RECENT ADVANCES IN ONCHOCERCIASIS RESEARCH AND IMPLICATIONS FOR CONTROL
CAMEROON ACADEMY OF SCIENCES

RECENT ADVANCES IN ONCHOCERCIASIS RESEARCH AND IMPLICATIONS FOR CONTROL

PRODUCED BY AN EXPERT COMMITTEE OF THE CAMEROON ACADEMY OF SCIENCES

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December 2012
Published by
The Cameroon Academy of Sciences
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Tel (237)2223 9741; Fax (237) 2222 9741
E-mail: cameroonacademyof.sciences@yahoo.com
Website: www.casciences.com

NOTICE

The project that is the subject of this study was supported by grant agreement n°IOM-5855-05-002 between the United States National Academy of Sciences and the Cameroon Academy of Sciences.

International Standard Book Number 9956-26-38-x

Additional copies of this publication are available from the Cameroon Academy of Sciences, P.O. Box 1457 Yaoundé, Cameroon or http://www.casciences.com

Cover pictures provided by Drs Achukwi and Kamgno

Citation: CAS (2012). Recent Advances in Onchocerciasis Research and Implications for Control. Cameroon Academy of Sciences, Yaoundé, Cameroon.

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<th>Definition</th>
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<td>ABRs</td>
<td>Annual biting rates</td>
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<tr>
<td>APOC</td>
<td>African Programme for Onchocerciasis Control</td>
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<tr>
<td>ATPs</td>
<td>Annual transmission potentials</td>
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<tr>
<td>CAS</td>
<td>Cameroon Academy of Sciences</td>
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<tr>
<td>CDDs</td>
<td>Community-directed distributors</td>
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<tr>
<td>CDTI</td>
<td>Community-Directed Treatment with Ivermectin</td>
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<tr>
<td>CHC</td>
<td>Chlorinated hydrocarbon</td>
</tr>
<tr>
<td>CRFilMT</td>
<td>Centre for Research on Filariaisis and other Tropical Diseases</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability-Adjusted Life-Years</td>
</tr>
<tr>
<td>DDT</td>
<td>Dichlorodiphenyltrichloroethane</td>
</tr>
<tr>
<td>DEC</td>
<td>Diethylcarbamazine</td>
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<tr>
<td>EAC</td>
<td>Expert Advisory Committee</td>
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<tr>
<td>FAO</td>
<td>Food and Agriculture Organisation of the United Nations</td>
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<tr>
<td>GABA</td>
<td>(\gamma)-aminobutyric acid</td>
</tr>
<tr>
<td>GTZ</td>
<td>Gesellschaft fur Technische Zusammenarbeit (German Technical Cooperation)</td>
</tr>
<tr>
<td>HKI</td>
<td>Helen Keller International</td>
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<tr>
<td>IAMP</td>
<td>Inter Academy Medical Panel</td>
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<tr>
<td>IAP</td>
<td>Inter Academy Panel on International Issues</td>
</tr>
<tr>
<td>IEF</td>
<td>International Eye Foundation</td>
</tr>
<tr>
<td>IMPM</td>
<td>Institut de Recherches Médicales et d’Etudes de Plantes Médicinales</td>
</tr>
<tr>
<td>IRAD</td>
<td>Institute de Recherche Agricole pour le Développement</td>
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<tr>
<td>IRD</td>
<td>Institut de Recherche pour le Développement</td>
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<tr>
<td>IVM</td>
<td>Ivermectin</td>
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<tr>
<td>JPC</td>
<td>Joint Programme Committee</td>
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<td>LCIF</td>
<td>Lions Club International Foundation</td>
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<td>MDD</td>
<td>Mass Drug Distribution</td>
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<td>MDP</td>
<td>Mectizan Donation Programme</td>
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<td>MEC</td>
<td>Mectizan®Expert Committee</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>NASAC</td>
<td>Network of African Science Academies</td>
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<tr>
<td>NGDOs</td>
<td>Non Governmental Development Organizations</td>
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<tr>
<td>NGOs</td>
<td>Non Governmental Organizations</td>
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<tr>
<td>NOCP</td>
<td>National Onchocerciasis Control Programme</td>
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<td>NOTF</td>
<td>National Onchocerciasis Task Force</td>
</tr>
<tr>
<td>OCGGE</td>
<td>Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies</td>
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<tr>
<td>OCP</td>
<td>Onchocerciasis Control Programme</td>
</tr>
<tr>
<td>ORSTOM</td>
<td>Office de la Recherche Scientifique et Technique Outre-Mer</td>
</tr>
<tr>
<td>PLERI</td>
<td>Probable <em>L. loa</em> encephalopathies related to the treatment with Ivermectin</td>
</tr>
<tr>
<td>RAPLOA</td>
<td>Rapid Epidemiological Assessment of Loiasis</td>
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<tr>
<td>RBF</td>
<td>River Blindness Foundation</td>
</tr>
<tr>
<td>REA</td>
<td>Rapid Epidemiological Assessment of Onchocerciasis</td>
</tr>
<tr>
<td>REMO</td>
<td>Rapid Epidemiological Mapping of Onchocerciasis</td>
</tr>
<tr>
<td>ROD</td>
<td>Reactive onchodermatitis</td>
</tr>
<tr>
<td>SAEs</td>
<td>Severe Adverse Events</td>
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<tr>
<td>SSI</td>
<td>Sight Savers International</td>
</tr>
<tr>
<td>TCC</td>
<td>Technical Consultative Committee</td>
</tr>
<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases (TDR) of the WHO</td>
</tr>
<tr>
<td>TWAS</td>
<td>Third World Academy of Sciences (the Academy of Sciences for the Developing World)</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Programme</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>USNAS</td>
<td>United States National Academy of Sciences</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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The Cameroon Academy of Sciences (CAS) was formally recognized by declaration N° Reg. 00701/RDA/J06/BAPP of 29 May 1991 by the Cameroon Government in accordance with law N° 90/053 of 19 December 1990, regulating freedom of association. It is a non-profit society of distinguished scholars engaged in promoting excellence and relevance in science and technology and providing advice to the government of Cameroon and other partners.

The vision of the Cameroon Academy of Sciences is to be the prime mover of science and technology, making scientific knowledge available to decision and policy makers with a view to influence investment priorities in science and technology, and promoting the use of science and innovation in the economic, social and cultural development of Cameroon. Consequently, the Academy produces robust forum and committee advisory documents as well as reports on priority problems that are delivered to policy and decision makers and the public. The independence, highly qualified membership, multidisciplinary composition and rigorous procedures for objective and unbiased analysis enable the Academy to effectively deliver credible advice.

In carrying out its work, the Academy collaborates with the various ministries of the Government of Cameroon, the United States National Academy of Sciences (USNAS), the Academy of Sciences for the Developing World (TWAS), Royal Society (UK), the Network of African Science Academies (NASAC), Inter Academy Panel on International Issues (IAP), Inter Academy Medical Panel (IAMP) and other international and national organizations.

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Acknowledgements

The Cameroon Academy of Sciences (CAS) Expert Committee is appreciative of the contributions and efforts of all those who helped in the realisation of this project. The Committee thanks the Members of the CAS Forum on Public Health for choosing this subject and for their guidance and support throughout the period of the study.

The Committee gratefully acknowledges the United States National Academy of Sciences (USNAS) for facilitating financial support from Bill and Melinda Gates Foundation and for providing technical support for this work within the framework of its African Science Academy Development Initiative (ASADI). Gratitude is conveyed to Dr. Patrick Kelley, Ms. Patricia Cuff, Mr. Jim Banishashi and Ms. Angela Mensah for making possible the collaboration between the Cameroon Academy of Sciences and the USNAS. Dr. Kelly and Ms. Cuff also provided guidance on carrying out consensus studies.

We would like to thank Drs. Marcelline Ntep and Benjamin Biholong of the National Onchocerciasis Control Programme, Yaounde, Cameroon for providing information, input and assistance that facilitated the writing of this report.

The review process for the study was overseen by Dr. David A. Mbah, Executive Secretary of the Cameroon Academy of Sciences.

This report was reviewed independently by experts who were selected for their technical competence. They provided candid and critical comments that greatly improved the quality of this report. The Committee would like to thank the following for the review:

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Responsibility for the final content and quality of this report is totally that of the Expert Committee and CAS.
Preface

As part of its present strategic plan, the Cameroon Academy of Sciences (CAS) organises workshops and seminars and carries out research and consensus studies in order to provide information for evidence-based actions by various stakeholders. It has so far organised several seminars and workshops either alone or in collaboration with other partners.

In its meeting of 21 April 2011, the Academy’s Forum on Public Health decided to carry out its first consensus study. From among several themes that were short-listed during the meeting, it was decided that a consensus study should be carried out on recent advances in onchocerciasis research and implications for control. The members of the Forum felt that Cameroonian scientists, their partners (British, German, Ghanaian and French) and others had done significant scientific research in recent years on onchocerciasis which could even be described as ground breaking. They also believed that the studies had important implications for the control of the disease in Cameroon. Unfortunately, this crucial scientific information is buried in different scientific journals and is not readily available to stakeholders involved in treatment and control efforts in developing countries in general and Cameroon in particular. Consequently, the Forum members asked the Academy to carry out a consensus study. Accordingly, CAS in recognition of its advocacy role in giving visibility to Cameroonian research efforts and that of its partners and other scientists, convened an expert panel to bring together the data on recent research on onchocerciasis, analyse it and present sound advice and reasoning for reorientation of the current onchocerciasis control strategies in Africa in general and in Cameroon in particular.

In view of all of the above, it is hoped that the report herein presented will provoke dialogue among stakeholders and draw public attention.
Executive Summary

The Cameroon Academy of Sciences convened an expert panel to bring together the data on recent research on onchocerciasis, analyse it and present sound advice and reasoning for reorientation of the current onchocerciasis control and research strategies in Cameroon in particular and the world in general.

Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus* and transmitted via the bites of a black fly of the genus *Simulium*. It is a debilitating dermal filariasis which is endemic mainly in tropical Africa and to a lesser extent in Central and South America and the Arabian Peninsula particularly in Yemen. The clinical and socio-economic effects are most severe in sub-Saharan Africa where it causes blindness and severe skin diseases. Presently, onchocerciasis is recognised as the world’s second leading infectious cause of blindness. Figures on its global magnitude cited in the literature are quite varied. The World Health Organization estimates that about 37 million people are currently infected with the parasite with about 99% of them living in sub-Saharan Africa. Almost 1.5 million are visually impaired and about 500,000 are blind. A total of 90 million people are at risk of becoming infected with the parasite.

Over the years, attempts to control the disease have been based on vector control and drugs. Despite more than forty years of control in Africa, the disease is still a public health concern in many African countries, where the prevalence in some foci is still very high. It is therefore important to seek for complementary strategies so that the current control strategies can be improved.

**Vector control**

Early efforts to control onchocerciasis were based on treatment of water courses with insecticides to kill the larvae of the *Simulium* vectors. This approach, used by the Onchocerciasis Control Programme (OCP) in West Africa successfully reduced the burden of disease in the areas covered by the programme. This strategy can still be used in combination with other approaches today. The two recent cases of vector elimination in Itwara (Uganda) and Bioko Island (Equatorial Guinea) applied the OCP methodology with the help of the African Programme for Onchocerciasis Control (APOC).

*In view of the on-going construction of new hydroelectric dams in Cameroon, the authorities of the projects should already build into their operational activities, some black fly vector control components so as to be prepared to handle any unforeseen *S. damnosum* population explosion after the construction. The main rivers of Cameroon should also be the target of focal black fly control activities as they all contribute to the breeding of *S. damnosum*. Furthermore, operational research is needed to improve monitoring and establish thresholds that determine when and where vector control is needed. It is also necessary to evaluate the adverse environmental effects of the insecticides used in any control operations.*

**Community-Directed Treatment with Ivermectin**

Ivermectin (Mectizan) donated by Merck & Co was introduced in 1987 for mass treatment of onchocerciasis. APOC launched in 1996 the Community-Directed Treatment with Ivermectin (CDTI) strategy. Ivermectin is
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Microfilaricidal and its use successfully reduced the morbidity of onchocerciasis in various communities. It had been hoped that CDTI would eliminate the disease by breaking transmission but this has not happened, probably as a result of specific epidemiological, sociological and logistical factors that make elimination using ivermectin alone unlikely in some areas.

The main limitation of ivermectin is that it has little effect on the adult worms that continue to produce microfilariae and hence re-treatment is required at intervals that experts in many on-going programmes have not definitely determined or agreed upon. A major obstacle for onchocerciasis control using ivermectin has been the occurrence of post ivermectin severe adverse events in areas co-endemic with loiasis.

In view of the above, we suggest that CDTI should be improved by the following:

- There is need for the research organisations in charge of medical research in Cameroon to investigate the epidemiological, sociological and logistical factors that contribute to the maintenance of high levels of the prevalence of onchocerciasis after more than 17 years of treatment with ivermectin using the CDTI approach in areas where loiasis is absent.
- The National Onchocerciasis Control Programme should intensify communication to inform the population on the benefits of treatment with ivermectin. Efforts should also be made to seek for permanent non compliers in order to inform, educate and properly treat them.
- The strategy of the control programme in the Americas which is based on at least twice yearly treatment and which has resulted in the near elimination of onchocerciasis in that area should be adopted in all endemic foci in general and Cameroon in particular where the results of the epidemiological evaluation are not as good as was expected. This should be accompanied by epidemiological surveillance to detect and control disease resurgence. Therapeutic approaches to reduce the load of L. loa infections are also necessary to increase ivermectin coverage. Hypoendemic areas should also be covered under the new strategy of “Test and Treat” that is being developed.

To date, there is a lot of controversy regarding the emergence of resistance of *O. volvulus* to ivermectin. In addition to the phenotypic suspicions of resistance, many studies have revealed that selection occurs in some genes of the parasite. Despite these phenotypic and genotypic studies, the unequivocal proof of resistance is yet to be established. Further studies are therefore needed to clarify this situation in order to preserve the benefits of past and current onchocerciasis control programmes.

**Antibiotic therapy of human onchocerciasis**

The symbiosis of filarial nematodes and intracellular *Wolbachia* bacteria has been studied as a target for antibiotic therapy of filariasis in cattle using *O. ochengi*. The results showed that doxycycline is macrofilaricidal. As a result of the close phylogenetic relationship between *O. volvulus* and *O. ochengi*, antibiotic treatment may also be macrofilaricidal in humans. Trials in humans have demonstrated that:

- antibiotic treatment of *O. volvulus* results in sterility and inhibits larval development and adult worm viability;
- depletion of bacteria following treatment with doxycycline resulted in a complete and long-term blockage of embryogenesis;
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- Doxycycline also had macrofilaricidal effect on *O. volvulus*;
- The endosymbiont *Wolbachia* is absent from *L. loa* and this fact can be exploited for the administration of antibiotherapy for the treatment of onchocerciasis in areas where *L. loa* is co-endemic;
- The large scale administration of doxycycline for six weeks is feasible in co-endemic villages of loiasis and onchocerciasis using community directed approach with high therapeutic coverage and very high compliance rates.

In view of the above results, we recommend as follows:

- The recently completed community-directed intervention (CDI) trials using a 6-week course of doxycycline at 100 mg/day demonstrated that prolonged courses of treatment can be effectively delivered either through individual or mass treatment using doxycycline. Consequently, doxycycline at this regimen could be used for individual treatment and should be a reserve in cases of ivermectin resistance.
- Given that the cost of purchase and delivery of doxycycline for the six week treatment per patient is relatively high for most onchocerciasis patients living in endemic communities, research efforts should be maintained to develop shorter regimens of this drug. Lobbying should be made by governments and Non Governmental Development Organisations for the reduction of the prices of this drug.

**Vaccination**

Vaccination can be a complementary tool for the present onchocerciasis control efforts as it can protect vulnerable groups particularly children living in endemic areas against infection and reduce adult worm burden and fecundity, thus reducing the pathological effects caused by the microfilariae. Many research groups have identified a number of *O. volvulus* larval vaccine candidates. Trials with some of them have obtained proof-of-principle of vaccination against L3 infection as it was shown that microfilarial loads reduced significantly in animal models. Consequently, we recommend that donors should provide funding for research groups which have identified promising vaccine candidates for the purpose of vaccine design, formulation and delivery.

**Sustainability and ownership of control programmes**

APOC’s mandate is expected to end in 2015. At that time, it will transfer full responsibility for onchocerciasis control to national control programmes. Governments would be expected to provide adequate technological and financial support for national control programmes to enable them take on the responsibilities that would be transferred from APOC. The inability of national control programmes to sustain disease control efforts can have important ramifications as disease resurgence can reverse the gains in public health produced by both OCP and APOC over the years.

To create sustainable disease control efforts beyond APOC’s mandate, we urge National Programmes to develop technical and technological competence that would enable them to function properly after the withdrawal of APOC. We appeal to National Governments and donors not to abdicate their financial responsibility which is needed to ensure that the substantial investments and progress made towards eliminating onchocerciasis in Africa are sustained for the future.
Resumé

L’Académie des Sciences du Cameroun a réuni un panel d’experts afin de rassembler les données relatives aux recherches récentes sur l’onchocercose, les analyser et prodiguer des conseils pratiques et judicieux aux fins de donner une nouvelle orientation aux stratégies de lutte contre l’onchocercose au Cameroun en particulier et dans le monde en général.

L’onchocercose est une maladie parasitaire causée par *Onchocerca volvulus*. Elle est transmise par les piqûres d’une mouche du genre *Simulium*. Il s’agit d’une filariose dermique débilitante, endémique surtout en Afrique tropicale et dans une moindre mesure en Amérique Centrale et du Sud, ainsi que dans la Péninsule arabique et au Yémen en particulier. Les effets cliniques et socio-économiques sont plus néfastes en Afrique subsaharienne car elle y entraîne la cécité et des dermatoses sévères. De nos jours, l’onchocercose est connue comme la deuxième cause de cécité d’origine infectieuse dans le monde. Les statistiques relatives à son impact sont très variées. Les estimations de l’Organisation Mondiale de la Santé font état de près de 37 millions de personnes infectées par le parasite avec approximativement 99% vivant en Afrique subsaharienne. Près de 1,5 millions de personnes souffrent de déficience visuelle et près de 500 000 sont aveugles. Un total de 90 millions de personnes est à risque d’infection par le parasite.

Au cours des années écoulées, les tentatives relatives à la lutte contre la maladie ont été basées sur la lutte antivectorielle et la chimiothérapie. Malgré plus de quarante années de lutte en Afrique, la maladie représente toujours un problème de santé publique dans plusieurs pays, et la prévalence dans certains foyers reste très élevée. Il est donc très important de rechercher des stratégies complémentaires afin d’améliorer la lutte contre l’onchocercose.

Lutte antivectorielle

Les efforts de lutte contre l’onchocercose portaient plus sur le traitement des cours d’eaux à l’aide d’insecticides afin d’éliminer la lave de la simulie. Cette approche utilisée par le Programme de Lutte contre l’Onchocercose en Afrique de l’Ouest ou encore *Onchocerciasis Control Program in West Africa* (OCP) a considérablement réduit l’endémicité de la maladie dans les zones couvertes par ce Programme. Cette lutte antivectorielle peut encore être utilisée de nos jours en association avec d’autres approches. Les deux derniers cas d’éradication de l’agent vecteur à Itwara (Ouganda) et sur l’île de Bioko (Guinée Equatoriale) ont appliqué la méthode du programme OCP avec l’aide du Programme Africain de Lutte contre l’Onchocercose (APOC).

Compte tenu de la construction en cours de nouveaux barrages hydroélectriques au Cameroun, les responsables des projets devraient déjà concevoir dans leurs activités opérationnelles, des plans de lutte contre les mouches noires, vecteurs de la maladie, afin d’être prêts à gérer tout imprévu relatif à une croissance exponentielle de la population de *S. damnosum* après la construction des barrages. Les principaux fleuves du Cameroun devraient également être la cible des activités de lutte contre la mouche noire puisqu’ils contribuent tous à la reproduction du vecteur. Aussi, une recherche opérationnelle s’avère nécessaire en vue de déterminer les seuils à partir desquelles la lutte contre le vecteur s’impose. Par ailleurs, il est important d’inclure dans les projets de lutte antivectorielle, une composante environnementale sur l’effet des larvicides sur la flore et la faune aquatique.
Traitement par ivermectine sous directives communautaires


La principale limite de l’ivermectine réside dans le fait que ce médicament a un effet limité sur les vers adultes qui continuent de produire les microfilaries, soulignant ainsi la nécessité de traitements biannuels une ou deux fois par an. Un autre obstacle à la lutte contre l’onchocercose à l’aide de l’ivermectine reste la survenue des effets secondaires graves dans des zones co-endémiques avec la loase.

A la lumière de ce qui précède, nous suggérons que le TIDC soit amélioré en tenant compte des propositions suivantes :

- Il est nécessaire que les structures de recherche dans le domaine de la santé au Cameroun mènent des études sur les facteurs épidémiologiques, sociologiques et logistiques qui contribuent à maintenir des prévalences élevées de l’onchocercose, après plus de 15 années de traitement à l’ivermectine.

- Le Programme National de Lutte contre l’Onchocercose doit intensifier la communication afin d’informer la population sur les avantages du traitement à l’ivermectine. Des efforts doivent également être déployés pour identifier les sujets qui restent en marge du traitement de façon permanente afin de les informer, les éduquer et les traiter convenablement.

- La stratégie du programme de lutte dans les Amériques basée sur l’administration d’au moins deux doses par an et qui a abouti à une élimination presque totale de l’onchocercose dans cette zone devrait être adoptée dans toutes les zones où le programme a des difficultés à éliminer la maladie (les zones où les prévalences restent élevées malgré plusieurs années de traitements, avec des niveaux de transmission très élevés). Les approches thérapeutiques de réduction de la charge des infections de la filariose à L. loa sont également nécessaires pour réduire le risque d’effets secondaires graves et ainsi accroître la couverture à l’ivermectine. Les zones hypo-endémiques doivent être incluses dans le programme de traitement si l’on veut réellement éliminer la maladie.

Jusqu’à nos jours, il y a beaucoup de controverse autour de l’émergence de la résistance de l’*O. volvulus* à l’ivermectine. En plus des suspicions phénotypiques sur la résistance, des recherches ont prouvé qu’une sélection intervient dans certains gènes du parasite. En dépit de ces études phénotypiques et génotypiques, la preuve de la résistance n’est pas encore établie. D’autres recherches doivent donc être effectuées afin de clarifier cette situation et préserver les acquis programmes de lutte contre l’onchocercose.
Thérapie à base d’antibiotiques pour le traitement de l’onchocercose chez l’homme

La symbiose entre les nématodes et la bactérie intracellulaire Wolbachia a été bien étudiée chez le bétail avec le modèle O. ochengi. La bactérie Wolbachia est une cible pour le traitement de l’onchocercose à base d’antibiotique. Les résultats ont montré que la doxycycline est macrofilaricide. Du fait qu’O. ochengi est proche phylogénétiquement d’O. volvulus, le traitement à base d’antibiotiques peut être également macrofilaricide chez les êtres humains. Des essais sur l’homme ont démontré que:

- Le traitement d’O. volvulus à base d’antibiotiques abouti à la stérilisation des vers, l’inhibition du développement larvaire et la mort du ver adulte.
- La bactérie Wolbachia n’est pas en symbiose avec L. loa, et ce fait peut être exploité pour l’administration de l’antibiothérapie dans le traitement de l’onchocercose dans des zones où le L. loa est co-endémique.
- L’administration à grande échelle de doxycycline pendant six semaines est réalisable dans des villages co-endémiques pour la loase et l’onchocercose en utilisant le schéma de traitement sous Directives communautaires.

Vu les résultats ci-dessus, nous recommandons que:

- Les travaux de recherche continuent, pour la détermination des schémas thérapeutiques plus court et utilisable en traitement de masse avec moins de difficultés.
- La doxycycline soit une alternative au cas où la résistance à l’ivermectine se confirme. Un lobbying devraient être fait par les gouvernements des pays endémiques afin d’obtenir la doxycycline à des prix raisonnable.

Vaccination

La vaccination peut être un outil complémentaire pour les efforts actuels de lutte contre l’onchocercose dans la mesure où elle peut permettre de protéger les groupes vulnérables, et surtout les enfants vivant dans les zones endémiques. Elle peut aussi permettre de réduire le nombre de vers adultes et la fécondité, réduisant ainsi les effets pathologiques causés par les microfilaires. Plusieurs groupes de recherche ont identifié un certain nombre de vaccins contre les stades larvaires d’O. volvulus. Des essais de certains d’entre eux ont démontré l’efficacité de la vaccination contre l’infection par les larves L3. Dans le modèle animal, il a été démontré que la vaccination entraîne une réduction significative des charges microfilarienne. Nous recommandons par conséquent aux bailleurs et aux gouvernements de soutenir les groupes de recherche qui ont identifié les vaccins candidats les plus prometteurs en vue de leur développement, leur formulation et leur utilisation dans la lutte contre l’onchocercose.

Viabilité et responsabilité des programmes de lutte

Le mandat du Programme Africain de Lutte contre l’Onchocercose s’achève en principe en 2015. Il transférera alors toute la responsabilité de la lutte contre l’onchocercose aux programmes nationaux de lutte. Les gouvernements devront alors apporter une assistance technique et financière adéquate aux programmes nationaux de lutte afin de leur permettre de prendre les responsabilités qui leurs seront confiées par l’APOC. L’incapacité des programmes nationaux à maintenir les efforts de lutte contre la maladie pourrait avoir des
conséquences importantes puisque la résurgence de la maladie peut anéantir les acquis obtenus par les programmes OCP et APOC pendant des années.

Afin de maintenir des efforts de lutte durable contre la maladie après le mandat d’APOC, nous recommandons aux programme nationaux d’assurer une bonne préparation (formations des expertises nationales dans la perspective du retrait du programme APOC), et aux différents gouvernements et autres bailleurs de ne pas renoncer à leurs responsabilités financières qui est nécessaire afin de s’assurer que les investissements substantiels et les progrès réalisés dans le sens de l’élimination de l’onchocercose en Afrique perdurent.
Background information on onchocerciasis

Introduction

Onchocerciasis is a parasitic disease caused by *Onchocerca volvulus* and transmitted by the bites of a black fly of the genus *Simulium*. It is a debilitating dermal filariasis which is endemic mainly in tropical Africa and to a lesser extent in Central and South America and the Arabian Peninsula, particularly in Yemen (WHO, 1995a). The clinical and socio-economic effects are most severe in Guinea and Sudan savanna areas where it causes blindness in exposed humans (Leveque, 1989).

In 1875, O’Neill working with patients from the Gold Coast (Ghana) who had “craw craw”, a skin manifestation, established the link between microfilariae and “onchocerciasis”. However, it was Leuckart in 1893 who examined nodules extracted from patients from Gold Coast and discovered that the nodules contained adult worms which he then named *Filarial volvulus*. Independently of the work of Leuckart, Theobald (1903) examined black flies from the Democratic Republic of Congo (DRC) and named them *Simulium damnosum*. In spite of all the above, the relationship between the vector and the disease remained unknown until 1926 when Blacklock working in Sierra Leone, demonstrated the development of microfilariae into infective larvae in *S. damnosum* (Blacklock, 1926 a,b). The first clinical presentation of onchocerciasis, the ocular form of the disease, was described in Guatemala (Robles, 1919).

Global magnitude

Presently, onchocerciasis is recognised as the world’s second leading infectious cause of blindness. Figures on its global magnitude cited in the literature are quite varied. The World Health Organization estimates that about 37 million people are currently infected with the parasite, with about 99% of them in sub-Saharan Africa. Almost 1.5 million are visually impaired and about 500,000 are blind. A total of 90 million people are at risk of becoming infected with the parasite (APOC, 2005; Boatin and Richards, 2006; WHO, 2011). In hyperendemic areas in Africa, about 15 to 40% of adults could be blind because of onchocerciasis. Before the launching of the control programme, for example in Burkina Faso, it was estimated that 46% of males and 36% of females living in onchocerciasis hyperendemic areas became blind before their death (Prost, 1986).

The disease is endemic in Africa, Latin America and Yemen. In sub-Saharan Africa, the African onchocercal belt extends from Senegal in the west to Ethiopia in the east involving 30 countries and as far south as Angola and Malawi (Figure 1). The disease is also called river blindness because the blood sucking blackfly (*Simulium* spp) which transmits the disease breeds in fast flowing rivers and blindness is an important clinical manifestation. In onchocerciasis, chronic skin (dermatitis) and eye lesions are also common. It is a major public health problem in many tropical countries (WHO, 1995a). The initial infestation often occurs in childhood, and many of the affected individuals remain asymptomatic for long periods. A positive association has been found between river blindness and excess mortality in infected people, either blind or not (Pion *et al.*, 2002; Little *et al.*, 2004).
Recent advances in onchocerciasis research and implications for control

Figure 1. Distribution of onchocerciasis showing current status of global onchocerciasis control
Red areas represent areas receiving ivermectin treatment. Yellow areas represent areas requiring further epidemiological surveys. The green area is the area covered by the Onchocerciasis Control Programme in West Africa. Pink zones indicate the special intervention zones, i.e., previous OCP areas receiving ivermectin and some vector control. Map from Basañez M.G. et al. (2006).

Onchocerciasis in Cameroon

Onchocerciasis is an important public health problem in Cameroon. It was first described in the country by Füllerborn (Kamgno, 2005). In the Mbam valley in Cameroon, a case control study demonstrated an association between onchocerciasis and epilepsy (Boussinesq et al., 2002) with a huge demographic impact of this disease in hyperendemic communities (Kamgno et al., 2003).

A Rapid epidemiological mapping of onchocerciasis (REMO) survey undertaken in Cameroon (Mace et al., 1997) revealed that about 50% of the rural population was at risk. Other unpublished reports put this percentage at 62%, suggesting that about 9 million people were at risk of infection, 5 million people infested by the worm, among which 30,000 were blind. There are many fast flowing rivers in the country which favour the propagation of the black fly vectors of the disease.

Helen Keller International’s (HKI) work to combat the disease began in Cameroon in 1992. A major milestone was achieved in 1995, when non governmental organizations, the World Bank, the World Health Organisation, Donor countries and endemic countries launched the African Programme for Onchocerciasis Control (APOC). APOC figures show that by 2007 in Cameroon (Figure 2), the number of communities treated with ivermectin was 9,445 and the geographic coverage of the country was 99.5%. By the same period, the number of people treated with ivermectin was 4,427,481 and the treatment target (in terms of number of people treated) was 5 950 489 giving at the time, a therapeutic coverage rate of 74.4%.
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Figure 2. Rapid epidemiological mapping of onchocerciasis in Cameroon

The areas in red show where community-directed treatment with ivermectin is needed. People affected by onchocerciasis are shown as: Number of communities in meso/hyper endemic (red) areas (2006): 9419; Total population in meso/hyper endemic (red) areas (2006): 5 798 818. Source of map: www.WHO.int/apoc/countries/cm_web.jpg

Bio-ecology of *S. damnosum*

The role of *Simulium* as a vector of onchocerciasis was suspected by Robles in 1919 in Guatemala, and confirmed in Sierra Leone a few years later (Blacklock, 1926a; Blacklock, 1926b).

*S. damnosum* is a Diptera belonging to the family *Simuliidae*. The females are haematophagous but also take plant juices while the males feed exclusively on plant juices. The females are mainly anthropophilic (could also feed on animals), absorbing up to one mg of blood during a meal. The proteins in the blood are necessary for egg (between 500 and 1000 can be laid) production. The adult resting place is unknown, making it difficult to control the insect by spraying with insecticide (Bellec and Hebrand, 1980). The female can live for up to four weeks in the savanna but for a shorter period in the forest zone. A batch of eggs is laid on the surface of submerged vegetation in fast flowing sections of rivers 3 to 4 days after a blood meal. The eggs hatch in about 3 days and the larval stages (1 to 7) remain attached to the substrate by the terminal segment of their abdomens. The larvae feed by fanning any drifting debris into their mouths and the digestive system using their modified mandibles. The larval stage lasts 6 to 9 days, depending on the temperature of the water, before moulting into a nymph (non feeding stage) and the adult. The female copulates (once in its lifetime) a few hours after immersing and seeks a blood meal.
**Life cycle of Onchocerca volvulus**

Onchocerca worms survive in their natural host for several years and the adult worm life span is generally estimated to range from 10 to 15 years (Plaisier et al., 1991; Ottesen, 1995) despite ongoing cellular immune responses and high titres of parasite-specific IgG and IgE antibodies. There is some evidence that an active modulation of the host’s immune system is one of the strategies permitting long-term survival of the parasite (Maizels et al., 1993). Throughout its life span, the adult fertilized female worm reproduces continuously, giving birth to millions of microfilariae that are released per day and migrate to invade the skin and eyes. In the latter case, they provoke ocular pathology resulting in blindness in humans. During feeding on the skin, the blood-sucking black fly vector *Simulium damnosum* (Philippon, 1977) ingests the skin dwelling microfilariae which eventually develop into the third stage infective larvae (Figure 3). When the infective black fly bites a human being again, the infective larvae from the head of the fly enter the wound and penetrate the tissues. In this definitive host, these infective larvae moult (Figure 4) and develop to become immature adult worms enclosed in collagenous, subcutaneous or deeper worm bundles as palpable nodules, where they develop to maturity.

Many *Simulium* species have been incriminated to a greater or lesser extent in the transmission of *O. volvulus* (Crosskey, 1990), their relative vectorial capacities contributing to shape diverse transmission patterns in different endemic areas. *S. damnosum* concurrently transmits both *O. volvulus* and animal *Onchocerca* species such as *O. ochengi*. Under field conditions humans are exposed to such animal-derived *Onchocerca* spp L3 (Figure 3) but they do not develop in them. The larvae of these flies are aquatic dwellers and occur mainly in fast-flowing water, requiring a minimum flow of about 50 cm/s for survival. In Africa, the *S. damnosum* species complex, which includes approximately 60 cytotypes, is responsible for more than 95 percent of onchocerciasis cases (Crosskey, 1990; Crosskey and Howard, 2004). *S. Neavei* whose larvae are phoretic on crabs transmits the infection in East Africa. In Latin America, *S. ochraceum*, *S. exiguum*, *S. metallicum* and *S. guianense* are the main vectors, respectively, in Mexico and Guatemala, Colombia and Ecuador, northern Venezuela and southern Venezuela and Brazil (Bradley et al., 2005; WHO, 2005).
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**Figure 3.** Transmission cycle of *Onchocerca volvulus, O. ochengi and O. ramachandrini*

Wharthogs are implicated in the life cycle of *O. ramachandrini*. Copied with permission from Renz and Wenk (www.riverblindness.eu)

**Figure 4.** Life cycle of *O. volvulus*

Copied and modified with permission from Renz and Wenk (www.riverblindness.eu)
Pathology of onchocerciasis

In endemic areas, the majority of *O. volvulus*-infected persons develop a generalized form of the disease which is characterized by varying microfilariae densities and numbers of adult parasites. Most often, this is accompanied by a low degree of inflammatory processes in the skin. Generally there is a wide spectrum of ensuing pathological events which represent the cumulative tissue and functional outcomes of a long-standing interplay between the host and parasite. The adult worms are enclosed in collagenous tissues where they form palpable nodules in the skin. The nodules in humans typically range from the size of a pea to about 1-4cm in diameter and may contain two to four adult worms that can reach a length of 80 cm. In bovine *O. ochengi*, more than 12 adult male worms have been detected living with one female worm in one nodule (Achukwi, unpublished data). The microfilariae can survive 2 to 3 years.

After mating, the female worm releases around 1000 microfilariae larvae a day into the surrounding tissue. It is the microfilarial stage of the parasite that causes the pathology of onchocerciasis, comprising a variety of dermatological manifestations and eye lesions. Microfilariae concentrate in the dermis of the skin and the eyes and most clinical pathology is seen at these two sites. The clinical spectrum may show:

i. apparently immune, clinically normal individuals;
ii. individuals who are infected yet asymptomatic;
iii. persons with eye or skin pathology.

Blindness is the most serious complication of onchocerciasis. It has been indicated that disease progression may be influenced by factors such as an individual’s immune response (Ottesen, 1984) and the local incidence of infestation (Bundy et al., 1991). In general, the relative importance of ocular and skin complications varies with the parasite strain involved. Blindness tends to predominate in savannah areas and skin disease in forest areas.

Skin lesions

The skin manifestations of onchocerciasis are highly variable. Severe itching is fairly common. In endemic areas, a small proportion of patients often described as clinically symptomatic patients, have severe dermatological lesions that are usually confined to distinct areas of the body (Anderson et al., 1973; Büttner et al., 1982). The mechanism underlying the propensity of some patients to develop an extremely debilitating dermatitis known as reactive onchodermatitis (ROD) or sowda, has been a matter of controversy (Ali et al., 2003; Gallin et al., 1995; Mackenzie et al., 1985; Murdoch et al., 1997). The factors that predispose patients to developing ROD are not clearly defined, although it has been observed that there is an immunogenetic basis for the spectrum of cutaneous presentations in onchocerciasis (Murdoch et al., 1997). Sowda occurs in a small proportion of patients who exhibit a hyperactive form of onchocerciasis characterized by very low mf densities, only a few nodules with adult worms, pronounced cellular and humoral immune responses and the ability to eliminate the microfilariae (Büttner et al., 1982; Lucius et al., 1986; Brattig et al., 1987). The phenomenon of low microfilariae load is thought to result from an active down regulation of parasite burdens by the host (Büttner and Racz 1983). A clinical classification of onchocercal dermatitis defining six different patterns has been suggested by Murdoch et al. (1993) as follows:

i. Acute papular onchodermatitis – there is an early skin change characterised by widespread eczematous rashes with multiple small pruritic papules which progress to vesicles and pustules. This form often affects the face, the trunk and the extremities.
ii. **Chronic papular onchodermatitis** – this has a severely itching maculopapular rash containing scattered flat-topped papules and hyper pigmented macules, typically affecting the shoulders, the buttocks and the extremities early in the infestation.

iii. **Lichenified onchodermatitis** – it consists of hyperkeratotic and hyper pigmented confluent plaques most often affecting the lower extremities and associated with lymphadenopathy.

iv. **Onchocercal depigmentation or leopard skin** – has vitiligo-like lesions with hypo pigmented patches containing perifollicular spots of normally pigmented skin. Onchocercal depigmentation often affects the shins in a symmetrical pattern and is rarely associated with pruritis and excoriations.

v. **Onchocercal nodules** – these are asymptomatic subcutaneous nodules of variable sizes located over bony prominence and containing the adult worms. Other classic clinical pictures include lizard skins with dry ichthyose-like lesions with a mosaic pattern resembling the scales of a lizard.

vi. **Hanging groin** – characterised by folds of atrophic inelastic skin in the inguinal region associated with lymphadenopathy.

In a population where onchodermatitis is endemic, the most common skin manifestation is chronic papular onchodermatitis and followed by onchocercal depigmentation (Hagan, 1998).

**Eye lesions**

Ocular lesions can involve all eye tissues, ranging from punctuate and sclerosing keratitis (anterior segment) to optic nerve atrophy (posterior segment). Onchocercal ocular disease covers a wide spectrum, ranging from mild symptoms such as pruritis, redness, pain, photophobia, diffuse keratitis and blurring of vision to more severe symptoms of corneal scarring, night blindness, intraocular inflammation, glaucoma, visual field loss and eventually, blindness (Enk et al., 2003).

In untreated populations, the progressive nature of onchocercal ocular disease has been found to be responsible for the existence of entire villages in which the older population was blind and only young people had functional vision. This phenomenon was first observed in villages in proximity of rivers, the breeding site of the *Simulium* black fly, hence, the name river blindness. Ocular lesions are usually bilateral and can affect various structures of the anterior and posterior segments of the eye (Abiose, 1998). Anterior segment disease is related to the presence of living or dead microfilariae in the eye. In the anterior chamber, the microfilariae can be seen with a slit lamp.

A number of studies have reported a reduced vitamin A status in individuals with onchocercal infections (Mustafa et al., 1979; Zambou et al., 1999). An unpublished survey undertaken by the World Health Organization comparing foci in West African savannah and the forest area of Cameroon showed that lesions caused by vitamin A deficiency were more common in villages of the savannah areas with high *Onchocerca* parasite prevalence than in equivalent forest zone villages, where dietary vitamin A was not limited. Posterior eye lesions such as retinitis, chorioretinitis and optic nerve damage are also more common in the savannah. In Côte d’Ivoire, Lagraudet (1971) reported that individuals with onchocerciasis had lower serum vitamin A levels than comparative control groups. These findings are controversial given that in other studies, vitamin A levels in skin or plasma were found not to differ significantly between infected and uninfected people (Williams et al., 1985; Stürchler et al., 1987).
The pathogenesis of blindness is not clearly defined but it is thought that the immune reaction to the secreted products or to the contents of dead microfilariae is important and possibly compounded by the induction of autoimmunity to antigens of the eye. Dead microfilariae may cause severe anterior uveitis with formation of synaechiae, cataract and glaucoma. Confluent opacities may obscure major portions of the cornea, ultimately leading to a sclerosing keratitis with fibrovascular pannus and marked reduction of the visual functions. Posterior segment disease manifests as atrophy of the retinal-pigment epithelium and is associated with choroidoretinal scarring and subretinal fibrosis (Newland et al., 1991). Optic neuritis followed by post neuritic optic atrophy may also occur (Abiose et al., 1993).

It is thought that in chronic onchocercal infestations, a combination of both host- and parasite-mediated processes can synergize to control aberrant immune reactivity and damage to the host. This attenuation of the immune response tends to limit the host’s capability to clear the infection (Maizels and Yazdanbakhsh, 2003; Bourke et al., 2011).

**The role of Wolbachia bacteria in pathology**

Wolbachia bacteria living as symbionts of the major pathogenic filarial nematodes of humans, including *O. volvulus* have during the last decade provided a breakthrough in our understanding of the pathogenesis of onchocerciasis with dramatic implications for treatment and prevention programmes (Hoerauf et al., 2003a). Wolbachia bacteria belong to the order Rickettsiales and are abundant in all development stages of filarial nematodes, including the hypodermis and reproductive tissue of adult filariae.

Wolbachia species seem to have evolved as symbionts essential for worm development, survival, induction of inflammatory disease pathogenesis and fertility of the nematode host. Their depletion results in disruption of embryogenesis in the female worm (Bandi et al., 2001). Wolbachia-bacterial endosymbionts also drive the pathogenesis through the activation and regulation of host immunity (Taylor et al., 2010). Filarial and Wolbachia antigens elicit the release of pro-inflammatory and chemotactic cytokines by resident cells, which induce cellular infiltration and amplification of the inflammatory response (Hise et al., 2004). It was in the bovine *O. ochengi* model at the Veterinary Research Laboratory of the Institute of Agricultural Research for Development, Wakwa – Ngaoundere in North Cameroon that it was first shown that the elimination of Wolbachia organisms led to adult *Onchocerca* worm death (Langworthy et al., 2000). Thereafter, a series of field trials against onchocerciasis and lymphatic filariasis have demonstrated that 4–8 week courses of the antibiotic doxycycline deplete the bacteria and result in the long-term sterility and most importantly death of adult worms (Hoerauf et al., 2001).

**Socio-economic implications of onchocerciasis**

The blindness, dermatitis and chronic disability caused by onchocerciasis remain a huge socio-economic development impediment as the scarce labour force is weakened, the social life of several millions of people is compromised and poverty is sustained in affected communities.

There are high mortalities of the blind victims of onchocerciasis, particularly among male patients (Prost, 1986; Pion et al., 2002). High microfilarial loads have been reported to negatively affect the definitive host’s life expectancy even in non blind patients (Little et al., 2004). Clinical manifestations such as epilepsy which may
possibly be due to heavy infestation (Boussinesq et al., 2002) may be partially responsible for excess mortality. In most communities, epilepsy and onchodermatitis can lead to social stigmatization (Vlassoff et al., 2000).

Onchocerciasis is believed to be responsible for the annual loss of approximately one million disability-adjusted life-years (DALYs). Visual impairment and blindness account for 40% of DALYs associated with onchocerciasis. These are healthy life-years lost due to disability and mortality, more than half of them due to skin disease (Remme, 2004) which greatly reduces income-generating capacity (Oladepo et al., 1997), incurs significant health expenditures and exerts on a long-term basis, a very high negative socio-economic impact on the affected populations and their land use (Evans 1995).

In sub Saharan Africa, blindness greatly diminishes agricultural production while increasing poverty and famine. In West African valleys, onchocerciasis is known to prevent resettlement of arable lands (Hervouet and Prost, 1979).
Recent advances in onchocerciasis research and implications for control
Treatment and control of onchocerciasis

Introduction

A combination of several strategies has been used in the attempt to treat or control onchocerciasis. These include surgical treatment, vector control, drugs and occasional mass therapy and vector control.

Surgical treatment

Denodulization through surgery has been used to prevent high rates of blindness and eye lesions as it removes adult worms. The effect is however limited as the microfilariae remain in the body and can still be transmitted by biting flies to other persons. It is also difficult to remove all the adult worms as some nodules are located deeply in the tissues.

Vector control

Historical Background

Intensive work on the biology, bionomics and distribution of S. damnosum (Crosskey, 1958) and the development of chlorinated hydrocarbons (CHC) increased the prospects of onchocerciasis control by attacking the vector. The breakthrough came when it was shown that Dichlorodiphenyltrichloroethane (DDT), a CHC applied at very low dosage directly into the river or stream was effective in killing Simulium larvae, thus paving the way for the institution of vector control by larviciding. Effective vector control requires a good knowledge of the insect’s biology and ecology. The insecticide of choice in the early days of vector control was DDT but it was replaced quite appropriately by Temephos around 1972 as it was beginning to go out of favour due to its adverse effects on the environment (Leveque, 1989).

Onchocerciasis vector control activities in Africa were executed in three phases. The first phase or pre-Onchocerca Control Programme (OCP) phase started with bush clearing activities (1932-1944) and was followed by the use of CHC insecticides, especially DDT (1944-1972). The second phase or OCP phase was characterized by the use of Temephos, an organophosphate and other larvicides (Phoxim, Pyracyljos, Permethrin, Etofenprox, Carbosulfan and Bacillus thuringiensis H 14). The third phase or post OCP phase consisted of the introduction of focal vector control by the African Programme for Onchocerciasis Control (APOC). In this last phase, vector control activities were carried out using OCP guidelines and were put in place as a means to stop transmission of onchocerciasis in some isolated foci.

In this section, we review the use of vector control in curbing black fly nuisance and the elimination of onchocerciasis in some parts of Africa (Brown, 1962; McMahon, 1967; Davies, 1994; Walsh 1990) and discuss the role it can play as a complement to the efforts of the African Programme for Onchocerciasis Control (APOC) in the elimination of this disease in Cameroon and Africa.
The phases of vector control in Africa

The pre OCP phase (1932 – 1972)

Simulium vector control, prior to the OCP was largely experimental as there were no reference points to guide the activities. It was characterized by environmental modifications such as bush clearing and larviciding with DDT to control Simulium vectors. For example, bush clearing in the Kodera district in Kenya led to the eradication of S. neavei from a small focus in Riana (Buckley, 1951). The same action in S. damnosum larval habitats around Kinshasa did not produce the same results (Henry and Meredith, 1990). The successful demonstration of DDT as a larvicide against Simulium larvae led to intensive pioneering experiments in Kenya and Uganda.

The control projects of this phase were largely localized schemes which lasted for short periods while others went on for many years. Such control schemes were carried out in West and Central Africa in countries like Chad, Cameroon, Nigeria, Benin, Burkina Faso, Côte d’Ivoire and Mali (Duke, 1964; Davies, 1968; Hitchen and Going, 1966; Walsh, 1970).

Successful vector control projects: Some of the control projects produced good results. In Benin, treatment of the Yerpo River which was infested with S. damnosum with 6 rounds of DDT at a dose of 1-4 ppm/30 min greatly reduced the population of adult flies. In Burkina Faso, treatment of the Black Volta and its tributaries with DDT emulsion at the rate of 0.5 ppm/30 min from October 1962 to February 1963 at 10 day intervals reduced the Simulium biting densities from 700 flies/man/week to 1 fly/man/week (McMahon, 1967). Small scale Simulium vector control schemes using DDT were successfully conducted in Cameroon between 1956 and 1966 around Tiko, Limbe and Edea to curb biting fly nuisance especially around the plantations of the Cameroon Development Corporation (Duke 1964; Brown 1962). In March 1978, Temephos at the dose of 0.05 – 0.10 ppm/10 min. was used to successfully control S. squamosum nuisance at the Songloulou dam site in the forest zone. However, resistance to Temephos was observed in June 1980 necessitating a larvicide rotation (Chlorphaxim replaced Temephos) in 1985 (Hougard et al., 1992).

Control activities in Ghana from 1954 to 1955 achieved complete control of S. damnosum around the Kanyania, Sisili, Kamba and the Black Volta Rivers. In 1959, DDT applied at 0.1 ppm/30 min. to the Black Volta and the Kamba Rivers led to a complete control of S. damnosum for 80 km. To reduce the level of nuisance at the Akosombo dam site, several treatments with DDT (0.1 – 0.3 ppm/30 mins) were applied. Fly biting rates reduced at variable rates between 1962 and 1963 until the reservoir was filled up inundating the breeding sites upstream (McMahon, 1967).

In Côte d’Ivoire, two S. damnosum control schemes (northern savanna area and forest zone in the south) were executed between 1963 and 1970. Both of them were to protect two important agricultural communities from S. damnosum nuisance (400 flies/man/day) in the rainy season. The Bagoe and the Bandama were treated at the rate of 0.1 to 0.5 ppm/ 30 min. The results were good (McMahon, 1967). These projects were integrated into the OCP as from 1975.

In Uganda control activities with DDT were able to eliminate the vector from three foci: the Bundongo forest in 1954, the Victoria Nile in 1973 and the Ruwenzori falls in 1976/77 (McMahon et al., 1958; Davies, 1994).

One of the most successful vector control projects was in Kenya where onchocerciasis was eradicated as a result of the total elimination of the vector, S. neavei (Garnham and McMahon, 1947; Garnham and McMahon, 1981;
McMahon, 1967; McMahon et al., 1958). The developing stages of S. neavei in Kenya remained unknown until McMahon in 1950, found the early stages of this fly to be breeding in phoretic association with the fresh water crab (Potamonautes niloticus) in Kipsonoi River, near Kericho. The eradication of S. neavei and consequently onchocerciasis from Kenya benefited from very favourable conditions, namely, a single vector, foci isolated from one another and good follow-up of activities. Three main foci: Mount Elgon, North Nyanza (Kakamega/Kaimosi) and South Nyanza (Kisii, Kericho, Kodera, Riana) were identified. S. neavei was eradicated from the Riana sub-focus by bush clearing. This vector control method has never been repeated successfully anywhere else. All the other foci were treated with DDT. The dosages varied from 1 to 2 ppm/30 min every 14 days, culminating in the demise of onchocerciasis whose prevalence was up to 45% in some communities with 10% blind (McMahon et al., 1958).

The results of the Rapid Epidemiological Mapping of Onchocerciasis (REMO) indicate that Kenya, a country which used to be hyperendemic for the disease is still free (Noma et al., 2002).

Unsuccessful vector control projects: Other vector control schemes were complete failures. For example, the Mayo Kebi River scheme (1955 – 1959) in Chad was carried out in a 55km stretch between Tessoko and Mayo Ligam. The treatment targeted both adults and larvae of S. sirbanum. Six applications of gamma-BHC at 1-2.5 ppm/30 min were made at 3 different points on the ground. At the same time, 10 adulticide applications were made with 2% lindane in gas oil emitted as aerosols from Bell helicopters. Both adults and larvae disappeared one week after treatment but the flies returned in the rainy season of the same year. The failure of the project was attributed to factors such as adult aestivation, insufficient dosing points and reinvasion from the untreated Mayo Wemba, a tributary of the Benoue (Brown, 1962).

Other failed schemes include those carried out in Guinea Bisau (Davies, 1994) and in Nigeria around Kaduna, Lokoja, Enugu, Niger River and Kainji dam which succeeded in reducing the Simulium populations but did not reduce transmission as the infective rates (ranging from 0.7% to 2.95%) and the prevalence (88.04% in 1957 to 73.71% in 1960 - 1966) of the disease remained high (Davies et al., 1978; Davies, 1968; Davies, 1994).

The OCP phase (1975-2002)

The available information on the biology, bionomics and distribution of Simulium species and the existence of ongoing small control schemes led to the convening of a meeting, sponsored by the United States Agency for International Development (USAID), ‘Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies’ (OCCGE) and WHO in Tunis in July 1968. The purpose of the meeting was to bring together scientists to discuss the feasibility of onchocerciasis control. The meeting concluded that a large-scale control campaign rather than eradication was the solution. A programme was recommended involving 10-15 years of aerial larvicide spraying and simultaneous revamping of the health care systems of the endemic countries. The area selected to start the trials was the Volta River Basin and extending into Senegal, Mali and Guinea. The Onchocerciasis Control Programme (OCP) was thus born and after all technical, financial and administrative arrangements were completed, it was launched in 1974 under the aegis of the WHO and it was operational from 1974 to 2002. Its mandate was to eliminate onchocerciasis as a disease of public health importance and as an obstacle to socio-economic development.

The basic strategy of OCP was to interrupt the transmission of O. volvulus by destroying the S. damnosum at its larval stage by aerial application of selective insecticides in infested rivers so that adult onchocercal parasites could eventually die out naturally in the human hosts (Hougard, 1993). The first aerial treatments began in 1974 and by the end of 1977, a total of 654,000 sq. km, spread over seven countries (Burkina Faso, Mali, Niger, Cote d’Ivoire,
Benin, Ghana and Togo) was covered. As the operations were going on in the original programme area, entomological observations revealed that reinvasion of the zone was compromising the control scheme. The OCP was therefore extended to Western Mali, South Eastern Guinea, Northern Sierra Leone, Southern basins of Cote d’Ivoire, Benin, Ghana and Togo. The insecticide selected for the operations was Temephos, an organo-phosphate which selectively kills the larvae of \textit{S. damnosum} but is less toxic to non target fauna.

The overall authority for policy-making, planning, programming, implementation and financing of OCP operations was vested in the Joint Programme Committee (JPC), composed of representatives of the participating countries, the donors and the sponsoring agencies. The Expert Advisory Committee (EAC), made up of 12 scientists, carried out annual, independent evaluation of OCP operations and gave technical and scientific advice to the JPC and the Programme Director. The Committee of Sponsoring Agencies (UNDP, FAO, WHO, World Bank) monitored the Programme operations, considered management issues and reviewed the documentation for JPC.

Aerial treatment using helicopters and fixed wing small aircrafts was supplemented by ground larviciding where appropriate. Rigorous monitoring methodologies were put in place for the follow up of both \textit{Simulium} populations and aquatic fauna during the entire life of the programme. In the course of OCP activities, it was observed that \textit{S. damnosum} developed resistance to Temephos and other larvicides (Phoxim, Pyraclofos, Permethrin, Etofenprox, and Carbosulfan). This led to the introduction of larvicide rotation. This method was able to check the development of larval resistance to an individual insecticide (WHO, 1987a, b).

The OCP also set the criteria for declaring a vector control programme a success as follows:

\begin{itemize}
  \item[a)] The “tolerable level of onchocerciasis infection” in a community: “The attainment and maintenance of all persons living therein who were not infected with \textit{O. volvulus} in the outset of the campaign, of a zero incidence of the serious and irreversible ocular lesions resulting from onchocerciasis”.
  \item[b)] An annual transmission potential (ATP) of 100 larvae was the maximum permissible transmission level.
  \item[c)] The calculation of ATPs and annual biting rates (ABRs) was based on at least four catching days in a month throughout the year.
\end{itemize}

In the same light, the Environmental Monitoring Group was set up with the responsibility of monitoring the environmental impact of the large quantities of larvicides on the aquatic fauna. Specifically, it:

\begin{itemize}
  \item[a)] organized and evaluated the long-term monitoring of the aquatic fauna;
  \item[b)] assessed the level of toxicity of new products or formulations and approved or rejected their operational use;
  \item[c)] reviewed the nature and magnitude of the ecological problems connected with the programme and with associated economic development projects proposed in areas freed from onchocerciasis in order to identify the environmental and human ecological implications of such developments.
\end{itemize}

\textbf{OCP achievements:} The success of the OCP was outstanding and this led to the cessation of larviciding and the eventual closure of the programme in 2002 (Yameogo, 2003). The OCP was the largest vector control scheme to be attempted and it was born out of the experience gained from several pilot projects executed in Burkina Faso, Cote
d’Ivoire, Mali, Ghana, Benin and Togo (Walsh et al., 1979). The success of the OCP and the standards it set make it stand out as the reference for all other Simulium control schemes in Africa.

It has been estimated that from 1974 to 2002, skin infection and eye lesions were prevented in 40 million people in 11 countries, 600,000 cases of blindness were prevented, 25 million hectares of abandoned arable land reclaimed for settlement and agricultural production capable of feeding 17 million people annually. The economic rate of return was calculated at 20% (Hodgkin et al., 2007).

The post OCP phase (2002 – today)

This phase of onchocerciasis control was characterized by vector control activities pioneered by APOC. In its effort to control the disease in Africa, APOC included focal vector control in areas where the foci were shown to be so isolated and there was no risk of re-invasion of the foci by migratory black flies. Three such projects were identified in Bioko Island in Equatorial Guinea (Traore et al., 2009), Itwara in Uganda (Kipp et al., 1992; Garms et al., 2009) and Tukuyu in Tanzania (APOC, 2005). Whereas the vector was eliminated in the first two foci, the Tukuyu focus suffered from re-invasion problems and larviciding was suspended.

Problems of vector control

Despite the successes mentioned above, vector control as described in this section was also plagued by problems such as resistance of the vector to larvicides, effect of the larvicides on non target organisms and reinvasion of control areas by the vector.

Resistance of the vector to larvicides

This generally is a result of the development of genetic resistance to the organic compounds used in the control process. Resistance involving two of the seven species of the S. damnosum complex namely, S. sanctipauli and S. subrense was reported against the organophosphate, Temephos, in the OCP. This is thought to have developed through selection of resistant individuals under long and intensive larvicide treatment spreading out through dissemination. Generally, the development of resistance can be controlled by alternating the use of different compounds. Unfortunately this approach can result in the development of resistance to multiple compounds as was the case against chlophoxim and temephos along the tributaries of the Niger in Mali and the upper reaches of the Sassandra River (Norgbey, 1997; Leveque, 1989).

Effect of the larvicides on non target organisms

The larvicides used in the vector control of onchocerciasis also had adverse environmental impacts. As a result of studies carried out early in the course of larvicide applications, organochlorine insecticides were abandoned in favour of organophosphates that were more readily biodegradable. Even the organophosphates have been shown to have negative environmental impacts. For example, a routine spraying operation with Temephos using (0.05-0.1 mg/l for 10 min) can produce a massive detachment of insect fauna, which is reflected by a rise in the drift, after a 15-45 min period of latency. The mortality rate of drifting organisms has been shown to be very high. Generally, temephos and other insecticides cause a reduction of about 30% of invertebrate fauna (Norgbey, 1997). There is not much data on the effects of larvicides on aquatic flora. It has however, been suggested that aquatic plants can
break down into microscopic parts resulting in food scarcity and then reduction in fish populations following spraying.

The results described above which had a strong impact on invertebrate organisms were for the first applications of temephos and chlorphoxim. However, the results obtained after many years’ treatment showed little long-term effect of the various larvicides on the non-target fauna. The treated rivers had fairly strong resilience and a great capacity for recovery (Leveque, 1989).

**Reinvasion of control areas by the vector**

Reinvasion by insect vectors following chemical control is a common phenomenon. It is often observed in Tse-tse fly control activities. It was a major problem in the OCP operations where flies were often carried by prevailing winds from untreated zones close to OCP areas. The strategy employed in controlling the problem was to expand the control area to cover the sources of departure of reinvading flies.

**Drug treatment**

There was no ideal drug for treating onchocerciasis before 1987. Two microfilaricides, diethylcarbamazine (DEC) citrate and suramin were used until the 1970s when they became unpopular because of severe side effects. The drug of choice recommended by the WHO is ivermectin (Mectizan®). Its antiparasitic properties were discovered in 1970, but it was in 1980 that clinical trials confirmed its efficiency against *O. volvulus* (Diallo *et al*., 1986; Lariviere *et al*., 1989a,b,c; Greene *et al*., 1985a).

Control activities by APOC have been based largely on mass drug administration using ivermectin. Here we described the role of ivermectin in the control of onchocerciasis in Africa.

**Ivermectin in the control of onchocerciasis**

**Ivermectin family and chemical structure**

The avermectins to which ivermectin belongs are macrocyclic lactones derived from the product of fermentation of *Streptomyces avermitilis*. This germ was isolated from a soil sample collected near a golf course at Katawana in Ito city, Shizuoka Prefecture in Japan. The avermectins were isolated by solvent extraction from the mycelia solvent partition and column chromatography (Miller *et al*., 1979). This process of isolation was improved using selected strains of *S. avermitilis*. A selective hydrogenation of avermectin B1 led to the synthesis of two molecules, the 22, 23-dihydroavermectin B1a (80%) and the 22, 23-dihydroavermectin B1b (20%). The combination of these two molecules constitutes ivermectin (Figure 5).
Effect of ivermectin on *O. volvulus*

The anthelminthic activity of avermectins was first discovered in 1979 (Miller *et al.*, 1979; Burg *et al.*, 1979; Egerton *et al.*, 1979). Avermectins act at multiple sites and various species have different sensitivities (Turner and Schaeffer, 1989). Ivermectin acts as an agonist of glutamate-gated chloride ion channels (Glu-Cl) and Y-aminobutyric acid (GABA)-related chloride ion channels receptors present in nerve and muscle cells of nematodes, insects and ticks. Interactions between ivermectin (IVM) and these receptors and/or channels prevent their closure, thus increasing the permeability of synapse membranes to chloride ions, which leads to hyperpolarization of the neuronal membrane and consequently to the paralysis of the somatic muscles, particularly the pharyngeal pump (Omura and Crump, 2004). The paralyzed microfilariae are then drained through the lymphatic system and then destroyed by the immune system, notably by macrophages at the level of the lymph nodes. This mechanism also leads to the disruption of the ingestion of nutrients and explain the rapid drop of microfilaridermia after a unique dose of ivermectin (Vuong *et al.*, 1992; Knab *et al.*, 1997). On the adult female worm, there is a prolonged effect of ivermectin on the uterus muscles which hinders the release of microfilariae out of the uterus. These microfilariae are accumulated in the genital tract and degenerate in situ (Wildenburg *et al.*, 1998).

Clinical trials with Ivermectin

The efficicacy of ivermectin on *O. volvulus* was demonstrated for the first time in Senegal in 1982 (Diallo *et al.*, 1984; Aziz *et al.*, 1982). In the trial, 32 patients with moderate microfilaridermia were randomly allocated into four groups which received respectively, 5, 10, 30 and 50µg/kg of ivermectin. In all groups, ivermectin was well tolerated. Neurologic, ophthalmologic and haematologic tests performed did not show any abnormality.
Phase two trials were conducted in Paris and in Ghana. In Paris, patients were treated with 150 and 200µg/kg. In Ghana, patients were treated with 50, 100, 150 or 200µg/kg. The microfilaricidal effect was more important from 100µg/kg. Adverse events were described with the increase of the doses. These included swelling, Mazzotti reactions, conjunctivitis with transitory blurred vision and the appearance of microfilariae in the anterior chamber of the eye (Coulaud et al., 1983, 1984; Awadzi et al., 1995).

Phase three trials compared a unique dose of 200µg/kg of ivermectin to 7 to 8 days of Diethylcarbamazin in Senegal (Diallo et al., 1986), Mali (Lariviere et al., 1985), Liberia (Albiez et al., 1988; Taylor et al., 1986; Greene et al., 1985b) and Ghana (Awadzi et al., 1986). In general, these trials showed more pronounced effects of ivermectin compared to DEC with less adverse events in ivermectin treated groups. The microfilaridermia remained low (below 10%) during the year following the administration of a unique dose of ivermectin. An important observation was the decrease of microfilariae in the anterior chamber of the eye. Another phase three trial with larger sample sizes was carried out in Côte d’Ivoire, (Lariviere et al., 1989a,b,c), Ghana, (Dadzie et al., 1989; Awadzi et al., 1989) Mali (Vingtain et al., 1988), Togo (Hussein et al., 1987) and Liberia (Taylor and Greene, 1989; Newland et al., 1988; White et al., 1987). All the results of phase I, II and III indicated that ivermectin could be used for mass treatment of onchocerciasis. The phase IV studies were then carried out with the objective of measuring the effect of repeated treatments on microfilaridermia, the symptoms of onchocerciasis and the transmission of the disease.

**African Programme for Onchocerciasis Control**

In Africa, two key events marked onchocerciasis control in 1987. In October of that year, ivermectin (Mectizan®), which proved to be both well tolerated and efficient against *O. volvulus* microfilariae, was authorized for commercialization for the treatment of human onchocerciasis in France. Soon after, Merck and Co., Inc took an unprecedented decision to provide it free of charge as long as needed, to those who would ask for it to treat onchocerciasis everywhere in the world. Merck took this decision, working in collaboration with renowned experts in public health and parasitology, the World Health Organization and other agencies to combat the disease in the endemic countries. This historic decision came nearly five years after the first human clinical trials in Dakar, Senegal (Aziz et al., 1982). The Mectizan Donation Programme (MDP) was created the same year to coordinate the activities related to the donation (Boussinesq et al., 1997). The drug donation facilitated the launching of the African Programme for Onchocerciasis Control (APOCH).

**APOCH objective and strategy**

The objective of APOCH was to control onchocerciasis as a public health problem from the 19 endemic countries outside OCP area by establishing sustainable ivermectin-based treatment projects in zones where onchocerciasis was meso or hyperendemic.

The strategy was based on the Community-Directed Treatment with Ivermectin (CDTI). This relied on the massive participation of endemic communities. Members of these communities were invited to appoint people called community-directed distributors (CDDs), who were then trained by the local health officers and NGO. The CDDs’ tasks were to sensitize the population, carry out a census of the community members, distribute Mectizan®, monitor treated individuals for SAEs and report them to the nearest health facilities. The CDDs worked under the supervision of the local health staff (Homeida et al., 2002).
Recent advances in onchocerciasis research and implications for control

The objectives of MDP are to supply Mectizan® to countries in need and to ensure an adequate use of drug as well as the appropriate medical monitoring of adverse events. The MDP also put in place an expert committee (Mectizan® Expert Committee, MEC) made up of independent scientists who provide technical support (MEC/TCC, 2004). This committee assess the quality of Mectizan® distribution projects submitted to MDP by endemic countries, follow Mectizan® distribution process and seek to ensure the best possible use of the drug (Alleman et al., 2006). This drug donation led to the involvement of Non Governmental Organizations in the control of onchocerciasis. Between 1989 and 1994, Non Governmental Development Organizations (NGDOs) set up ivermectin distribution programmes in several onchocerciasis foci in Africa. In 1991, an NGDOs coordination group for onchocerciasis control was born in Geneva at the WHO headquarters. In 1995, building on the OCP experience, many international organizations launched in partnership with endemic countries, donor countries and the NGOs coordination, the African Programme for Onchocerciasis Control (APOC). The programme was based on a partnership involving various United Nations organizations, the governments of the participating countries, endemic countries, NGOs, donor countries and the private sector (Merck & Co., Inc through the Mectizan® Donation Programme). About thirty NGOs are presently involved in onchocerciasis control in Africa. Some of them are: Christoffel Blinden mission, Global 2000 River blindness Programme of The Carter Centre, Healthnet International, Helen Keller International, Inter Church Medical Assistance, Lions Club International Foundation, l’Organisation pour la Prévention de la Cécité and Sight Savers. In some countries, local NGOs take part in APOC activities. Examples of these include Perspectives in Cameroon, Mission to Save the Helpless in Nigeria and Christian Association of Liberia in Liberia (Cross, 2000). WHO is the programme executing agency, with the headquarters in Ouagadougou, Burkina Faso. The financial agent is the World Bank, which set up a special fiduciary fund where contributions from donors were paid to finance the programme activities. The Bank coordinated actions from all the donors and mobilized funding for the programme. The endemic participating countries are Angola, Burundi, Cameroon, Congo, Democratic Republic of Congo, Ethiopia, Equatorial Guinea, Liberia, Malawi, Nigeria, Uganda, Central-African Republic, Sudan, Tanzania and Chad.

Effect of the drug on the transmission of onchocerciasis

The use of ivermectin at the usual dose induces an important reduction of microfilaridermia. This reduction persists for three to six months (Pion et al., 2011; Basanez et al., 2008) and has an impact on the number of microfilariae that the vector can ingest during a blood meal. The impact of treatment on the transmission was demonstrated for the first time in Liberia (Cupp et al., 1986). These authors compared the number of microfilariae intake by Simulium from patients treated with ivermectin, DEC and placebo three weeks before. This intake was significantly reduced in patients treated with ivermectin. In Ghana, two months after a unique dose of ivermectin, it was shown that transmission indicators were reduced from 85 to 65% compared to the initial value (Remme et al., 1989). In the Vina valley in Cameroon, after five years of annual treatment with ivermectin, the prevalence of microfilaridermia in children aged 5 to 7 years old who had never been treated was reduced to 55.4%, demonstrating a reduction in the transmission of onchocerciasis (Boussinesq et al., 1995).

Repeated treatments with ivermectin significantly contributed to the reduction of the impact of onchocerciasis in more than 25 countries. In addition, the transmission of the disease has been interrupted in some foci in at least 10 countries and onchocerciasis is no longer seen in children in many formerly known endemic countries. Consequently, ivermectin monotherapy for onchocerciasis control has grown tremendously, receiving funding, technical and logistical support from international public health donors.
Problems associated with the use of ivermectin for onchocerciasis control

The control of onchocerciasis presently depends on mass drug distribution (MDD) using ivermectin. As at now, it is the only drug that is being used for the mass treatment of onchocerciasis. It is given free of charge by Merck and Co. for as long as needed. This and the use of vector control measures have been extremely effective in abating the public health impact of onchocerciasis (Molyneux, 2005; Boatin et al., 1997). Unfortunately, there are many problems with the use of ivermectin for onchocerciasis control. Some of these are described below:

- Ivermectin is effective against the microfilariae that cause the severe manifestations of the disease. Its main limitation is that it has little effect on the adult worms that continue to produce microfilariae and hence re-treatment is required at intervals that clinicians in many on-going programmes have not definitely determined or agreed upon. It reduces microfilariae load but does not interrupt transmission as it is incapable of reducing the levels of infestation below those necessary to sustain transmission. At least two treatments per year need to be continued for a long period of time. Pregnant women, breastfeeding mothers and children below 5 years are also excluded in ivermectin treatment programmes.

- There is mounting clinical and molecular evidence that resistance to ivermectin by *O. volvulus* is emerging (Ardelli and Prichard, 2004; Awadzi et al., 2004a,b; Bourguinat et al., 2007; Osei-Atweneboana et al., 2007; Lustigman and McCarter, 2007; Canul-Ku et al., 2011). The emergence of resistance to ivermectin was first suggested in Ghana where sub-optimal responses were reported in *O. volvulus* multi-treated populations (Awadzi et al., 2004a,b). Recently, it was noticed that the ability of ivermectin to suppress microfilariae repopulation was reduced in some communities which had received mass treatment for 6 to 18 years (Osei-Atweneboana et al., 2007, 2011). Besides these phenotypic suspicions of resistance, many studies have revealed that selections are occurring in some genes of the parasite such as ABC transporters (Ardelli and Prichard, 2004, 2007; Ardelli et al., 2006a), P-glycoprotein (Ardelli et al., 2005, 2006b; Eng and Prichard, 2005), β-tubulin (Eng and Prichard, 2005; Eng et al., 2006; Bourguinat et al., 2006, 2007) and P-glycoprotein like protein (Bourguinat et al., 2008). In studies conducted in the Mbam valley, a hyperendemic region for onchocerciasis in Cameroon, it was shown that the genetic selection induced by ivermectin treatments was associated with a lower reproductive rate of the heterozygote female parasites (Gardon et al., 2002).

Despite these phenotypic and genotypic studies, the unequivocal proof of resistance has yet to be established. It was demonstrated that some confusing factors related the host immunological status (Ali et al., 2002; Babayan et al., 2010), the drug compliance (Cabaret, 2010) and the population dynamics of the parasite (Pion et al., 2011) can be implicated in drug failure, leading to an inaccurate conclusion of resistance.

- Adverse events following treatment with ivermectin have been described, especially in patients harbouring very high microfilarial loads. The pathogenesis of these post treatment adverse events is not yet well described. These adverse events are categorised as follows:

  - **Minor and moderate adverse events**

In the savanna regions, adverse events are minor or moderate. These adverse events occur after 24 to 48 hours after treatment and consist of itching, fever, joint pain, muscle pain, headache, dizziness, general pain, oedema and cutaneous eruption. The intensity of these adverse events depends on the intensity of infection (Whitworth et
More serious clinical adverse events (orthostatic hypotension) were described in West Africa (Awadzi, 2003; Chijioke and Onkonwo, 1992; Awadzi et al., 1989; De Sole et al., 1989a,b). The incidence of these adverse events also depends on the prevalence of onchocerciasis and the regions. It has been reported to vary from 13 to 59.1% (Njoo et al., 1993; De Sole et al., 1989b; Kipp et al., 2003). The incidence of adverse events decreases significantly with the years of treatments.

Immunological and pathological studies have demonstrated that minor and moderate adverse events after treatment with ivermectin are due to inflammatory reactions associated with the destruction of microfilariae (Wildenburg et al., 1994; Ackerman et al., 1990). It had been suggested that lipopolysaccharides (LPS) released by endosymbiotic Wolbachia play a role in the pathogenesis of adverse events (Cross et al., 2001; Keiser et al., 2002). It has now been shown that Wolbachia does not contain LPS and that the inflammation is driven by Wolbachia lipoproteins (Turner et al., 2009). At the level of the eye, ivermectin provokes a transitory increase of the number of microfilariae in the cornea, inducing a transitional blurred vision (Boussinesq, 2005). All these minor and moderate adverse events regress spontaneously but some may need symptomatic treatment such as antalgic, anti-inflammatory or antihistaminic drugs.

**Severe adverse events in loaisis co-endemic areas**

The major obstacle in the control of onchocerciasis, particularly in Central Africa, is the occurrence of severe adverse events (SAEs) after treatment with ivermectin in areas where onchocerciasis is co-endemic with loaisis. These post treatment reactions occur in patients harbouring high Loa loa microfilarial loads (> 8000 mf/ml) (Boussinesq et al., 1998; Gardon et al., 1997). These adverse events are classified in two main categories, SAEs without neurological signs and probable L. loa encephalopathies related to treatment with ivermectin.

- **Adverse reactions without neurological signs**

The first category corresponds to patients who do not present neurologic signs but their conditions necessitate hospitalisation. Reactions in these patients start twelve to twenty-four hours after treatment. Predominant symptoms are severe headaches, fever, general pain, severe joint pains, anorexia, nausea, vomiting and diarrhoea. These symptoms are so severe in some patients that they cannot stand up. In some patients, there are conjunctiva and retinal haemorrhages (Fobi et al., 2000) while others develop kidney problems (Ducorps et al., 1995). The duration of these reactions is variable. Hospitalisation is generally around 4 days but in some rare cases it has been prolonged to two weeks. Patients with these reactions recovered without sequels. It is difficult to know if providing prompt and proper medical care to patients with SAEs can avoid their worsening into neurological cases and coma, but observations in some areas in Cameroon tend to confirm this hypothesis (Fokom Domgue, 2006). Patients developing this first category of SAEs are those with 8000 mf/ml of L. loa and above.

- **Probable L. loa encephalopathies related to the treatment with ivermectin (PLERI)**

PLERI are SAEs with neurological involvement occurring after treatment with ivermectin in patients with very high microfilarial loads (> 30 000 mf/ml) (Boussinesq et al., 1998; Gardon et al., 1997; Twum-Danso, 2003a,b). To be admitted as a PLERI patient, neurological symptoms should start within the week after the treatment of a healthy individual. Four case definitions have been adopted for neurological post ivermectin SAEs (Twum-Danso, 2003b):
- **Definite Case of Loa encephalopathy**
  - Encephalopathy in which brain tissue obtained by autopsy or by needle sampling has microscopic findings consistent with *L. loa* encephalopathy (vasculopathy with evidence of *L. loa* microfilariae as a likely aetiology);
  - Onset of Central Nervous System (CNS) symptoms and signs within 7 days of treatment with ivermectin; illness progressing to coma without remission.

- **Probable Case of Loa encephalopathy**
  - Encephalopathy (without seizures, usually with fever) in a person previously healthy and who has no other underlying cause for encephalopathy;
  - Onset of progressive CNS symptoms and signs within 7 days of treatment with ivermectin; illness progressing to coma without remission;
  - Peripheral blood *L. loa* > 10,000 mf/ml pre-treatment or > 1,000 mf/ml within 1 month post-treatment or > 2700 mf/ml within 6 months of treatment; and/or *L. loa* microfilariae present in cerebrospinal fluid (CSF) within 1 month post-treatment.

- **Possible Case of Loa encephalopathy**
  - Encephalopathy (without seizures, usually with fever) in a person previously healthy and who has no other underlying cause for encephalopathy;
  - Onset of progressive CNS symptoms and signs within 7 days of treatment with ivermectin; illness progressing to coma without remission;
  - Semi-quantitative or non-quantitative positive (i.e. +, ++, +++) *L. loa* microfilariae in peripheral blood within 1 month post-treatment.

- **Encephalopathy of other known aetiology**
  - Encephalopathy with sufficient clinical information to determine an etiology other than *L. loa* (e.g. cerebral malaria)

**Pathophysiology of post Ivermectin SAEs:** Many hypotheses have been put forward to explain the pathophysiology of post ivermectin SAEs. The first is the mechanical phenomenon due to the paralysis of an important number of microfilariae in the blood stream following treatment with ivermectin. These microfilariae are drained to the microcirculation, creating micro-embolism and difficulty in the oxygenation of the brain and other organs. The conjunctivae and retinal haemorrhage that occur at the level of the capillaries (Fig. 6) are in favour of this hypothesis (Fobi et al., 2000). Another hypothesis is the passage of the microfilariae into the brain parenchyma. The third hypothesis is the vasoconstriction of the capillaries following a complex formed by the *L. loa* antigen and antibody following the death of microfilariae. The last hypothesis is the intravascular disseminated coagulation. In some cases, it has been described as generalized haemorrhage in the brain, the kidney and the liver (Kamgno et al., 2010).

It has also been suspected that strain variation may be responsible. Consequently, it has been hypothesized that those who developed SAEs may be infected by a strain of Simian *L. loa* which has nocturnal periodicity. The
periodicity of *L. loa* was studied in cases of SAEs and controls that took the treatment but did not develop SAEs. The periodicity was similar in cases and controls (Kamgno *et al.*, 2009). The results of this study suggest that post-ivermectin SAEs are not related to an infection with a simian Loa strain. Autopsy examinations in the Adamaua Region of Cameroon also revealed no microfilaria in the brains or in other tissues examined. The lungs samples showed a neutrophil infiltration of the alveolar walls and space probably due to acute pneumonia. Two major changes were described in the brain in association with the small and medium size blood vessels. A moderate perivascular accumulation of inflammatory cells and significant thickenings of the basement membrane and associated pericytic layer of various size vessels (Kamgno *et al.*, 2008). These lesions in the brain have similarities with those described in previous reported cases of death due to *L. loa* following diethylcarbamazin treatment.

![Sub-conjunctival haemorrhage in a post ivermectin SAE case](image)

**Figure 6.** Sub-conjunctival haemorrhage in a post ivermectin SAE case

**Incidence of SAEs:** A pilot study of post ivermectin SAEs which was carried out in the Lékié area of the Centre Region of Cameroon showed an incidence of PLERI of 1.1 cases per 10,000 treatments and the non neurological SAEs of 5 per 10,000 treatments (Gardon *et al.*, 1997). In a recent review, a cumulative incidence of 4.2 cases of SAEs per 100,000 treatments including PLERI and non neurological SAEs over a period of 10 years in Cameroon (1999 to 2009) was reported (Kamgno *et al.*, 2011).
In addition to all of the above, there can be acute accidental intoxication with ivermectin (7 – 8 mg/kg) which is correlated with a clinical presentation showing vomiting, sedation and mydriasis. On the other hand, doses of 120 mg/kg, ten times the normal adult dose for onchocerciasis treatment, was administered to healthy subjects, without any toxicity (Guzzo et al., 2002).

There have been suggestions that ivermectine can cause teratogenic effects. However, studies have not shown any such effects on animals treated with normal doses (Poul, 1988; Keisler et al., 1993). In Cameroon and Liberia, a follow up of pregnant women who ignored their pregnancy status and took ivermectin during mass treatment was conducted. No difference was found between children of accidentally treated pregnant women and those of untreated ones (Chippaux et al., 1995; Pacque et al., 1990).

**APOC achievements**

It was estimated in 2005 that 500,000 DALYs per year were averted, 177,000 communities were mobilized and a workforce of 261,000 community distributors was trained and made available for other programmes. For the past Quarter century (1987–2012), over 800 million people have been treated with ivermectin for the control of onchocerciasis in 16 countries. The economic rate of return was put at 17% and US$7 per DALY was averted (Hodgkin et al., 2007). However, in assessing the benefits accrued through these control programmes, it is important to also consider the number of deaths avoided in addition to the cost-effectiveness of treatment and the number of people prevented from becoming blind (Benton, 1998; Waters et al., 2004).

The sustained political commitment of national governments, bilateral donors, and NGDOs and the long-term support of onchocerciasis control coupled with the regional approach, the contribution of a diverse group of stakeholders (Seketeli et al., 2002) and the emphasis on continued operational research contributed to a large extent in the success levels attained by APOC.

**APOC challenges**

Despite the achievements of OCP and APOC, onchocerciasis has not been eradicated. Early hopes that mass treatment with ivermectin would eradicate the disease by breaking transmission have not been realized (Borsboom et al., 2003). Estimations based on REMO show that the mean infestation rate among countries targeted by APOC is around 38%, with 87 million people at risk of infection (Hotez and Kamath, 2009). In 2005, APOC estimated that in Africa, 37 million people carried *O. volvulus* and 90 million were at risk (APOC, 2005).

Wars and treatment complications linked to onchocerciasis and loasis co-endemicity have been major impediments to the expansion of APOC activities in Central Africa. In areas that are hyperendemic with *L. loa*, ivermectin is contraindicated as there is a risk of (SAEs) following treatment in people who have a high microfilaraemia of *L. Loa*. This can result in encephalopathy (Gardon et al., 1997; Boussinesq et al., 2006).

Furthermore, the difficult terrains in most of Africa, specific epidemiological conditions and socio-economic limitations have contributed in maintaining onchocerciasis in the continent. The movement of human populations and frequent social and political upheavals in the African Region increases the risk of transmission and/or re-emergence of onchocerciasis.
Onchocerciasis control strategies in Cameroon

Introduction

Cameroon set up a national programme for onchocerciasis control in 1991. Its structure was a reflection of the Cameroonian public health system. It has three levels: a central level made up of the central departments of the Ministry of Public Health and the General and Central Hospitals, intermediary level made up of Regional Delegations of Public Health and Regional Hospitals and a peripheral level comprising 189 Health Districts and 1689 Health Centres. The Health District is the basic implementation level of health programmes and projects and hosts a district hospital. There are two dialogue structures whose members are elected by the populations at the district level: the management Committee of the District and the District Health Committee. The health district consists of several health areas, some of which may have Integrated Health Centres run by nurses. At the level of a health area, there is a Health Committee and a Management Committee. These are dialogue structures participating in the mobilization of the populations around health-related projects and programmes.

The National Onchocerciasis Control Programme (NOCP) works under the aegis of the National Onchocerciasis Task Force (NOTF) presided over by the Director of Disease Control of the Ministry of Public Health. The other members of this group are: the persons in charge of health facilities in endemic areas, the representatives of the NGDOs participating in onchocerciasis control in Cameroon, Lions Club International and members of research institutes working on filariasis in Cameroon. In 2003, a loasis Technical Adviser in charge of the surveillance system of SAEs events that occur after treatment with ivermectin was added to this organization and in 2005, the Centre for Research on Filariasis and other Tropical Diseases (CRFilMT) was also added to it. The programme is run on a daily basis by a Permanent Secretary who ensures its coordination.

Identification of priority populations to be treated in Cameroon

At the time of the NOCP initiation, very little data regarding onchocerciasis endemicity were available in Cameroon, even though the main foci were already known. As a result, a survey based on the Rapid Epidemiological Assessment of Onchocerciasis (REA) and REMO principles was carried out in 1992 throughout the entire Cameroonian territory (Ngoumou et al., 1994). These surveys led to the mapping of areas where onchocerciasis was meso- or hyper-endemic (that is where the nodule prevalence in men aged 20 or more is over 20%) in the country and priority areas where ivermectin should be distributed. This mapping was particularly important in forest areas endemic for loasis where there is a risk of SAEs after treatment with ivermectin. Consequently, it was essential to properly define onchocerciasis endemic areas in order to reduce the risk of treated individuals developing post-therapeutic SAEs, when the advantage associated with the treatment is not well established. Therefore in these areas, REA was conducted to refine the distribution of onchocerciasis. Rapid Epidemiological Assessment of Loiasis (RAPLOA) (Takougang et al., 2002; Wanji et al., 2005) and parasitological surveys were also conducted to determine the level of endemicity of loiasis (Kamgno et al., 1997; Kamgno and Boussinesq, 2001) and to put in place proper measures for the prevention and management of post ivermectin SAEs following the Technical Consultative Committee (TCC) and Mectizan Expert Committee (MEC) recommendations. The results of these surveys as well as those achieved in the parasitological surveys (Kamgno et
al., 1997; Kamgno et al., 1998; Kamgno and Boussinesq, 2001) helped to determine the meso- and hyper-endemic areas eligible for CDTI as well as hypo-endemic areas that are not CDTI-eligible in the whole country.

Evolution of onchocerciasis control strategies in Cameroon

Early large scale distributions

In 1987, ivermectin distribution focusing on a few thousand people was organized in the framework of phase IV clinical drug trials. These studies were carried out in the Vina valley by ORSTOM team (currently called IRD) and in the South West Province by a team from the Institute of Medical Research and Medicinal Plant Studies (IMPM) (Boussinesq et al., 1993a,b; Somo et al., 1993a,b; Chippaux et al., 1999).

In 1989, the German Technical Cooperation, GTZ (Gesellschaft fur Technische Zusammenarbeit) launched the ivermectin distribution programme in the Littoral province. Between 1992 and 1995, three NGDOs namely, the River Blindness Foundation (RBF) (now the Carter Center), International Eye Foundation (IEF) and Helen Keller International (HKI) signed agreements with the Ministry of Public Health to set up distribution programmes in other provinces of Cameroon. Treatment strategies varied according to regions.

Community-based strategies

In 1994, the NGDOs for onchocerciasis control gathered around Lions Club International Foundation (LCIF) to form a coalition for onchocerciasis control in Cameroon. In 1995, the LCIF launched the “Sight First” project. Thereafter, another NGDO, Sight Savers International (SSI), started a Mectizan® distribution programme in Nanga Eboko district.

Ivermectin was distributed through two strategies described as “advanced strategy” (wherein nurses moved around with their motor cycles from village to village to administer the drug) and “community-based”. In the latter case, community-directed distributors (CDDs) appointed by the population distributed the tablets but the health staff still had an important role to play in the process. They had to number the households, order Mectizan®, determine the distribution period, monitor the adverse events and write up the distribution reports. Community members helped the health staff and participated in the population mobilization. The distribution costs were still very high and the geographic and therapeutic coverage rates were most often very low due to difficulties to reach some communities.

The advent of the African Programme for Onchocerciasis Control in Cameroon

In 1996, APOC objectives and strategies were presented to Cameroonian authorities. The following year, a convention covering the period from 1996 to 2001 was signed between the Ministry of Public Health and the Directorate of APOC. The first distributions organized in the framework of APOC took place in 1999. The two memoranda covering the period from 2001 to 2007 and the disengagement of APOC (2008-2010) were signed in 2001. These conventions allowed different partners to submit requests for funding to APOC for CDTI projects covering either a province of the country or a part of the province. These projects were funded up to 75% by APOC and the NGDO for the first year, and the remaining 25% by Cameroon Government. APOC participation, which was
agreed to last 5 years, was supposed to decrease gradually while that of the government had to increase progressively to ensure the sustainability of the programme. To date, 15 CDTI projects have been funded in Cameroon that cover the ten regions of the country.

**Difficulties related to onchocerciasis control in Cameroon**

The difficulties associated with onchocerciasis control in Cameroon are: duration of treatment programmes, cost recovery and SAEs.

1. **Duration of treatment programmes**

Mectizan® is a microfilaricide, with a limited effect on adult worms (Duke *et al.*, 1991). It should be administered on a repetitive basis each year. Mathematical simulations showed that, in order to be able to eliminate onchocerciasis as a public health problem, 25 years of Mectizan® distribution would be necessary if programmes were able to keep the therapeutic coverage rate at 65 %. According to previsions from developed models, if the interval between treatments is six months rather than 12, then the duration of the programme might be halved (Winnen *et al.*, 2002), but this assertion is not true in all contexts.

2. **Cost recovery**

The strategy for onchocerciasis control in Cameroon underwent, like the health system of the country, a number of modifications since the NOCP was established. In 1991, when the NOCP was set up, cost recovery was a strong principle of the Cameroon health system. As such, the NOCP adopted it. Mectizan® was received from MDP free of charge but delivered to patients against a payment of CFA 100 (0.25 $). This cost recovery lasted until 1996 when APOC was being established.

During the consultations with APOC officials, Cameroon expressed the wish to maintain the principle of cost recovery despite APOC’s reticence, which dreaded its negative impact on the population’s compliance with treatment. In this way, Cameroon unlike other countries adopted the CDTI strategy recommended by APOC but with a particularity, the cost recovery. The CDDs received 25 F per treatment. Later on, under the pressure of NGDOs and taking into account the fact that in some poor families, parents could afford their own drug but not that of children, the treatment cost was reduced (10 F CFA) for children less than 15 years-old. It was also decided that treatment should be free of charge for poor people.

In 2002, due to a very low coverage, notably in areas where SAEs occurred, the government decided that treatment should henceforth be free for everybody. When this decision was taken, the problem of the payment of CDDs emerged. The Cameroon government therefore decided to pay them directly at the rate of 25 F CFA per treated individual. This is the policy applied to date.

3. **Severe adverse events occurring after treatment with ivermectin**

In Cameroon, adverse events occurring after treatment with ivermectin constitute an important obstacle depending on the geographic areas. In areas where loasis is absent or where the prevalence and parasite load are below 20%, adverse events are minor or moderate. On the contrary, in areas where onchocerciasis and loasis are co-endemic, SAEs may occur after treatment with ivermectin. These therapeutic accidents occur in people whose parasitic loads of *L. loa* are very high (> 8000 mf/ml) (Gardon *et al.*, 1997; Boussinesq *et al.*, 1998).
Chemotherapy and immunology of onchocerciasis: insights from the bovine model

Introduction

Research in onchocerciasis particularly that concerned with chemotherapy and immunity has been limited by the lack of suitable animal models for *O. volvulus* since the parasite is very host restricted and naturally infects only humans and gorillas. Of all animal models used to date, it is only in chimpanzees that the infection closely resembles that in humans. This is, however, impractical for use on a large scale for research due to the cost, ethical and conservation concerns (Copeman, 1979).

*O. ochengi/cattle model for onchocerciasis research*

As a result of the availability of cattle Onchocerca parasites from abattoir material and their generic relationship to *O. volvulus*, bovine Onchocerca species have been extensively used in comparative studies. *O. gibsoni* has been used in drug evaluation (Copeman, 1979). Unfortunately, the deep anatomical location of many bovine species makes them unsuitable for many research studies as their viability can only be assessed on a single occasion at post-mortem of the host (Trees et al., 1998). This difficulty does not apply to *O. ochengi*.

The cattle *O. ochengi* forms nodules that closely resemble those formed by *O. volvulus* (Renz et al., 1995; Achukwi et al., 2007). The adults of *O. ochengi* which are widely distributed in West Africa form multiple intradermal or subcutaneous nodules that can be enumerated non-invasively by palpation and sequential nodulectomies undertaken easily to study the kinetics of the response of the macrofilariae to drugs. *O. ochengi* also shares some characteristics in common with *O. volvulus*, such as a common arthropod vector, *S. damnosum* (Wahl et al., 1998) and a very close phylogenetic relationship (Bain, 1981; Xie et al., 1994). Drug activity against microfilariae can be evaluated by skin biopsies of the abdominal skin (Trees et al., 1998; 2000). These characteristics render the readily accessible cattle *O. ochengi* a favourable model system for in vivo immunological and chemotherapeutic studies on onchocerciasis that are not possible in humans.

A lot of studies have been carried out on this model. Published results of the studies have direct relevance to the development of complementary therapy for river blindness given the difficulties of eliminating onchocerciasis with ivermectin alone (Borsboom, 2003) and rising concerns about suspected resistance to this drug (Awadzi, 2004a; Bourguinat et al., 2007).

*O. ochengi and chemotherapeutic studies*

*Chemotherapeutic studies with anthelmintics*

In the early 1990s, a team of researchers from the Veterinary Research Laboratory of IRAD Wakwa-Ngaoundere...
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and partners from the University of Tubingen (Germany) and the Liverpool School of Tropical Medicine (UK) started to evaluate various chemotherapeutic agents in cattle naturally infected with multiple *O. ochengi* nodules. The studies were financed by the WHO-MACROFIL Programme.

As a result of the close phylogenetic relationship between *O. volvulus* and *O. ochengi*, drug activity against both parasites would be expected to be similar. In fact, drugs with known activities against *O. volvulus*, have established the predictive value of *O. ochengi* in cattle. It has been shown that the effects of a number of anti-filarial anthelmintics, including ivermectin, suramin and melarsomine on *O. ochengi* are similar to those against *O. volvulus* (Renz et al., 1995; Trees et al., 1998). Melarsomine had lethal effects on both microfilariae and adult worms. Suramin only had partial effects on all worms.

Ivermectin, which was originally developed for veterinary use, has been integrated in onchocerciasis control strategies despite the fact that there is a major stage-related change in its efficacy against *O. volvulus*. Even at high doses, it is lethal only to the L1 larvae and not to the adult worms. In adults, there is induction of some degenerative changes in some worm tissues and the abrogation of embryogenesis but this is reversible (Kläger et al., 1993). Its effect on the infective larvae (L3) and hence its prophylactic potential is uncertain. Tchakouté et al. (1999) assessed the prophylactic potential of ivermectin against naturally transmitted *O. ochengi* in a controlled prospective study in Wakwa-Ngoundere involving calves. Calves exposed to natural, fly transmitted challenge were treated monthly with ivermectin at either 200 µg/kg or 500 µg/kg for 21 months. Infection was completely prevented in 15 treated calves while 5 out 6 untreated controls became infected and had patent microfilaridermias. The implication of this for humans is that strategic chemotherapy at times of maximal transmission can be considered prophylactic as well as therapeutic against *O. volvulus* infection. However, for this to be applied for mass human treatment, studies are needed to establish treatment intervals and doses required to provide prophylaxis.

The efficacy of UMF-078, a modified flubendazole was assessed *in vivo* in *O. ochengi* at two dosage rates by Bronsvoort et al. (2008). Following treatment at 150 mg/kg intramuscular, nodule diameter, worm motility and worm viability declined significantly. Embryogenesis was abrogated and death of all adult worms occurred by 24 weeks post treatment. These effects were less pronounced at 50 mg/kg intramuscular. Although no toxic signs were observed in this trial, other studies have raised concerns regarding neuro- and genotoxicity with UMF-078 (Trees et al., 1998; El-Makawy et al., 2006).

**Antibiotic therapy for onchocerciasis**

The Cameroonian, British and German research group at IRAD Wakwa in North Cameroon through a chance observation found that in an animal infected with over 100 *O. ochengi* nodules intended for a chemotherapeutic trial, repeated treatment with oxytetracycline for an incidental skin infection of *Dermatophilus congolensis* led to the resolution of all nodules. Also, all microfilariae were cleared from the skin of a similarly treated animal being used for infective larvae production. In this latter case, there was subsequently no uptake of mf by feeding black flies with a resultant zero infective larvae development in the black fly. These observations and increasing knowledge of the existence of intracellular bacteria (*Wolbachia*) in filarial nematodes (Kozek and Marroquin, 1977; Henkle-Dührsen et al., 1998; Taylor and Hoerauf, 1999) encouraged the researchers to carry out a trial. They demonstrated that treatment with oxytetracycline was macrofilaricidal. Embryogenesis was blocked in the female worm, and existing microfilariae in the skin eventually disappeared as they were cleared by attrition when they
reached the end of their natural life span. The *O. ochengi* intradermal nodules were also resolved by nine months post treatment in cattle treated intermittently for six months (Langworthy *et al.*, 2000). Serial electron-microscopic examination showed that the macrofilaricidal effects were related to the elimination of intracellular bacterial organisms. The sequential changes in the physical integrity of the organisms preceded the death of worms. Contrary to long-term intermittent treatment, short-term intensive treatment that is given daily for 2 weeks induces only transient and inconsequential effects on *Wolbachia pipiens* numbers and is not macrofilaricidal (Gilbert *et al.*, 2005).

Sequencing of a fragment of the 16s rRNA gene from the *O. ochengi* micro-organisms showed them to be *Wolbachia* organisms of the order *Rickettsiales* and were closely related to that of other *Onchocerca* species, particularly *O. volvulus* (Bandi *et al.*, 1998; Henkle-Duhrsen *et al.*, 1998).

The existence of *Wolbachia* as obligate intracellular bacteria in *O. volvulus* was first described by Kozek and Marroquin (1977). Many filarial nematodes have a mutually dependent relationship with *Wolbachia* bacteria. These endosymbionts are essential for worm development, fertility, survival and induction of inflammatory disease pathogenesis. They are also required for successful early moulting as it has been demonstrated that the crucial moulting step from L3 to L4 larvae is blocked by exposure of *Wolbachia*-infected worms to tetracycline (Smith and Rajan, 2000). They are *Rickettsia*-like, matrilineally inherited and infect many species of invertebrates (Werren *et al.*, 1995; Stouthamer *et al.*, 1999; Hise *et al.*, 2004).

**Implications for chemotherapy in humans**

*Wolbachia*, like other *Rickettsial* bacteria, are susceptible to the tetracycline family of antibiotics (e.g. doxycycline), azithromycin and rifampicin (Bandi *et al.*, 1999 a, b; Townson *et al.*, 2000). The existence of an almost identical *Wolbachia* in *O. volvulus* suggests that anti-*Wolbachia* treatment with these antibiotics may also be macrofilaricidal. This can augment the success of long-established mass treatment programmes by reducing side-effects that may result from the release of intact bacteria and *Wolbachia* products from dying nematodes (Cross *et al.*, 2001). Pre-treatment targeting of *Wolbachia* may abrogate inflammatory responses and allow a wider range of anti-filarial drugs to be used (Hise *et al.*, 2004). As a result of the fact that antibiotics do not affect the *Wolbachia*-negative *L. loa* which can provoke serious adverse reactions following ivermectin therapy, antibiotics can present us a new strategy for onchocerca treatment in areas of co-endemicity with *L. loa*.

The greatest obstacle to the use of antibiotic therapy in the control of onchocerciasis is the long duration of treatment. Shorter treatment regimes are necessary if tetracyclines are to find their way into routine use against onchocerciasis. Presently at IRAD Wakwa in North Cameroon, experiments in the proven cattle model on chemotherapy of onchocerciasis which target *Wolbachia* endosymbionts of *O. ochengi* are being carried out with the aim of developing optimum treatment regimes using existing drugs.

**Mechanism of the macrofilaricidal action of antibiotics**

Supporting evidence that the effect of the antibiotic is on the bacterial endosymbiont has been provided by studies which showed that antibiotic treatment of *Acanthocheilonema viteae* and *L. loa* which do not contain *Wolbachia* had no effect on the worm development or reproduction (Hoerauf *et al.*, 1999; Brouqui *et al.*, 2001). Further
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evidence showing that antibiotics act indirectly by disrupting intracellular Wolbachia symbionts has been provided in the review by Taylor et al. (2005).

Nfou et al. (2006) provided evidence with studies involving O. ochengi in cattle which suggest that worm killing in onchocercomas is associated with a shift in the dominant granulocyte type surrounding the parasites, from neutrophils to eosinophils. The presence of Wolbachia provokes neutrophil infiltration into the nodules. When Wolbachia were eliminated following antibiotic treatment, few neutrophils were seen at sites where most bacteria were killed. On the other hand, eosinophils which are adapted to killing worms were present in increased numbers around worms and were observed degranulating on the filarial cuticle. These observations suggest that accumulation of degranulating eosinophils over a prolonged period is a cause rather than an effect of parasite death, and the macrofilaricidal mechanism of antibiotics may relate to facilitation of eosinophil infiltration around worms by ablation of Wolbachia-mediated neutrophilia.

It is still unclear whether the eosinophils are involved in parasite killing or if they are attracted secondarily to dying worms. Hansen et al. (2010) tried to investigate this by giving adulticidal regimens of oxytetracycline or melarsomine regimens to cattle infected with O. ochengi. Unlike oxytetracycline, melarsomine did not directly affect Wolbachia viability. In the oxytetracycline group, eosinophil degranulation increased significantly and nodular gene expression of bovine neutrophilic chemokines was lowest. Moreover, intense eosinophil degranulation was initially associated with worm vitality, not degeneration. The data suggest that Wolbachia confers longevity on O. ochengi through a defensive mutualism, which diverts a potentially lethal effector cell response.

The bacterial depletion by antibiotics results in sterility of worms (through the blocking of female worm development and embryogenesis), inhibition of larval development (by impairing microfilariae development into L3 and interfering with moulting from L4 to adults) and inhibition of adult worm viability (Hoerauf et al., 2000a; Casiraghi et al., 2002; Arumugam et al., 2008).

O. ochengi and immunological studies

As a result of the need for more control options for onchocerciasis, there has been growing interest in investigating the existence of protective immunity in humans and its mechanisms, in identifying candidate vaccine antigens and seeking evidence for prophylactic immunization. Again the O. ochengi cattle model has been an appropriate tool for understanding the immunology of O. volvulus in humans as the biological and molecular similarities between the two parasites and the ability to induce experimental O. ochengi infections in cattle have made it possible to study the kinetics of immune responses to various antigens and challenge infections. This is important for the possible development of vaccines.

Putative immunity

In endemic or hyperendemic areas, there are non-infected individuals commonly referred to as endemic normals or putatively immune (PI). The nature of this protective immunity has been difficult to examine in humans for ethical reasons. Hence, Tchakoute et al. (2006) carried out a series of experiments with O. ochengi in cattle to investigate the nature of functional immunity in onchocerciasis involving either exposure to natural field challenge
or experimental single-pulse challenge. In an area endemic for *O. ochengi*, the authors demonstrated on the basis of adult worm burdens that putative immunity also occurs in a subset within herds of infected cattle. The PI animals were shown to be significantly less susceptible to heavy field challenge than age matched naïve controls. Although they did not exhibit absolute refractoriness to *O. ochengi* infection, the burden of both adult parasites and microfilariae in these animals was substantially lower than that in the controls and accumulated at a slower rate.

Zooprophylaxis

It has been hypothesized that the predominant transmission of *O. ochengi* by *S. damnosum* in some areas of sub-Saharan Africa could lead to the protection of humans against onchocerciasis caused by *O. volvulus*. In order to provide evidence for this, Achukwi et al. (2007) investigated whether exposure to *O. volvulus* could protect cattle from *O. ochengi*. Gudali calves were vaccinated with live *O. volvulus* infective larvae and subsequently challenged with *O. ochengi* infective larvae whilst raised in a fly-proof house. The vaccinated-challenged animals had 83–87% less adult *O. ochengi* parasites than non-vaccinated challenged animals. These findings support the idea of cross-protection (zooprophylaxis) due to inoculation of humans with *O. ochengi* infective larvae under natural transmission conditions in endemic areas. In this experiment, no *O. volvulus* adult worms developed in the vaccinated group. This is either due to their host specificity or the infective larvae were recognised and destroyed by the cattle immune system before they could have a chance to grow to adult worms. The live *O. volvulus*-infective larvae most likely behaved like irradiation-attenuated filarial larvae of other filariae parasites reported in jird (Lucius et al., 1991).

*O. volvulus* and *O. ochengi* exhibit extensive antigenic cross-reactivity as indicated by the serological recognition of *O. volvulus* recombinant antigens by cattle infected with *O. ochengi* (Achukwi et al., 2004; Graham et al., 1999). They can also generate cross-protective responses both experimentally (Achukwi et al., 2007) and naturally (Wahl et al., 1998a,b). Further evidence for all of this is provided by the fact that, molecular and biochemical comparisons between *O. volvulus* and *O. ochengi* reveal almost identical antigenic and genomic profiles (Xie et al., 1994).

Vaccination trials

As a result of the fact that *O. volvulus* and *O. ochengi* have broad antigenic cross-reactivity and generate cross-protective responses (Achukwi et al., 2004, 2007; Graham et al., 1999; Wahl et al., 1998a,b), the bovine *O. ochengi* system was utilised to evaluate a recombinant vaccine in a field trial in a hyperendemic area of North Cameroon (Makepeace et al., 2009). Naïve calves, reared in fly-proof accommodation, were immunised with eight recombinant antigens of *O. ochengi*, administered separately with either Freund’s adjuvant or alum. The selected antigens were orthologues of *O. volvulus* recombinant proteins that had previously been shown to confer protection against filarial larvae in rodent models and, in some cases, were recognised by serum antibodies from putatively immune humans. The vaccine was highly immunogenic, eliciting a mixed IgG isotype response. Four weeks after the final immunisation, vaccinated and adjuvant treated control calves were exposed to natural parasite transmission by the black fly vectors in an area of Cameroon hyperendemic for *O. ochengi*. After 22 months, all the control animals had patent infections, compared with only 58% of vaccinated cattle. This study shows that vaccination can reduce both the pathology and transmissibility of the infection and thus suggests that a vaccine against microfilariae to prevent development of disease in humans may be achievable. Given that the disease is associated with the microfilarial stage in onchocerciasis and that this stage is the key to transmission, an
Recent advances in onchocerciasis research and implications for control

Anti-microfilarial vaccine could be a very useful control option since it can abrogate transmission.

Tchakoute et al. (2006) also reported that vaccination with irradiated L3 of *O. ochengi* induced significant protection against experimental challenge. Significantly lower worm burdens were observed in vaccinated animals compared to controls after almost 2 years of continuous exposure to intense natural challenge from infected *Simulium*. This is at variance with the failure of cattle to develop immunity after drug-abbreviated infections. *O. volvulus*-infected humans treated with suramin, also became re-infected after chemotherapy and developed microfilariae loads at pre-treatment levels (Duke, 1968). It seems that parasite death is an insufficient stimulus for the induction of protective immunity. It has been suggested that immunity induced by irradiated L3 is mediated by activated eosinophils (Bleiss et al., 2002; Le Goff et al., 2000; Abraham et al., 2004).
Antibiotic therapy for the control of onchocerciasis: current status and perspectives

Introduction

The problems associated with the use of ivermectin for onchocerciasis control especially in the forest zones of the Central African region where several cases of adverse reactions following ivermectin treatment were reported in patients infected with L. loa (Chippaux et al., 1996; Gardon et al., 1997) have prompted a search for new filaricides which could substitute ivermectin in areas of co-endemcity and/or could be used to treat onchocerciasis without affecting L. loa. In this regard, the discovery of Wolbachia endobacteria in some pathogenic human filarial nematodes (Taylor et al., 1999; Taylor et al., 2005) but not L. loa (Büttner et al., 2003; McGarry et al., 2003) presented an opportunity to take a novel approach to onchocerciasis treatment based on the use of antibiotics to target the endobacteria (Hoerauf et al., 2001; Debrah et al., 2006). Such strategies have now been shown to be effective in both the long-term reduction of parasite loads and morbidity (Hoerauf et al., 2001). In animal studies, it was observed that depletion of the Wolbachia using tetracycline not only had microfilaricidal effects but also led to the sterility of female worms (Hoerauf et al. 1999) and the death of adult worms (Langworthy et al., 2000). Similarly in humans, a 6-week course of doxycycline treatment against O. volvulus depleted the bacteria, resulted in a blockage of embryogenesis and killed the adult worms. These effects were reflected in sustained reductions in skin microfilariae (Hoerauf et al., 2003a,b). These findings have demonstrated the superior pharmacological efficacy of doxycycline for the treatment of onchocerciasis (Hoerauf, 2006). Macrofilaricides have a higher potential for sustainable onchocerciasis control but this can only be guaranteed through high coverage and compliance (Brieger et al., 2007). This is particularly important for a drug such as doxycycline that must be taken on a daily basis for 6 weeks.

In this section, we describe:

- Antibiotic therapy in onchocerciasis by highlighting the scientific basis for the use of antibiotics;
- Treatment options with different antibiotics and how antibiotic therapy could substitute ivermectin in problem areas where there are risks of SAEs and resistance by O. volvulus to ivermectin;
- The use of antibiotics for the treatment of onchocerciasis through the community directed approach.

A new opportunity for the treatment of onchocerciasis: the endosymbiont Wolbachia

The endosymbiont Wolbachia has generally been thought to be widespread in filarial nematodes, including the major pathogenic filariae of humans such as Wuchereria bancrofti, Brugia malayi and O. volvulus (Casiraghi et al., 2004). However, new evidence from a recent large-scale survey indicates that the number of Wolbachia-free filarial species is greater than expected among filariae of mammals (Ferri et al., 2011). They belong to the order Rickettsiales and are closely related to the genera Ehrlichia, Cowdria and Anaplasma. They are found in the body wall (the hypodermis), in oocytes, in all embryonic stages and in microfilariae. Wolbachia spp in filariae seem to have evolved as symbions essential for the fertility of their nematode hosts and are transmitted transovarially to the next worm generation like mitochondria.
Among the important filarial species investigated so far using PCR, only five species, the human filaria *Loa loa*, the rodent filariae *Acanthocheilonema viteae* and *Monanema martini*, the deer filaria *Onchocerca flexuosa* and the horse filaria *Setaria equina* appear to be free of symbionts. In filarial species positive for *Wolbachia*, all isolates examined have been found to harbour this bacterium, showing identical or nearly identical gene sequences throughout the geographical distribution of the worm (Bandi *et al.*, 1998; Fenn *et al.*, 2004). In addition, the phylogeny of *Wolbachia* endosymbionts is congruent with the phylogeny of their host nematodes. The distribution and phylogenetic patterns of *Wolbachia* in filarial nematodes indicate that the association is stable and specific and suggests a long co-evolutionary history (Bandi *et al.* 1998). This suggests co-adaptation and reciprocal dependence between filarial nematodes and their *Wolbachia*. These observations encouraged researchers to hypothesize that antibiotic treatment against *Wolbachia* may be detrimental to the nematode. This has been shown in animal studies on a variety of filarial species (Langworthy *et al.*, 2000; Smith *et al.*, 2000; Casiraghi *et al.*, 2002; Rao *et al.*, 2002). Antibiotics have been used to deplete the endosymbionts from filariae and show the mutualistic symbiosis between filarial *Wolbachia* and their hosts (Hansen *et al.*, 2010). Depletion of *Wolbachia* resulted in the disruption of embryogenesis in female worms.

**Anti-*Wolbachia* treatment: current status**

**Lessons from animal models**

As shown above, several reports have described the effects of antibiotics on filarial nematodes in experimental animal models. More importantly, members of the tetracycline family (oxytetracycline, doxycycline, minocycline) have been found to be effective against filarial worms. The modes of action of these antibiotics are generally on bacterial RNA polymerases, protein synthesis and other processes. They may affect similar pathways in both worms and their *Wolbachia*.

In several nematode infections, the antibiotics have multiple effects on worm growth and development, worm fertility (particularly female worm embryogenesis) and worm survival, with evidence suggesting that prolonged treatment can be detrimental to worms (Bosshardt *et al.*, 1993; McCall *et al.*, 1999; Casiraghi *et al.*, 2002). Moreover, when microfilaraemic animals are treated, their microfilarial numbers in circulation are considerably reduced (Hoerauf *et al.*, 1999). In contrast, in animals infected with *A. viteae* worms that lack *Wolbachia*, similar long-term treatment had no effect on worm biology and development, suggesting that these bacteria play a very important role in the growth and reproduction of the filarial worms that harbour them.

Combination studies using rifampicin and doxycycline in animal models have been found to have the potential to achieve acceptable short-term regimen plans (Townson *et al.*, 1999, 2000, 2006; Specht *et al.* 2008). Interestingly, in addition to anti-*Wolbachia* properties, tetracyclines markedly affected the normal embryogenesis profiles by causing damage and degeneration of intrauterine embryos. Polymerase chain reaction (PCR) assay also confirmed the clearance of *Wolbachia* DNA after prolonged therapy (Volkmann *et al.*, 2003; Kramer *et al.*, 2003). The reduction or clearance of bacterial specific hsp60 and *Wolbachia* surface protein (WSP) as determined by immunohistochemical staining indicated the absence or clearance of *Wolbachia* in treated worms (Kramer, 2003). Penicillin, gentamycin, the macrolides erythromycin and azithromycin, ciprofloxacin and chloramphenicol were shown to be ineffective against *Wolbachia* in the *L. sigmodontis* model and consequently, did not display antifilarial activity (Hoerauf *et al.*, 2000).
Anti-Wolbachia therapy: from animal models to humans

The availability of doxycycline has encouraged clinical investigators to test the hypothesis that elimination of Wolbachia may be beneficial in reducing the human filarial infections. The fact that doxycycline is already registered enabled a quick transition to phase Ila studies in human onchocerciasis, which have been carried out in Ghana over the past ten years.

Patients were given doxycycline (100mg/day) for six weeks under daily supervision by a physician. The activity of the drug against Wolbachia and adult worms was assessed from extirpated onchocercomas. Immunohistology with antibodies to Wolbachia proteins was used to assess the presence or absence of Wolbachia and monitor changes in embryogenesis. Nodules from patients not treated with doxycycline served as controls. Administration of doxycycline led to depletion of Wolbachia followed by an interruption of embryogenesis in worms, which could be observed for 18 months. In further trials using doxycycline at 200 mg/day for four or six weeks, interruption of embryogenesis was observed for 24 months (Hoerauf et al., 2001). This was the longest period of sterility of female worms ever achieved by an antifilarial drug without SAEs. Consistent with the blockage of embryogenesis, after additional treatment with ivermectin, more than 90% of the patients who had received doxycycline showed an absence of microfilaridermia after 18 months and the remaining patients showed very low numbers of microfilariae. In contrast, patients treated with ivermectin alone showed an increase in microfilarial counts as early as four months after administration of ivermectin.

Preliminary results with other doxycycline regimens indicate that 100 mg or 200 mg doxycycline per day for two weeks does not eliminate the endobacteria or interrupt embryogenesis. When given at the dose of 200 mg/day for four weeks, it gives the same efficacy as 100 mg for six weeks (Hoerauf et al., 2003a,b). In more recent studies, it was demonstrated that doxycycline alone, given at 200 mg/day for 5 weeks could kill 60-70% of adult worm populations (Hoerauf et al., 2009).

Anti-Wolbachia as alternative treatment for onchocerciasis in areas of co-endemicity with loiasis

The first clinical trial with doxycycline in areas of co-endemicity of onchocerciasis and loiasis was carried out in forest villages of Cameroon (Wanji et al., 2009). The results confirmed previous findings that a dose of doxycycline sufficient to deplete Wolbachia by 90% results in the death of adult worms. Histological and PCR analysis confirmed that doxycycline treatment resulted in loss of Wolbachia from the adult parasites, with an extensive loss of uterine contents reflecting a blockage of embryogenesis. Treatment with doxycycline alone is superior to ivermectin in achieving sustained reductions in skin microfilariae. The trial indicates that doxycycline treatment is well-tolerated in O. volvulus patients co-infected with low to moderate levels of L. loa. These findings support the use of a doxycycline only regimen to treat onchocerciasis patients coinfected with L. loa.

Scaling up the anti-Wolbachia treatment: the community-directed delivery approach

The argument for mass treatment with doxycycline in areas of co-endemicity with O.volvulus and L. loa relies heavily on its selective toxicity for O. volvulus and the absence of adverse reactions due to lack of action on L. loa. However, its acceptance as a complementary tool for mass treatment of onchocerciasis will very much depend on the development of effective strategies for the treatment of target communities.
In view of the above, a study was designed in Cameroon to assess the feasibility of a large scale delivery of doxycycline using the community-directed approach for the treatment of onchocerciasis in areas of co-endemicity with loiasis, with the specific objective of determining the therapeutic coverage and the compliance rate and identifying the side effects associated with the treatment (Wanji et al., 2009).

The study was carried out in communities in the Mbanga and Melong Health Districts in the Littoral Region of Cameroon. These communities had never received mass treatment with ivermectin prior to the study. A cascade mechanism involving advocacy meetings with all stakeholders (health system and community members) was used to introduce the community-directed delivery process to the population in the onchocerciasis/loiasis co-endemic areas. Community health implementers selected by community members were trained to deliver doxycycline and to document the treatment coverage, compliance and side effects. This work was carried out under the supervision of local officials of the Ministry of Public Health.

Of the 21,355 individuals identified, 17,519 were eligible for the treatment and 12,936 of these were treated with doxycycline, giving a general therapeutic coverage of 60.6% and a therapeutic coverage per eligible population of 73.83%. Of the 12,936 individuals that started treatment in the study area, 12,612 completed the 6 weeks treatment without missing a single treatment, giving a compliance rate of 97.5%.

Of the 371 people who had side effects recorded during the treatment, 270 (72.8%) had side effects that are well known and associated with doxycycline intake. These included nausea (13.74%), mild diarrhoea (12.6%), vomiting (13.7%), loss of appetite (1.1%), mild skin rash (5.9%), joint pains (7.4%), fever (4.1%), headache (6.2%), blurred vision (2.2%) and feeling tired (9.2%). Apart from one patient who received anti-inflammatory drugs to treat a swollen arm, these side effects were generally mild and subsided without any intervention or interruption of treatment.

The high therapeutic coverage achieved in this study is a prerequisite for the success of any disease control programme. This augured well for encouraging a subsequent implementation of a large-scale distribution of doxycycline for the treatment of onchocerciasis in areas co-endemic with L. loa.

Doxycycline combines the properties of being both a macro and microfilaricide on O. volvulus with 60 to 65% of the female worms dying following a six week treatment (Hoerauf et al., 2009). It also retards the development of O. volvulus larvae in the vector as microfilariae depleted of Wolbachia endosymbiotic bacteria develop poorly in Simulium spp (Albers et al., 2012).

Complying or conforming to treatment is absolutely necessary for effective treatments to have desired effects. High compliance to treatment is dependent on the willingness and motivation of patients to follow the regimen prescribed which is based on the information about the medication received by the patient, the complexity of the regimen, the side effects and the benefits they may derive from the treatment (Khalid et al., 2009). In the Cameroon study, 97.5% of the people who started treatment effectively completed it. This compliance was high despite the long regimen of doxycycline. This is a good indicator that doxycycline can be used on a large scale for the control of onchocerciasis using a community directed approach. The compliance rate did not vary with age or sex of the treated population. This is an indication of good acceptability of the drug by all categories of individuals in the community.

Several factors accounted for the high compliance rate achieved in the Cameroon study. The social awareness
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campaigns during which the population was well informed on the process and the role they were expected to play contributed much to its success. The fact that each partner in the CDI process adequately played his role was an important factor for success. The awareness of the burden of onchocerciasis and its socio-economic impacts on the population was a motivating factor for community adherence and compliance to treatment. The fact that the drug was delivered by community health implementers selected by community members guaranteed some trust and was a great motivating factor for the population’s adherence and compliance. It is known that interventions delivered by community health workers are more accepted by the population than those delivered using the normal health system (Gyapong et al., 2000) and that it significantly improves the accessibility of the treatment and treatment seeking behaviour of community members.

The fact that the drug was free was also an encouraging factor for the population to accept and adhere to the treatment. The positive effects experienced by those who took the drug motivated others to request for their own treatment.
Recent advances in onchocerciasis research and implications for control
The way forward for the elimination of onchocerciasis

The Onchocerciasis Control Programme (OCP) recognized the fact that stopping transmission could reduce the chances of children born after the programme was initiated getting the disease but could not prevent the disease from progressing in the adult population. Ivermectin treatment was therefore introduced to curb clinical symptoms and halt the aggravation of ocular lesions. Chemotherapy was thus recognized as a good and less expensive tool to control onchocerciasis and today the African Programme for the Onchocerciasis Control (APOCH) is using Community-Directed Treatment with Ivermectin (CDTI) as its main strategy against this disease. Studies in Mali and Senegal have established the proof-of-principle that onchocerciasis elimination with ivermectin treatment is feasible in at least some endemic foci in Africa. The results have been instrumental for the current evolution from onchocerciasis control to elimination in Africa (Traore et al., 2012). However, ivermectin has been shown to be less effective in some communities in Ghana and transmission is still ongoing in northern Cameroon after 17 years of ivermectin treatment (Katabarwa et al., 2011). The other problems associated with the use of ivermectin in onchocerciasis control as listed in previous sections of this document have not disappeared.

Recently, APOCH announced that it is now an elimination programme with a target date of 2025. For this to be achieved and considering the problems identified above, it is necessary for its efforts to be accompanied by various strategic options which should seek to be complementary. Here, we suggest some of these options.

Vector Control

The OCP which was a successful multilateral collaborative endeavour was originally based only on aerial larvicide spraying. This approach successfully interrupted the transmission of *O. volvulus* in many areas. Therefore, vector control could supplement other strategies where possible to accelerate the elimination of onchocerciasis.

*Simulium* control has been implemented in several areas of Cameroon as a focal activity. The on-going construction of new hydroelectric dams will bring human populations from all over Cameroon and beyond to settle around these dams. This is good for the economy but has the potential of creating new health situations as the workers come in with various transmissible diseases. The dam spillways may also constitute breeding sites for *S. damnosum*, while the lakes will be breeding grounds for vectors of malaria and intermediate hosts of schistosomiasis.

In view of the above, different control measures will need to be envisaged for various vector-borne diseases. In the case of onchocerciasis, vector management for black flies and drug treatment will have to be integrated for better results. In this regard, the main rivers of Cameroon shall be targeted as they all contribute more or less to the breeding of *S. damnosum*. In the savannah, where the transmission is seasonal, an *S. damnosum* control scheme will go a long way to break the transmission cycle and hasten the demise of the disease. In the forest region where transmission is perennial, the main river which is the Sanaga with its 4 dams (Edea, Song Loulou, Bamimdjin, and Mbakaou) and soon Lom Pangal, is not new to black fly control. The Memvele dam is presently being built.
Recommendation 1: in view of the on-going construction of new hydroelectric dams in Cameroon, the authorities of the projects should already build into their operational activities, some black fly vector control components so as to be prepared to handle any unforeseen S. damnosum population explosion after the construction. The main rivers of Cameroon should also be the target of focal black fly control activities as they all contribute to the breeding of S. damnosum.

A black fly control scheme as recommended above must include the following components:

1. Cartography – a good knowledge of the geography of the area with a trained team in place.

2. Hydrology – A team of hydro-biologists with a detailed knowledge of the rivers and their seasonal variations will monitor the larvicide treatment and its effect on the aquatic fauna.

3. Medical Entomologists – The entomologists have the duty of monitoring the black fly populations as treatment progresses and to inform the technical team whether their work is going on well or not and to raise an alarm in case it is not.

4. A technical team – a good technical knowledge of the treatment techniques will require persons trained in the management of insecticides and equipment used, including aircrafts and helicopters.

Recommendation 2: Operational research is essential to improve monitoring and establish thresholds that determine when and where vector control is needed. It is also needed to determine whether adult black flies can be lured by attractants to insecticide treated screens as used in tsetse control, and whether insecticide treated over-garments or bands at the wrists and ankles could reduce the impact of the flies on field workers.

Recommendation 3: Capacity building is indispensable to increase local knowledge of vector ecology, sampling procedures and control techniques.

The improvement of Community Directed Treatment with Ivermectin

Despite more than forty years of onchocerciasis control in Africa, the disease is still a public health concern in many African countries. The success of OCP in West Africa led to a significant decrease of the burden of onchocerciasis, but the disease is not yet eliminated. In APOC countries, the CDTI has improved significantly the treatment and geographical coverage with ivermectin. The evaluation fifteen years or more after the launching of CDTI has shown reductions in prevalence to less than 10% in some foci, and even less than 1% in some (Mas et al., 2006; Traore et al., 2012). However, the prevalence in some other foci is still very high as shown by Katabarwa et al. (2011) in North cameloon. It is important to understand why this is so. There may be specific epidemiological, sociological and logistical factors that make elimination using ivermectin alone unlikely in some areas.

Recommendation 4: There is need for research organisations in charge of medical research in Cameroon to investigate the epidemiological, sociological and logistical factors that contribute to the maintenance of high levels of the prevalence of onchocerciasis after more than 17 years of treatment with ivermectin through the CDTI approach in areas where loaisis is absent.

The fear of side effects in the forest communities in Cameroon where loaisis is co-endemic has led to a reduction in the ivermectin uptake with serious epidemiological consequences. In some surveys, it has been observed that in
some foci, some families had never taken Mectizan after five rounds of treatment. These families represented about 15% of the total population. In some other areas, people who experience SAEs refuse to continue treatment. These situations contribute to the maintenance of the transmission of the disease.

**Recommendation 5:** To improve the impact of treatment, the National Onchocerciasis Control Programme should intensify communication to inform the population on the benefits of treatment with ivermectin. Efforts should also be made to seek for permanent non compliers in order to inform, educate and properly treat them.

For CDTI in the field, the CDDs used to register the population of each village. This survey was important for the calculation of the treatment coverage that could help in understanding the impact of the mass treatment. In the last few years, this activity has not been taken seriously and has made it difficult to obtain accurate treatment coverage.

**Recommendation 6:** To enable the collection of data which contribute to the understanding of the impact of mass treatment, the village census should be done during CDTI field activities.

From the results of the ONCHSIM model (a microsimulation model for onchocerciasis transmission), developed by Plaisier et al. (1990), we need more than 15 years to achieve elimination of onchocerciasis in endemic areas with once a year treatment. With twice a year regiment, this time could be shortened by half (Winnen et al., 2002). This could be more effective in curbing transmission since it has been shown in many studies that repopulation of dermal microfilariae occurs as soon as four months after a single treatment with ivermectin.

Unlike the APOC strategy which used once a year treatment with ivermectin for a very long time, the treatment frequency strategy in the Americas was established very early in the programme to be twice annually after it was established that this would have an accelerating effect on stopping disease transmission (Cupp et al., 1992). The MDA approach was offered at least twice each year to all eligible individuals living in all endemic communities with the objective of reaching a minimum of 85% treatment coverage. As a result of these changes, the programme objective in the Americas has changed from simply controlling onchocerciasis to that of completely eliminating transmission of the disease by 2012 (Gustavsen et al., 2011).

**Recommendation 7:** The strategy of the control programme in the Americas which is based on at least twice yearly treatment and which has resulted in the near elimination of onchocerciasis in that area should be adopted in all endemic foci in general and Cameroon in particular where the results of the epidemiological evaluations are not as good as was expected. This should be accompanied by epidemiological surveillance to detect and control disease recurrence. Therapeutic approaches to reduce the load of *L. loa* infections are also necessary to increase ivermectin coverage.

In the efforts to eliminate onchocerciasis, hypoendemic areas should not be forgotten. The present strategy focuses on treating the meso and hyperendemic areas (with 20% and more prevalence of nodules). Areas with less than 20% prevalence (hypoendemic areas) of nodules could constitute a reservoir of transmission, hence the necessity for treating them. The treatment of these areas is now projected and in areas hypoendemic for onchocerciasis and endemic for loaisis, a new strategy of “Test and Treat” is now under development.

**Recommendation 8:** The National Onchocerciasis Control Programme of Cameroon should adopt the new strategy of “Test and Treat” that is being developed for hypoendemic areas.
To date, there is a lot of controversy regarding the emergence of resistance of *O. volvulus* to ivermectin. In addition to the phenotypic suspicions of resistance, many studies have revealed that selection occurs in some genes of the parasite. Despite these phenotypic and genotypic studies, the unequivocal proof of resistance is yet to be established.

**Recommendation 9:** Further studies are needed to clarify the emergence of resistance of *O. volvulus* to ivermectin in order to preserve the benefits of past and current onchocerciasis control programmes.

**Anti-Wolbachia treatment**

The need for new drugs for onchocerciasis to achieve elimination of transmission cannot be over emphasised in view of the many problems associated with the use of ivermectin for onchocerciasis control. The discovery of Wolbachia endobacteria in some pathogenic human filarial nematodes (Taylor et al., 1999, 2005) but not L. loa (Büttner et al., 2003; McGarry et al., 2003) gave an opportunity to study another approach to onchocerciasis treatment based on the use of antibiotics to target the endobacteria. Results of human trials using doxycycline (Hoerauf et al., 2001; Debrah et al., 2006; Wanji et al., 2009) have been very encouraging.

The argument for mass treatment with doxycycline in areas of co-endemicity with *O. volvulus* and *L. loa* relies heavily on its selective toxicity for *O. volvulus* and the absence of adverse reactions due to lack of action on *L. loa*. However, its acceptance as a complementary tool for mass treatment of onchocerciasis will very much depend on development of effective strategies for its delivery to the target communities.

The community-directed intervention (CDI) trials using a 6-week course of doxycycline challenges the notion that prolonged courses of treatment cannot be effectively delivered through CDI (Wanji et al., 2009). The Cameroon study showed that the intake of doxycycline on a large scale is accompanied by only mild side effects which are generally well known to be associated with doxycycline intake. This can justify the use of this drug to treat onchocerciasis in areas where *O. volvulus* and *L. loa* co-exist. The high compliance rate recorded was a good indicator that the mass administration of doxycycline for the treatment of onchocerciasis in areas of co-endemicity of loiasis can be a sustainable activity. RAPLOA which is a rapid diagnostic tool has been used to map areas of high risk of encephalopathy to define restricted areas where these regimens could be deployed (Wanji et al., 2001, 2012). These areas are now well known. The regimes described above, can already be considered as suitable treatment for individual cases of onchocerciasis in patients co-infected with *L. loa* and the further development of other anti-*Wolbachia* regimens compatible with MDA could offer an alternative tool for the control on onchocerciasis in Africa.

**Recommendation 10:** Given that the recently completed community-directed intervention using a 6-week course of doxycycline at a 100 mg/day demonstrated that prolonged courses of treatment can be effectively delivered either through individual or mass treatment using doxycycline, we recommend the use of doxycycline in *O. volvulus* and *L. loa* co-endemic areas and in cases of ivermectin resistance.

Mathematical simulations show that macrofilaricidal drugs have higher potentials of achieving elimination of onchocerciasis and require less number of rounds of mass drug administration (Alley et al., 2001). It can therefore be anticipated that with a general therapeutic coverage of 60% achieved with the community-directed administration of doxycycline, it may require less rounds of mass drug administration to bring the community
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**microfilarial load of O. volvulus** below the threshold level of transmission in a given endemic area. Nevertheless, it is necessary to develop a mathematical model based on data generated so far to determine the number of rounds as well as the periodicity of mass administration of doxycycline for the control of onchocerciasis.

**Recommendation 11:** It is necessary for epidemiologists to develop a mathematical model to determine the number of rounds as well as the periodicity of mass administration of doxycycline for the control of onchocerciasis.

For any health intervention to achieve its goal, the intervention must be cost effective. It should be affordable to the health system and donors or community members. Policy and decision makers are increasingly requesting for information on cost-effectiveness to minimise cost of interventions and to efficiently allocate health resources.

Few studies have investigated the cost effectiveness of community based interventions. In a recent multi-country study on community-directed interventions for major health problems in Africa involving eight research teams from five African countries, it was demonstrated that community-directed interventions are more cost-effective than conventional delivery systems for the integrated delivery of vitamin A, insecticide treated nets and anti-malarial drugs to communities. With lower implementation costs, the community directed approach achieved higher coverage than the conventional delivery system at the health district and front line health facility levels. As shown by Wanji et al. (2009), the community-directed approach will be more cost effective for the delivery of doxycycline than the conventional delivery system.

One important consideration for the large scale use of doxycycline for the treatment of onchocerciasis is the fact that this drug is not presently made available free of charge as is the case with ivermectin. The cost (purchase and delivery) of the six week treatment per patient is estimated at $2.5 (Wanji et al., 2009). Given the fact that most of the onchocerciasis patients living in endemic communities have incomes below the poverty level, this estimated cost may be a serious barrier to their accessibility to this therapy. It would therefore be necessary for the health systems of endemic countries to subsidize the cost of doxycycline for the end users in the large scale treatment of onchocerciasis where appropriate.

**Recommendation 12:** Given that the cost of purchase and delivery of doxycycline for the six week treatment per patient is relatively high for most onchocerciasis patients living in endemic communities, it is necessary for the health systems of endemic countries to subsidize the cost of the drug for the end users in the large scale treatment of onchocerciasis where appropriate.

Currently the treatment and control of onchocerciasis rely on a single drug, ivermectin which is used in mass drug administration (MDA) either annually or biannually or for individual every 3 to six months. It is effective at reducing microfilarial loads but is only marginally effective against adult worms and so requires sustained delivery for more than 15 to 17 years in order to interrupt transmission (Diawara et al. 2009; Taylor et al. 2010). Also, in areas of co-endemicity with loiasis, the MDA with ivermectin may have limited impact because of non compliance due to fear of severe adverse reactions by the target population (Wanji et al; unpublished data). Recent investigations with anti-Wolbachial drugs have demonstrated the superior efficacy of anti-Wolbachial drugs compared with existing anti-onchocercal drugs through permanent sterilization and macrofilaricidal activity against adult O. volvulus. It has been reported that more than 97% of some 13000 people from villages where the infection is endemic started and completed a six-week doxycycline treatment regimen after community directed explanation and organisation and 3 to 4 years after treatment, the impact of doxycycline treatment is superior to ivermectin treatment in reducing
the microfilarial prevalence and intensity (Wanji et al., 2009; Tamarozzi et al. 2011). This is a major step towards the large scale implementation of antibiotic therapy against onchocerciasis in areas of onchoecerciasis-loiasis co-endemicity. This should likely speed up the elimination of onchoecerciasis in those areas.

**Vaccination**

It is clear that the goal of onchocerciasis eradication will not be achieved in the near future if the control strategy is based only on vector control and ivermectin distribution. While the search for an efficient macrofilaricide remains an attractive option today, this can be complemented with additional tools, such as vaccines that can protect vulnerable groups particularly children living in endemic areas against infection and reduce adult worm burden and fecundity, thus reducing the pathological effects caused by the microfilariae.

Several strategic approaches have been used to search for vaccine candidates. These include the search for target antigens or molecules that will prevent the production of microfilariae by female worms so that severe pathology and/or transmission of microfilariae to the black fly will be abrogated and those that could stop infection by preventing the establishment of infective L3 larvae in the definitive host to become adult worms (i.e. prevents worm development and patency). Other strategies have used filariae infective larvae attenuated by irradiation in various animal models (Le Goff, 1997, 2000; Babayan et al., 2006; Tchakoute et al., 2006; Allen et al., 2008), recombinant proteins (Makepeace et al., 2009) and live infective larvae of *O. volvulus* in cattle (Achukwi et al., 2007).

Many research groups have identified a number of *O. volvulus* larval vaccine candidates. Trials with some of them obtained proof-of-principle of vaccination against L3 infection as it was shown that microfilarial load reduced significantly in animal models (Makepeace et al., 2009; Tchakoute et al., 2006).

**Recommendation 13:** Donors should provide funding for research groups which have identified promising vaccine candidates for the purpose of vaccine design, formulation and delivery.

**Sustainability and ownership of control programmes**

APOC’s mandate is expected to end in 2015. At that time, it will transfer full responsibility for onchocerciasis control to various national control programmes. Governments would be expected to provide necessary financial support. It is also hoped that non-governmental development organizations will continue to play their critical role. The overall goal is to establish country-led programmes capable of eliminating onchocerciasis as a public health problem in all endemic countries in Africa (2008).

However, the inability of national control programmes to sustain disease control efforts can have important ramifications as disease resurgence can reverse the gains in public health produced by both OCP and APOC over the years. The ability to create sustainable disease control efforts beyond APOC’s mandate will depend on the ability of national governments to provide adequate technological and financial support for national control programmes to enable them take on the responsibilities that would be transferred from APOC. Consequently, the international community must ensure that national control programmes and governments have the management and technical capacities, effective larvicides, microfilaricides, macrofilaricides and funds to continue control efforts.
**Recommendation 14:** To create sustainable disease control efforts beyond APOC’s mandate, we urge National Programmes to develop technical and technological competence that would enable them to function properly after the withdrawal of APOC.

**Recommendation 15:** We appeal to National Governments and donors not to abdicate their financial responsibility which is needed to ensure that the substantial investments and progress made towards eliminating onchocerciasis in Africa are sustained for the future.
References


Recent advances in onchocerciasis research and implications for control


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Appendices
Appendix A

Statement of task

Research in Onchocerciasis particularly that concerned with chemotherapy and immunity has been limited by the lack of an appropriate animal model for Onchocerca volvulus. Of all animal models used, only *O. volvulus* in chimpanzees closely resembles *O. volvulus* in man. This is, however, impractical for use on a large scale for research. Rodents are non-permissive to *O. volvulus*. In recent years, work carried out by a team of Cameroonian, British and German scientists in natural cattle infections at the Veterinary Research Laboratory of IRAD Wakwa, Ngaoundere, Cameroon and in experimental infections in the University of Liverpool, United Kingdom, identified the bovine species, *O. ochengi* as an analogue of *O. volvulus* for chemotherapeutic and immunological research. Published results of the studies have direct relevance to the development of improved means of controlling river blindness. In fact, another team of Cameroonian researchers working in collaboration with Ghanaian, British and German scientists have applied these results in human trials using mass community-directed approach. Another leading Cameroonian scientist has studied extensively the occurrence of adverse reactions to Mectizan treatment especially in areas of *O. volvolus* co-infection with Loa loa in Cameroon, the Democratic Republic of Congo, Angola and Sudan.

All of the above shows that Cameroonian scientists and their partners have generated a large amount of crucial scientific data that can be useful in the control of human Onchocerciasis. A lot of the data is really groundbreaking scientific development. Unfortunately, it is buried in different scientific journals and is not available to stakeholders (donors, policy makers, disease control officials and nongovernmental organisations) involved in treatment and control efforts.

In recognition of its advocacy role, the Cameroon Academy of Sciences (CAS) through its National Forum for Public Health decided to convene an expert panel to bring together the data, analyse it and offer conclusions and recommendations pertinent for research and policy reorientations for human Onchocerciasis. The panel synthesized and discussed relevant evidence and knowledge based on findings from research and recommended actions targeted at policy and decision makers, funding agencies, nongovernmental organisations, researchers and disease control officials.

The specific aims of the study were to:

- Describe the global magnitude of human Onchocerciasis and the situation in Cameroon.
- Describe the pathological and socio-economic effects of Onchocerciasis (River blindness) in humans.
- Examine current treatment and control strategies and the gaps therein.
- Carry out an analytical synthesis of onchocerciasis research carried out by Cameroonian scientists and their foreign partners with particular reference to:
  - Chemotherapy and immunology – using insights from the *O. ochengi/cattle model.*
Recent advances in onchocerciasis research and implications for control

- Key experimental findings of the *O. ochengi* cattle model that have direct relevance to the development of improved means of controlling river blindness.

- Use of doxycycline against onchocerciasis in clinical settings and mass community-directed approach in West and Central Africa.

- Observations on the current use of Mectizan in the control of *Onchocerca volvulus* in West and Central Africa.

  - Examine the effectiveness of alternative treatment and control strategies resulting from the above studies.
  
  - Recommend strategies to improve the control and possible elimination of onchocerciasis.

It was hoped that the report of this study would present, subject to available published evidence, sound advice and reasoning for reorientation of the current Onchocerciasis control strategies and funding for more research and also provoke dialogue among stakeholders and draw public attention.
Appendix B

Biographical sketch of committee members

Vincent N. TANYA, DVM, M.Sc., PhD, is Chief Research Officer with the Institute of Agricultural Research for Development (IRAD), Cameroon and Technical Adviser No 1 in Cameroon’s Ministry of Scientific Research and Innovation. He is also the Programme Officer for the Cameroon Academy of Sciences. He is a Fellow of the Cameroon Academy of Sciences. In recognition of his leadership role in the O. ochengi/cattle model system for immunological and chemotherapeutic studies on onchocerciasis and the groundbreaking results on the antibiotic therapy of onchocerciasis, he was elected into the Third World Academy of the Sciences in 2004. He attended the University of Ibadan, Nigeria, the University of Edinburgh, UK and the University of Florida, Gainesville, USA, and obtained the degrees of DVM, M.Sc. and PhD respectively. As an arbovirologist/epidemiologist, he has studied and supervised students on foot and mouth disease, bluetongue virus, rinderpest virus, avian influenza and onchocerciasis. He has been either principal investigator or co-investigator on research grants financed by the FAO, DFID (formerly ODA/NRI), MACROFIL (WHO), AUF (formerly AUPELF-UREF), Wellcome Trust and the European Union. He has been Head of the Veterinary Research Laboratory at the IRAD Regional Research Centre of Wakwa, Ngaoundere, the Chief of the IRAD Regional Centres at Wakwa, Ngaoundere and Bambui and the Scientific Coordinator for Animal and Fisheries Production at IRAD Headquarters. He has 75 articles in peer-reviewed journals. He is Chair of the CAS Panel for this study.

Samuel Wanji, B.Sc., M.Sc., Doc. Uni., HDR, is Associate Professor of Molecular Parasitology and Entomology at the University of Buea, Cameroon. He has degrees of B.Sc. from the University of Orleans, France, M.Sc. and Doctorate from the University of Montpellier II, France, and HDR from the University of Nantes, France. He is Executive Director of the Research Foundation in Tropical diseases and Environment, Buea, Cameroon. He is Member of the American society of Tropical Medicine and Hygiene (ASTMH), the French Society of Parasitology and the Cameroonian Society of Parasitology. He is a Consultant for the Special Programme for Research and Training in Tropical Diseases for the World Health Organisation, in which he is involved with the development and validation of the Rapid Assessment Procedures for Loiasis (RAPLOA) and community-directed interventions for major health problems in Africa. He has been involved in the mapping of Loiasis using RAPLOA in different African countries like the Democratic Republic of Congo, Republic of Congo, Sudan, Angola, Equatorial Guinea and Cameroon for the African Programme for Onchocerciasis Control (APOC). He has had several research grants as either principal investigator or co-investigator from the European Union, l’AUPELF-UREF, UNDP/World Bank/WHO Special Programme for Research and training in Tropical diseases, FICU, the African Programme for Onchocerciasis control (APOC), the Volkswagen Foundation, the Wellcome Trust, Medical Research Council,UK, and DFG Germany. He has 52 articles.

Joseph KAMGNO, MD, MPH, PhD, is Senior Lecturer in the Department of Public Health, Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I, Cameroon. After graduating as a medical doctor from the same University, he later on obtained the Diploma in epidemiology of transmissible diseases in Pasteur Institute in Paris, the degree of Masters and PhD in Public Health and epidemiology from the University of Paris 6. He has been a general practitioner (1994 – 1999) at the Pasteur Centre of Cameroon, Research Assistant (2000 -2002) at the same Centre and Technical Adviser (2003 – present) for the National Programme for Onchocerciasis Control. He is
Daniel M. ACHUKWI, DVM, PhD, is Chief Research Officer and Director of Scientific Research with IRAD in Yaounde, Cameroon. He obtained the degree of DVM from the University of Ibadan, Nigeria and later on the PhD from Strathclyde University in Glasgow, UK. He is also Head of IRADs Animal Health Programme. He was IRAD’s Regional Scientific Coordinator for the High Guinea Savanna Agro-ecological Zone from 2006 to May 2011. He has wide experience in local/rural agricultural production systems and tropical livestock diseases. He has attended several short courses including specialization in research-extension linkages, systems-oriented management and planning basis for the improvement of animal health in the tropics and immunology/molecular biology of vector transmitted parasitic diseases of livestock. He teaches immunology at postgraduate level to students of the Department of Biological Sciences, University of Ngaoundere, molecular parasitology at postgraduate level in the Faculty of Science, University of Buea and immunology at undergraduate level in the School of Veterinary Sciences and Medicine of the University of Ngaoundere, Cameroon. He is currently supervising 4 doctoral students. He has been either principal investigator (PI) or co-PI on competitive grants financed by IFS, FAO, MACROFIL (WHO), DFG, European Union, Leverhulme Trust, and AUSAid (CORAF/WECARD) for research on protozoan diseases of economic importance in livestock and onchocerciasis. He has 35 publications in peer-reviewed journals.

Peter Ayuk ENYONG, Lic. es Sc., Maitrise es Sc., DEA, Doct. es Sc., was a Senior Researcher of the Institute for Medical Research and Study of Medicinal Plants. For years, he was the Chief of the Tropical Medicine Research Station in Kumba. He is presently Senior Research Fellow at the Research Foundation in Tropical Diseases and Environment, Buea, Cameroon. He is holder of the degrees of Licence es Sciences (chemistry/biology), Maitrise es Sciences (chemistry/biology), DEA (animal biology), Maitrise es Sciences (entomology) and Doct. Es Sc. from the University of Paris-Sud Orsay, France. In collaboration with several colleagues, he has had several grants from the European Union, WHO/TDR, Edna McConnell Clark Foundation, AUPELF-UREF, NIH, The Wellcome Trust, Medical Research Council, UK, and DFG Germany. He continues to act as a consultant for the WHO and APOC and supervises graduate students. Throughout his long career, he studied the entomology of *Simulium damnosum*, the vector of *O. volvulus*, the biology and ecology of *Anopheles gambiae*, the control of nuisance of *Aedes caspius* in the Langueduc canals in Southern France, the control of *Culex quinquefasciatus* in Kumba, Cameroon and the malacology of Schistosomiasis and Paragonimiasis. He is presently working on a European Union funded research project on novel release system and bio-based utilities for mosquito repellent textiles and garments. The project entails the field testing of various repellent garments and bed net materials against mosquitoes (especially *Anopheles*). He has 45 articles in peer-reviewed journals.