required duration to 6-7 years, but such a statement cannot be generalized. Data from the River Gambia / Mako focus, where large-scale 6-monthly ivermectin treatment has taken place since 1989, suggests that mf prevalence fell rapidly after the first few treatments, but was still 10-20% after 6-7; additional treatments did not always lead to further decline. Nonetheless, mf prevalence was usually lower than in river basins with yearly treatment. Data: (Borsboom *et al.* 2003).
– Rapid success is important if APOC wants to move towards elimination, particularly because of the limited timeframe of APOC (closure in 2015). Additional evidence of feasibility of elimination will be needed to provide guidelines to countries on when they can shift their goal towards elimination and what needs to be done to achieve the new goal. It may also strengthen the commitment from policymakers, programme managers, donors, etc.
– Some questions remain regarding the reduction in transmission and time needed for elimination that would be achieved by increasing the treatment frequency. But there is potential for a significant benefit of such a change for elimination programmes, given the effect on adult worm burden, the potential win in time, the psychological effect reaching defined targets earlier, and the potential reduction in risk of resistance emergence.
– Because of the programmatic implications, programmatic changes should not suddenly be implemented in all countries. Critical evaluation of the epidemiological and programmatic situation in each country should precede a decision on strategic changes.
– Expected advantages should be balanced against the efficiency of increasing the frequency. For example, in mature programmes with long standing ivermectin treatment the added impact of increasing the frequency may be rather limited and not worth the extra expense. The same is true for low-endemic areas, where good results can be expected with annual treatment. But in new programmes with hyperendemicity, it may be efficient to start directly with 6-monthly treatment.
– The recommendation is to move on gradually, checking carefully where increased frequency would be beneficial and evaluating the impact of programmatic changes.

Annual treatment should, for the time being, be maintained in settings as below:
o Mature projects which show good progress towards elimination;
o Countries unable to scale up to good annual coverage: they should use current resources to scale up annual treatment.
o Low-endemic areas, which are currently not selected for CDTI, where good results can be expected with annual treatment

Twice yearly treatment should be considered in the following settings:

- o In younger projects, if evaluation studies and/or targeted research projects suggest that the total period of mass treatment can be reduced by increasing the frequency and if 6-monthly treatment seems programmatically feasible;
- o In other projects with good coverage, but poor epidemiological results;
- o In isolated transmission areas;
- o For mopping up in areas with breaks in good coverage;
- o In areas where there is a sub-optimal response to ivermectin, suggesting possible emerging resistance.

Session 6: Conclusions and Recommendations

State of the art of elimination of onchocerciasis transmission with current tools in Africa and identification of favourable and unfavourable factors, assessment of feasibility of elimination in different parts of the continent

The Mali / Senegal study provided convincing evidence that elimination of onchocerciasis is indeed possible in Africa with current tools. Reports from other regions (Guinea Bissau, Nigeria) further support this conclusion. Evidence is still insufficient to define the precise circumstances under which elimination is feasible and the interventions required to achieve this goal. In particular, we still lack information from forest areas, which form a large part of APOC's target zone.

The feasibility of elimination and efforts required to achieve this goal depend on the following factors:

Local circumstances	– Extent of transmission zones
	– Presence and extent of hyperendemic areas
	– Maximum endemicity level before start the start of interventions
	– Level of transmission in surrounding areas (including currently untreated low-endemic areas)
	– Vectorial capacity
	– Seasonal transmission
	– Immigrating flies
	– Human migration
	– Accessibility of the endemic area
Operational factors:	– Geographic coverage
	– Therapeutic coverage
	– Frequency of treatment
	– Years of ivermectin distribution
Severely restricting local circumstances:	– Political instability / conflict
	– *Loa loa* co-endemicity

The actual prediction of the feasibility of elimination per country is a challenging task, which requires a system to score countries on each of these factors and weight the different factors to arrive at a summary measure for feasibility. This requires good knowledge of the situations in different parts of Africa. Detailed scoring of countries or areas falls beyond the scope of the meeting, but we can draw some preliminary conclusions:

- – Co-endemicity with *Loa loa* and/or conflict situations are challenges to effective implementation

of mass treatment; prospects for elimination are currently poor in some countries with these problems.
- However, although elimination would be difficult to achieve in the whole of Africa, local elimination may be possible in geographically defined areas and shrinking of the current onchocerciasis regional map is feasible.
- For other countries, the feasibility of elimination primarily depends on local circumstances and operational factors listed above.

Action points for moving forward to elimination

The following action points must be considered in order to move towards elimination:

1. Generation of more empirical evidence on the feasibility of elimination and required interventions under different circumstances. This is important to motivate countries and donors and to advise countries on reinforcement of control measures or adjustment of the strategy.
2. Development of guidelines for countries on what has to be done to achieve, prove and maintain elimination of onchocerciasis infection and transmission. Guidelines should be developed from empirical data and can be supported by simulation modelling. Guidelines are needed for:
   a. Programmatic changes required to achieve elimination, depending on local circumstances (e.g. moving from yearly to 6-monthly treatment).
   b. Available guidelines for deciding when to stop and confirmation of elimination should be refined for use in APOC and tested/validated in the field.
   c. Routine surveillance after elimination, for timely detection and suppression of possible reintroduction of infection.
3. Redefine the target areas for mass treatment and delineate transmission zones.
   a. Redefinition of target areas is required, because low endemic areas are currently not targeted for treatment. Treatment is necessary in areas with self-sustainable low level transmission. Extension of mass treatment into areas, which are low-endemic because of a constant influx of infection from neighbouring areas, should also be considered.
   b. It is important to determine where transmission zones extend into neighbouring project areas or across national borders, to coordinate interventions throughout the zone to achieve elimination goals.
4. Define what has been accomplished in project areas to date and prepare projects for elimination where feasible. This includes:
   a. documentation of the epidemiological situation in each project area;
   b. an assessment of the feasibility of elimination (e.g. not possible, feasible on long term, feasible on relatively short term);
   c. where feasible: define the elimination strategy and target areas for initiating elimination with a clear workplan, defined endpoints, and monitoring and evaluation plan;
   d. in partnership with the MoH and endemic communities, initiate elimination plans in targeted countries. All data collected should be used to modify the elimination strategy as appropriate.
5. Continue investments in development of better tools for onchocerciasis elimination, including:
   a. tools to kill or sterilize viable adult worms: although it is shown that repeated mass ivermectin treatment can be sufficient to achieve elimination, availability of a macrofilaricidal drug would make it much easier to achieve that goal.
   b. diagnostic tools for measuring the presence and number of parasites in the human host, particularly viable adult worms. There still is a need for better, cheaper or more specific diagnostic tests to measure parasite numbers and transmission.

6. Examination of the opportunities for linking with LF elimination programmes. LF programmes aim to distribute ivermectin (in combination with albendazole) to a large part of the African population. Activities of both programmes need to be coordinated to optimize their implementation.
7. Establish a regular update mechanism for feedback on the above action items, such as an annual review of elimination prospects and status, to ensure engagement with key operational stakeholders and reporting on progression towards goals.

Research needs and priorities

APOC should proceed with the above action points to move towards elimination where feasible. Yet, to ensure programmatic success, research is needed on the following issues.

<u>Ad 1. Generation of more empirical evidence on the feasibility of elimination and required interventions under different circumstances.</u>
1. Create a database for the available data on the long-term effects of mass ivermectin treatment on various indicators of onchocerciasis infection. Update it when new data becomes available. Conduct statistical and model-based analysis of the above data to obtain a better understanding of the relationship between characteristics of interventions, local circumstances, and infection levels after mass treatment and of how variables can be modified to increase elimination probabilities.
2. Select pilot projects, in which the strategy will be changed for elimination, aiming to provide additional examples of successful elimination. Select project areas that are presumed to be closest to achieving elimination and which cover different epidemiological settings. If necessary, reinforce / intensify control efforts to make sure that criteria for stopping treatment are reached before 2012, so that elimination can be confirmed before APOC's closure in 2015.
3. Start operational research in the demonstration / pilot project areas to address the many strategic questions and remaining uncertainties:
   a. Test the feasibility of existing or adjusted guidelines for stopping treatment and confirmation of elimination in different epidemiological settings.
   b. Validate the endpoints for post-intervention surveillance in different epidemiological settings, using 3 years as a starting point and – where possible – 3 or more years later, to reconfirm that the infection has not been reintroduced (particularly where the system is "open" (see definitions section)).
   c. Comparative assessment of the value of the available diagnostic tests and sampling strategies in the field for each of the following tasks:
      i. Monitoring & evaluation in the end stage of mass treatment programmes
      ii. Decision to stop interventions
      iii. Confirm elimination
      iv. Routine surveillance
   d. Define the optimal treatment regimen for different transmission areas, including the need and feasibility of increasing frequency of treatment to a 6-monthly interval or making other adjustments to the treatment strategy (e.g. addition of vector control), for earlier achievement of elimination. This should include an assessment of the implications of these changes at the community level and the possibilities for countries to maintain these programmes after APOC's closure (if still needed).
   e. Assess the extent of systematic non-compliance, the existence of non-treated villages or hamlets, the implications for successful elimination and the necessary strategies to address these issues.
   f. Identify individuals who still carry infection after long term mass treatment and examine the reasons for their persistent infection (e.g. systematic non-compliance,

migration, poor response to treatment) and develop other possible treatment strategies.

    g. Evaluate the hypotheses that treatment in hyper- and mesoendemic core areas of a river basin will also cause elimination in surrounding, untreated low-endemic areas, without extending treatment into these areas.

4. Perform targeted studies in areas where people have a poor response to treatment, to examine whether it is caused by resistance and test possible solutions to deal with this problem.

<u>Ad 2. Development of guidelines on what has to be done to achieve, prove and maintain elimination of onchocerciasis infection and transmission</u>

1. Define the optimal use of diagnostics and criteria for measuring transmission and population of adult worms using, for:
    a. Delineating transmission zones
    b. Deciding when to stop in different epidemiological settings
    c. Confirming absence of transmission
    d. Post-elimination surveillance

This can include combinations of a rapid / cheap screening test (e.g. DEC patch test) with other tests for confirmation. The WHO guidelines should be used as starting point and adjusted where appropriate.

2. Assess, and if necessary improve, the validity of model predictions of the effects of long-term mass treatment on transmission and parasite density, using available data on the long-term effects of mass ivermectin treatment on various indicators of onchocerciasis infection (see recommendation 1). Identify key uncertainties for which better data are still needed to refine and improve the models.

3. Use suitable simulations models for a systematic assessment and comparison of the expected outcomes of elimination programmes, varying with respect to duration, coverage and other operational factors), under different epidemiological circumstances:
    a. To estimate breakpoints of transmission with the different indicators of infection (e.g. mf prevalence, CMFL, DEC patch test, or outcomes of PCR-based screening of pools of flies).
    b. To assess the importance of incoming infection via human migration or fly movements and determine cost-effective approaches to prevent recrudescence.
    c. To assess the potential benefits of changing the frequency of mass treatment from yearly to 6-monthly or other changes in the intervention, if implemented from the start of mass treatment or after varying periods of annual mass treatment.
    d. To assess the need for and potential benefits of extending mass ivermectin treatment into the low-endemic zones that border the areas currently selected for mass treatment.
    e. To assess the efforts required to eliminate onchocerciasis in transmission zones with only low-level transmission (no meso- or hyperendemic core), which are currently not considered for ivermectin mass treatment.
    f. To estimate the risk of failure to achieve elimination within a reasonable time frame, in relation to the diagnostics and criteria used to stop mass treatment and confirm elimination.
    g. To assess the speed of recrudescence in case of failure to achieve elimination and determine cost-effective approaches for post-elimination surveillance
    h. To assess the need for programmatic changes in areas with LF elimination programmes

<u>Ad 3. Reviewing target areas for mass treatment and delineation of transmission zones</u>
1. Redefining target areas for mass treatment:
   a. Identifying areas for which there are no data and therefore no treatment, and areas of insufficient data.
   b. Assess the usefulness and validity of existing REMO data for redefining target areas for mass treatment.
   c. Define how currently available diagnostic tools can best be used to determine areas with low-level transmission, including the 'tail'-areas of the already defined project zones and independent low-endemic areas that have previously not been considered for mass treatment.
2. Develop methods for delineation of transmission zones in the field, e.g. based on ecological, entomological, or parasitological findings or results of the DEC patch or OV 16 antibody tests. Take into consideration specific circumstances, e.g. with respect to human migration or the presence of breeding sites in the direct environment.

<u>Ad 4. Defining what has been accomplished in project areas to date and preparing projects for elimination where feasible</u>
(no specific research activities related to this action point)

<u>Ad 5. Development of better tools for achieving elimination. This includes:</u>
1. Continue the investment in research for a macrofilaricidal drug.
2. Test the accuracy and usefulness of different diagnostics for determining when to stop treatment or confirming elimination.
   a. Validation of diagnostic tests for detection of low-level infection at the individual level, with particular attention to specificity (including DEC patch tests, mf skin snip, and perhaps the OV16 antibody test, particularly in children)
   b. Determine the accuracy of and correlation between the outcomes of available methods for detecting low level transmission and parasite density, via a systematic comparison of all methods in different epidemiological settings. This should include methods based on the DEC patch test, mf skin snip, OV 16 and PCR screening of pools of flies. Specific attention is needed for the OV 16 antibody test, considering the current uncertainty about its usefulness and the high investments still needed to develop a rapid format test.
3. Further development of modern diagnostic tests that appear to be useful in different phases of the elimination programme (monitoring & evaluation, defining when to stop, confirm elimination, post-elimination surveillance)
   a. For entomological monitoring:
      i. new fly traps, to trap parous flies
      ii. looking into ways to improve the efficiency of PCR tests and upscaling the throughput.
   b. Rapid format OV 16 antibody test (card test or dipstick), if additional studies show it to be an accurate and useful tool for determining when to stop treatment or to confirm elimination.
   c. New diagnostic tool to detect viable adult worms and/or fertile female worms.

<u>Ad 6. Examination of the opportunities of linking with LF elimination programmes</u>
1. Overlap in target areas, with particular attention to the low-endemic areas where APOC has not yet started its operations.
2. Study the added benefit of albendazole treatments with onchocerciasis control.
3. Study the possibilities, need and cost-effectiveness of changing the strategy to synchronize time schedules of LF and onchocerciasis elimination programmes.

Acknowledgements:

References

African Programme for Onchocerciasis Control (APOC) (2008). Addendum for the plan of action and budget 2008-2015. Ouagadougou, African Programme for Onchocerciasis Control (APOC), World Health Organization.

Agoua H, Alley ES, Hougard JM, Akpoboua KL, Boatin B and Sékétéli A (1995). Études entomologiques de post-traitement dans le programme de lutte contre l'onchocercose en Afrique de l'Ouest. *Parasite* **2**: 281-288.

Borsboom GJ, Boatin BA, Nagelkerke NJ, Agoua H, Akpoboua KL, Alley EW, Bissan Y, Renz A, Yameogo L, Remme JH and Habbema JD (2003). Impact of ivermectin on onchocerciasis transmission: assessing the empirical evidence that repeated ivermectin mass treatments may lead to elimination/eradication in West-Africa. *Filaria J* **2**: 8.

Cupp EW (1992). Treatment of onchocerciasis with ivermectin in Central America. *Parasitology Today* **8**: 211-214.

Cupp EW, Duke BO, Mackenzie CD, Guzman JR, Vieira JC, Mendez-Galvan J, Castro J, Richards F, Sauerbrey M, Dominguez A, Eversole RR and Cupp MS (2004). The effects of long-term community level treatment with ivermectin (Mectizan) on adult *Onchocerca volvulus* in Latin America. *Am J Trop Med Hyg* **71**: 602-607.

Cupp EW and Cupp MS (2005). Impact of ivermectin community-level treatments on elimination of adult *Onchocerca volvulus* when individuals receive multiple treatments per year. *Am J Trop Med Hyg* **73**: 1159-1161.

Dadzie Y, Neira M and Hopkins D (2003). Final report of the Conference on the eradicability of Onchocerciasis. *Filaria J* **2**: 2.

Diawara L, Traore MO, Badji A, Bissan Y, Doumbia K, Goita SF, Konate L, Mounkoro K, Sarr MD, Seck AF, Toe L, Toure S and Remme JHF (2009) Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: first evidence from studies in Mali and Senegal. *PLoS Neglected Tropical Diseases* **3**: e497.

Dowdle WR and Hopkins DR, Eds. (1998). *The eradication of infectious diseases. Report of the Dahlem Workshop on the eradication of infectious diseases, Berlin, March 16-22, 1997*. Series. Chichester, John Wiley & Sons Ltd.

Duerr HP, Dietz K and Eichner M (2005). Determinants of the eradicability of filarial infections: a conceptual approach. *Trends Parasitol* **21**: 88-96.

Katabarwa M, Eyamba A, Habomugisha P, Lakwo T, Ekobo S, Kamgno J, Kuete T, Ndyomugyenyi R, Onapa A, Salifou M, Ntep M and Richards FO (2008). After a decade of annual dose of mass ivermectin treatment in Cameroon and Uganda, onchocerciasis transmission continues. *Trop Med Int Health* **13**: 1196-1203.

Plaisier AP, Van Oortmarssen GJ, Habbema JD, Remme J and Alley ES (1990). ONCHOSIM: A model and computer simulation program for the transmission and control of onchocerciasis. *Computer Methods and Programs in Biomedicine* **31**: 43-56.

Noma M, Nwoke BE, Nutall I, Tambala PA, Enyong P, Namsenmo A, Remme J, Amazigo UV, Kale OO and Seketeli A (2002). Rapid epidemiological mapping of onchocerciasis (REMO): its application by the African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* **96** Suppl 1: S29-39.

Osei-Atweneboana MY, Eng JK, Boakye DA, Gyapong JO and Prichard RK (2007). Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet* **369**: 2021-2029.

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

WHO (2001). Certification of elimination of human onchocerciasis: criteria and procedures, guidelines. Geneva, World Health Organization.

Winnen M, Plaisier AP, Alley ES, Nagelkerke NJ, van Oortmarssen G, Boatin BA and Habbema JD (2002). Can ivermectin mass treatments eliminate onchocerciasis in Africa? *Bull World Health Organ* **80**: 384-391.

Appendix I: Agenda of the meeting

<table>
<tr><td colspan="3" align="center">INFORMAL CONSULTATION ON ELIMINATION OF ONCHOCERCIASIS
TRANSMISSION WITH CURRENT TOOLS IN AFRICA
OUAGADOUGOU, BURKINA FASO
25 – 27 FEBRUARY 2009</td></tr>
</table>

OBJECTIVES OF THE MEETING:		

4. To review the state-of-the-art of elimination of onchocerciasis transmission with current tools in Africa, and to predict the feasibility of elimination in different parts of the continent.
5. To identify critical issues for the feasibility and optimal strategies of elimination in different epidemiological settings.
6. To identify research needs and priorities to answer key challenges related to elimination of transmission.

<table>
<tr><td colspan="3" align="center">PROVISIONAL ANNOTATED AGENDA</td></tr>
<tr><td colspan="3" align="center">DAY I – Wednesday 25 February 2009</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>MORNING:</td><td colspan="2">OPENING   CHAIR - Professor M. Homeida</td></tr>
<tr>
<td rowspan="2">09:00-12:40</td>
<td>Welcome Remarks by:
    -   Director, APOC, Dr Uche Amazigo
    -   WHO Representative in Burkina Faso

Opening Remarks by:
    -   Dr Julie Jacobson, Bill & Melinda Gates Foundation
    -   Dr Adrian Hopkins, the Mectizan Donation Programme
    -   Professor M. Homeida, Chair of the meeting

Introduction of participants</td>
<td>09:00-09:30</td>
</tr>
<tr>
<td>

ELIMINATION WITH IVERMECTIN: STATE OF THE ART

(i)   Elimination of Onchocerciasis in the Americas, current evidence/ critical issues - *Drs Frank Richard (10min)/Mauricio Sauerbrey (10 min)*

(ii)   Elimination in Africa, current evidence/critical issues – *Drs Hans Remme(10min) /Richard Ndyomugyenyi (10 min)*</td>
<td>09:30-09:50

09:50-10:10</td>
</tr>
</table>

Tea Break	10:10-10:40
Discussion on presentations (i) and (ii)	10:40-12:10
Summary of key issues	12:10-12:40
Lunch Break	12:40-15:00

<table>
<tr><td colspan="2">AFTERNOON: PREDICTIONS OF ELIMINATION WITH IVERMECTIN</td></tr>
<tr>
<td rowspan="2">15:00-18:10</td>
<td>(i)   Long term impact of ivermectin treatment on survival and reproductivity of the parasite – Drs Kwabla Awadzi (10min) and Ed Cupp (10min)

(ii)   Model predictions of elimination: strategies, assessment and critical factors – joint presentation by Dr Wilma Stolk (10 min) and Hans-Peter Duerr (10min)</td>
</tr>
</table>

(i) ...	15:00-15:20
(ii) ...	15:20-15:40
Discussion on Presentations (i) and (ii)	15:40-16:30
Tea Break	16:30-17:00
Discussion on presentations (i) and (ii) (cont'd)	17:00-17:40
Summary of key issues	17:40-18:10

DAY II – Thursday 26 February 2009		
CHAIR - Professor M. Homeida		
MORNING: SPATIAL ISSUES IN ELIMINATION		
09:00-12:30	*(i)* Vector migration and vector/parasite complexes, human migration issues – *Drs Frank Walsh (10min)/Daniel Boakye (10 min)*	09:00-09:20
	(ii) Target areas/populations for ivermectin treatment and non-treated areas – *Drs Mounkaila Noma (10 min)/Hans Remme (10 min)/Frank Richards (10 min)*	09:20-09:40
	Discussion on Presentations (i) and (ii)	09:40-10:30
	Tea Break	10:30-11:00
	Discussion on presentations (i) and (ii) (cont'd)	11:00-11:40
	Summary of key issues	11:40-12:10
	Lunch Break	12:10-15:00
AFTERNOON: ASSESSING INFECTION AND TRANSMISSION		
15:00-17:15	(i) Diagnostic tools, evaluation and post treatment surveillance strategies – *Dr Tom Unnasch (10 min)/Laurent Toe (10 min)*	15:00-15:20
	(ii) Discussions	15:20-16:05
	Tea Break	16:05-16:35
	Summary of key issues	16:35-17:05
19:00 – 21:00	*Dinner*	

DAY III – Friday 27 February 2009		
CHAIR – Prof M. Homeida		
MORNING: CONCLUSION AND RECOMMENDATIONS		
08:30-13:00	(i) Introduction by the Chair	08:30-08:35
	(ii) Presentation of key issues - *Rapporteurs*	08:35-08:50
	(iii) Conclusion and recommendations	08:50-10:30
	Tea Break	10:30-11:00
	(iv) Conclusion and recommendations (Cont'd)	11:00-13:00
	Closure	13:00

Appendix II: List of participants

1. Prof. Adenike ABIOSE, P.O. Box 29771, Secretariat Main Office, Ibadan, Oyo State, Nigeria – Tel: 234-2-7517329; 234-8037865702 - Fax:1-509-5628212 - E-mail: **adenikeabioseo@yahoo.com**

2. Prof. Oladele Benjamin AKOGUN, Parasite and Tropical Health, Federal University of Technology, Yola, Nigeria – Tel: (234) 75 627281 – Mobile: (234) 8037220460 – E-mail: **akoguno@yahoo.com**

3. Dr Uche Veronica AMAZIGO, Director, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 22 77 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **dirapoc@oncho.afro.who.int**

4. Dr Kwablah AWADZI, Clinician, P.O. Box 2018 Mamprobi, Ghana– Tel: +233-21-40-22-50 – Fax: +233-21-668871 or + 233-21-93-522-111 – E-mail: **awadzi@ghana.com; ayodele13@live.co.uk**

5. Prof. Daniel BOAKYE, Head, Parasitology Department, Noguchi Memorial Institute for Medical Research, P.O. Box LG581, Legon, Accra, Ghana – Mobile: +233 266 237 365 – E-mail: **dboakye@noguchi.mimcom.org or yawbadjei@yahoo.co.uk**

6. Dr Joseph Dossou CATRAYE, Zone des Ambassades, parcelle J, 03 BP 2503, Cotonou, République du Bénin – Tel : (00229) 97188144 – Fax : (00229) 21 33 64 06 - E-mail: **jcatraye@basp96.org**

7. Dr Ed Wayne CUPP, Entomologist/Geneticist, – Tel: 270-296-1559 – E-mail: **cuppedd@auburn.edu**

8. Dr Hans-Peter DUERR, Institut fuer Medizinische Biometrie, Universitaet Tuebingen, Westbahnhofstr. 55, 72070 Tubingen, Germany – Tel: ++49 (0) 7071 29 78259 - Fax: ++49 (0) 7071 29 5075 - E-mail: **hans-peter.duerr@uni-tuebingen.de**

9. Mr. Paul EJIME, Communication Officer, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **ejimep@oncho.afro.who.int**

10. Dr Grace FOBI, Community Ownership and Partnership Officer, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **fobig@oncho.afro.who.int**

11. Ms. Nathalie GARON, Senior Development Officer, Western and Central Africa Regional Program, Geographic Programmes Branch, Canadian International Development Agency, 200 Promenade du Portage, Gatineau (Québec), Canada K1A 0G4 – Tel: +819-994-7088 – Fax: +819-997-5453 – E-mail: **nathalie.garon@acdi-cida.gc.ca**

12. Prof. Mamoun HOMEIDA, Professor of Medicine and Therapeutics, President, University of Medical Sciences & Technology, P.O. Box 12810, El Riyad, Khartoum, Republic of Sudan – Tel: (00249) 183 224762 – Fax: (00249) 183 224799 - E-mail: **homeidam@umst-edu.org** or **amst33@hotmail.com**

13. Dr Adrian HOPKINS, Director, Mectizan® Donation Program, 325 Swanton Way, Decatur, GA-30030, USA – Tel: +404-371-1460 – Fax: +404-371-1138 – E-mail: **ahopkins@taskforce.org**

14. Dr Chikwe IHEKWEAZU, Consultant Regional Epidemiologist, South East of England, 7th Floor, Holborn Gate, 330 High Holborn, London WC1VPP, United Kingdom – Tel: +442077592856 – (PA +442077592842) – Mobile: +447961993056 – e-mail: **chikwe.ihekweazu@gmail.com**

15. Dr Julie JACOBSON, Bill & Melinda Gates Foundation, Seattle, USA E-mail: **Julie.Jacobson@gatesfoundation.org**

16. Dr Annette Christiane KUESEL, Scientist, TDR, World Health Organization (WHO), 20 Avenue Appia, Ch-1211, Geneva 27, Switzerland – Tel: +41 22 791-1871 – Fax: +41 22 791-4774 – E-mail: **kuesela@who.int**

17. Dr Stephen LEAK, Technical Officer, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **leaks@oncho.afro.who.int**

18. Mr. Yacouba NIANDOU, Information System Officer, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **niandouy@oncho.afro.who.int**

19. Dr Mounkaïla NOMA, Chief Epidemiology and Vector Elimination Unit, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **nomam@oncho.afro.who.int**

20. Dr Kenneth Nnamdi OPARA, Faculty of Science, Department of Zoology, University of Uyo, Nigeria – E-mail: **nkopara@yahoo.com**

21. Dr Hans REMME, Epidemiologist, 120 Rue des Campanules, 0120 Ornex, France – Tel: +33 64 545 74 04 – E-mail**: hansremme@gmail.com**

22. Dr Frank RICHARDS, Director, River Blindness Program, One Copenhill, 453 Freedom Parkway, Atlanta, GA 30307, USA – Tel : +770-488-4511/4502 *direct* – Fax: +770-488-4527 – E-mail**: frichØ1@cdc.gov**

23. Dr Wilma A. STOLK, Department of Public Health, Erasmus MC University Medical Center Rotterdam, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands – Tel: +31 10 7043730 (dir) +31 10 7038460 (secretary) – Fax: +3110 7038474 – E-mail: **w.stolk@erasmusmc.nl**

24. Dr Laurent TOE, Head of Molecular Biology Laboratory, Multi Diseases Surveillance Center (MDSC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **toel@oncho.afro.who.int**

25. Dr Thomas R. UNNASCH, Molecular Biologist/Diagnostics, Global Infectious Diseases Research Program, Department of Global Health, College of Public Health, University of South Florida, 3720 Spectrum Blvd., Suite 304, Tampa, FL 33612, Florida, USA – Tel: 001-813-974-0507 – Fax: 001-813-974-0992 - Cell: 001 205-807- 2505 – E-mail: **tunnasch@health.usf.edu**

26. Dr Frank WALSH, Chairman, Uganda Onchocerciasis Elimination, 80 Arwdel Road, Lytham St. Annes, Lancashire FY8 IBN, Great Britain – Tel: +44 1253 737765 – E-mail: **frank@walsh.me.uk**

27. Dr Laurent YAMEOGO, Coordinator Director's Office, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **yameogol@oncho.afro.who.int**

28. Mr. Honorat Gustave ZOURE, Responsible Biostatistics and Mapping, African Programme for Onchocerciasis Control (APOC), N° 1473, Avenue Naba Zombré, 01 BP 549, Ouagadougou 01, Burkina Faso – Tel: (226) 50 34 29 53 – Fax: (226) 50 34 28 75 or 50 34 36 47 – E-mail: **zoureh@oncho.afro.who.int**