

FINAL REPORT
of the
Conference on the Eradicability
of
Onchocerciasis

**The Carter Center
Cecil B. Day Chapel
Atlanta, Georgia, USA
January 22-24, 2002**

"Sightless Among Miracles" by R.T. Wallen

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Onchocerciasis

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TABLE OF CONTENTS

Acknowledgements	iii
Acronyms	iv
Executive Summary	1
French	3
Spanish	5
Conference Organization and Opening Remarks	7
Introduction	8
Summary of Discussions	
African Perspective	10
American Perspective	12
Modeling of Onchocerciasis Control	13
Ivermectin Resistance	14
Sustainability of Ivermectin Delivery	14
<i>Loa loa</i> as an Obstacle to Control or Eradication of Onchocerciasis	15
Human Migration, and Political and Social Aspects of Eradication	15
Economic Aspects of Eradicating Onchocerciasis	16
Conclusions and Recommendations	
Key Conclusions and Recommendations	17
Other Selected Conclusions and Recommendations from Working Groups	17
Appendices	
A. Agenda	21
B. List of Participants with Group Photo	26
C. Papers submitted by Conference Speakers	35
D. Working Group Presentations	134

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ACRONYMS

ABR	Annual Biting Rate
AFRO	Regional Office for Africa (WHO)
APOC	African Program for Onchocerciasis Control (WHO)
ATP	Annual Transmission Potential
BSE	Bovine spongiform encephalopathy
CAR	Central African Republic
CBM	Christoffel Blindenmission
CBTI	Community-Based Treatment with Ivermectin
CD	Community Distributor
CDC	Centers for Disease Control and Prevention
CDD	Community Directed Distributors
CDHW	Community-Directed Health Workers
CDTI	Community-Directed Treatment with Ivermectin
CMFL	Community Microfilarial Load
CNS	Central Nervous System
CPE	Department of Control, Prevention and Eradication (WHO)
DEC	diethylcarbamazine
DNA	deoxyribonucleic acid
DRC	Democratic Republic of Congo
EAC	Expert Advisory committee
ELISA	Enzyme Linked Immunosorbent Assay
FMD	Foot and Mouth Disease
GDP	Gross Domestic Product
GIS	Geographic Information Systems
HTS	High Throughput Screening
IACO	InterAmerican Conference on Onchocerciasis
ICT	Immuno-Chromatographic Antibody Card Test
IDB	InterAmerican Development Bank
IDP	Internally Displaced Person or Ivermectin Distribution Program
IEC	Information, Education and Communication
IRD	Institut de Recherche pour le Developpement
ITFDE	International Task Force for Disease Eradication
IVM	Ivermectin
IVR	Ivermectin
L3	Third Stage Larvae
L4	Fourth Stage Larvae
LCIF	Lions Clubs International Foundation
LF	Lymphatic filariasis
MDA	Mass Drug Administration
MDP	Mectizan® Donation Program
MEC	Mectizan® Expert Committee
Mectizan®	Ivermectin (Merck & Co. product name)
mf/MF/Mf	Microfilaria
MfAC	Microfilaria in the Anterior Chamber

MOH	Ministry of Health
MOX	Moxidectin
MSF	Medicins sans frontieres
MSU	Michigan State University
NGDO	Non-Governmental Development Organization
NGO	Non-Governmental Organization
NR	Nuclear Receptor
OCP	Onchocerciasis Control Program
OCRC	Onchocerciasis Chemotherapy Research Center
OEPA	Onchocerciasis Elimination Program of the Americas
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PHC	Primary Healthcare
PK	Punctate Keratitis
R&D	Research & Development
RAPLOA	Rapid Assessment for Loa
REA	Rapid Epidemiological Assessment
REMO	Rapid Epidemiological Mapping of Onchocerciasis
SAE	Serious Adverse Effect
TCC	Technical Consultative Committee (APOC)
TDR	Special Program for Research and Training in Tropical Diseases (WHO)
tRNA	Transfer Ribonucleic Acid
UAB	University of Alabama at Birmingham
ug/kg	Microgram per kilogram
UTG(2)	twice the Ultimate Treatment Goal
WHO	World Health Organization

Executive Summary

Sixty-four experts from a variety of disciplines attended a Conference on the Eradicability of Onchocerciasis at The Carter Center, in Atlanta GA, held January 22-24, 2002. The Conference, which was organized by The Carter Center and the World Health Organization, with funding from the Bill & Melinda Gates Foundation, addressed the question: ‘Is onchocerciasis (River Blindness) eradicable with current knowledge and tools?’ The Conference consisted of a series of presentations by invited expert speakers (Appendix C) and further deliberations in four workgroups (Appendix D) followed by plenary discussion of major conclusions. Former US President Jimmy Carter attended part of the final plenary proceedings on January 24.

The presentations underlined epidemiological and entomological differences between onchocerciasis in Africa and the Americas. Whilst onchocerciasis in Africa covers extensive areas and is associated with striking human and fly population migrations and remarkably efficient black fly vectors, in the Americas onchocerciasis is found in limited foci. Human and fly population migration are not major problems in the Americas, where most black fly species are inefficient, though some efficient black flies are also found there. Vector control has been effectively applied in the Onchocerciasis Control Program in West Africa (OCP) with remarkable results, interrupting transmission in most parts of the original Program area. The use of ivermectin has given variable results: while ivermectin treatment has been effective in all endemic areas in controlling onchocerciasis as a public health problem, its potential for interrupting transmission is more promising in hypo- and mesoendemic areas. The African Program for Onchocerciasis Control (APOC), which supports onchocerciasis control in endemic African countries outside the OCP, applies ivermectin--its principal control tool--to communities in high-risk areas as determined by rapid epidemiological mapping of onchocerciasis (REMO) and Geographic Information Systems (GIS). In the Americas, through support of the Onchocerciasis Elimination Program in the Americas (OEPA), a strategy of bi-annual ivermectin treatment of at least 85% of the eligible populations in all endemic communities is showing very good results and promises to be effective in eliminating onchocerciasis in the region.

The Conference concluded that onchocerciasis is not eradicable using current tools due to the major barriers to eradication in Africa. However, the Conference also concluded that in most if not all the Americas, and possibly Yemen and some sites in Africa, transmission of onchocerciasis can be eliminated using current tools.

The Conference recommended that where interruption of transmission is feasible and cost-effective, programs should aim for that goal using all appropriate and available interventions so that the *Onchocerca volvulus* can eventually be eliminated and interventions halted. Although interruption of transmission of onchocerciasis cannot currently be achieved in most of Africa, the Conference recommended that efforts be made to preserve areas in West Africa made free of onchocerciasis transmission through the Onchocerciasis Control Program over the past 25 years. In the remaining hyper and mesoendemic foci in Africa, continued annual distribution of ivermectin will keep onchocerciasis controlled to a point where it is no longer a public health problem or constraint to economic development.

Although not yet identified to exist, the specter of the emergence of resistance to ivermectin in *O. volvulus* was considered a future potential threat to the great progress and considerable investment made so far in research and control against this disease. In particular, there is need for additional research in developing macrofilaricides (drugs which could kill or permanently sterilize the adult *O. volvulus* parasite), tools for ivermectin resistance monitoring, and improved diagnostics.

Résumé analytique

Soixante quatre experts appartenant à diverses disciplines sont venus assister à une Conférence sur l'éradication de l'onchocercose au Centre Carter à Atlanta GA, tenue du 22 au 24 janvier 2002. La conférence qui était organisée par le Centre Carter et l'Organisation mondiale de la Santé, grâce à un financement de la Fondation Bill & Melinda Gates se penchait sur la question suivante : Est-il possible d'éliminer l'onchocercose (cécité des rivières) avec les connaissances et les outils actuels ? » La Conférence consistait en une série de présentations de la part d'orateurs invités (Annexe C) et de délibérations dans quatre groupes de travail (Annexe D) suivies d'une discussion en plénière des grandes conclusions. L'ancien Président américain, M. Jimmy Carter a assisté à une partie des débats de la plénière.

Les communications ont mis en exergue les différences épidémiologiques et entomologiques entre l'onchocercose en Afrique et aux Amériques. Si l'onchocercose en Afrique couvre de vastes étendues et si elle est associée aux attaques contre les humains et aux migrations de populations de mouches et aux vecteurs de la mouche noire, extrêmement actives, par contre aux Amériques, l'onchocercose est confinée à des foyers restreints. Les migrations des populations humaines et de mouches ne sont pas des problèmes importants aux Amériques où la plupart des espèces de mouches noires ne sont pas actives bien qu'il en existe également certaines qui sont actives sur ce continent. La lutte contre le vecteur a été appliquée efficacement dans le cadre du Programme de lutte contre l'onchocercose en Afrique de l'Ouest (OCP) obtenant des résultats remarquables et mettant fin à la transmission dans la plupart de la région initiale couverte par le programme. L'emploi de l'ivermectine a obtenu des résultats variables : le traitement à base d'ivermectine a été efficace dans les régions à caractère endémique pour lutter contre l'onchocercose en tant que problème de santé publique mais son potentiel pour interrompre la transmission est plus prometteur dans les régions à caractère hypo-endémique et méso-endémique. Le Programme africain de lutte contre l'onchocercose (APOC) qui soutient la lutte contre la maladie dans des pays africains endémiques à l'extérieur du PLO applique l'ivermectine – son principal outil de lutte- dans les communautés des régions à risque élevé tel que déterminé par une cartographie épidémiologique rapide de l'onchocercose (REMO) et les systèmes d'informations géographiques (GIS). Aux Amériques, grâce au Programme d'élimination de l'onchocercose dans les Amériques (OEPA), une stratégie de traitement bisannuelle à base d'ivermectine couvrant au moins 85% des populations concernées dans toutes les communautés à caractère d'ivermectine enregistre de très bons résultats et a toutes les chances d'être efficace pour éliminer l'onchocercose dans la région.

La Conférence a conclu que l'onchocercose ne pouvait pas être éliminée en utilisant les outils actuels à cause des grandes barrières qui entravent l'éradication en Afrique. Néanmoins, la Conférence a également conclu que dans l'ensemble voire partout aux Amériques et probablement au Yémen et dans certains endroits en Afrique, la transmission de l'onchocercose pouvait être enrayée en utilisant les outils actuels.

La Conférence a recommandé que dans les endroits où il était faisable et efficace par rapport aux coûts de mettre fin à la transmission, les programmes devaient viser ce but en utilisant toutes les interventions adéquates et disponibles de sorte à éliminer *Onchocerca volvulus* et à mettre fin à

la transmission. Même si l'interruption de la transmission de l'onchocercose n'est pas possible actuellement dans la plupart des pays de l'Afrique, la Conférence a recommandé de préserver les régions de l'Afrique de l'Ouest qui se sont débarrassées de l'onchocercose ces 25 dernières années grâce au Programme de lutte contre l'onchocercose. Dans les foyers africains restants, à caractère hyper-endémique et méso-endémique, une distribution annuelle continue d'ivermectine permettra de garder l'onchocercose sous contrôle au point où la maladie n'est plus un problème de santé publique ou une contrainte au développement économique.

Bien que son existence n'ait pas encore été vérifiée, le spectre de l'éventuelle résistance à l'ivermectine chez *O.volvulus* a été jugé un risque possible pour les progrès importants et l'investissement considérable fait dans la recherche et la lutte contre cette maladie. Il s'agit notamment de faire des recherches supplémentaires pour mettre au point des macrofilaricides (médicaments qui tuent ou stérilisent de manière permanente le parasite adulte *O.volvulus*), des outils pour le suivi de la résistance à l'ivermectine et pour améliorer le diagnostic.

Resumen de conclusiones

Sesenta y seis expertos en diversos campos asistieron a una Conferencia sobre la Posibilidad de Erradicación de la Oncocercosis, celebrada en el Carter Center, de Atlanta, GA, durante el 22 y el 24 de enero de 2002. La Conferencia, organizada por el Carter Center y la Organización Mundial de la Salud y patrocinada por la Bill & Melinda Gates Foundation, planteó el interrogante siguiente: ‘¿Es erradicable la oncocercosis (o ceguera de los ríos) con los conocimientos y medios de que disponemos?’ La Conferencia consistió en una serie de presentaciones realizadas por expertos invitados (Apéndice C) y las deliberaciones posteriores de cuatro grupos de trabajo (Apéndice D), seguida de la discusión plenaria sobre las principales conclusiones. El expresidente estadounidense Jimmy Carter asistió a algunas de las reuniones plenarias finales celebradas el 24 de enero.

Las presentaciones subrayaron las diferencias epidemiológicas y entomológicas que existen entre la oncocercosis en África y América. Mientras la enfermedad en África está presente en vastas zonas y está asociada con sorprendentes migraciones de poblaciones humanas y de moscas y con muy eficientes vectores (moscas negras), en las Américas, la oncocercosis se encuentra en focos muy limitados. Migraciones humanas y de moscas no representan mayor problema en las Américas, donde la mayoría de las especies de moscas negras son vectores ineficientes, aunque también existen algunas especies eficientes. El Programa de Control de la Oncocercosis en África Occidental (OCP) ha aplicado con eficacia el control vectorial obteniendo óptimos resultados al interrumpir la transmisión en la mayoría de las zonas originales del programa. El uso de ivermectina ha demostrado resultados variables: mientras el tratamiento con ivermectina ha sido efectivo en todas las zonas endémicas al controlar la oncocercosis como problema de salud pública, su potencial para interrumpir la transmisión es más promisorio en áreas hipo y mesoendémicas. El Programa Africano de Control de la Oncocercosis (APOC), el cual apoya el control de la oncocercosis en países africanos endémicos que no pertenecen al programa OCP, utiliza ivermectina como su principal herramienta de control en comunidades de alto riesgo determinadas por medio de Mapeo Epidemiológico Rápido de la oncocercosis (REMO) y los Sistemas de Información Geográfica (SIG). En las Américas, a través del apoyo del Programa para la Eliminación de la Oncocercosis en las Américas (OEPA), la estrategia de tratamiento semestral con ivermectina a por lo menos el 85% de la población elegible en todas las comunidades endémicas, está demostrando excelentes resultados y promete ser efectiva en la eliminación de la oncocercosis en la región.

La Conferencia llegó a la conclusión de que la oncocercosis no es erradicable usando las herramientas existentes actualmente debido a las grandes dificultades presentes para la erradicación en África. Sin embargo, la conferencia también concluyó que en la mayoría, si no en todas las Américas, y posiblemente Yemen y en algunos lugares de África, la transmisión de la enfermedad puede ser eliminada usando las herramientas actuales.

La Conferencia recomendó que cuando la interrupción de la transmisión sea posible y económicamente viable, los programas deben esforzarse por lograrla utilizando todos los procedimientos adecuados y disponibles, con el fin de que la *Onchocerca volvulus* pueda ser eventualmente eliminada y suspendidas las intervenciones. Aunque la interrupción de la

transmisión de la oncocercosis no puede ser actualmente lograda en la mayoría del África, la Conferencia recomendó que se hicieran los esfuerzos necesarios para preservar las áreas de África Occidental en las que se ha logrado eliminar la transmisión de la oncocercosis a través del Programa de Control de Oncocercosis los últimos 25 años. En los restantes focos hiper y mesoendémicos en África, la distribución anual constante de ivermectina mantendrá la oncocercosis bajo control hasta que deje de ser un problema de salud pública y un obstáculo para el desarrollo económico.

Aunque no se ha confirmado su existencia, el espectro del apareamiento de resistencia a la ivermectina en *O. volvulus* fue considerado como una posible amenaza futura para el progreso alcanzado y las importantes inversiones a la fecha realizadas para la investigación y control de esta enfermedad. En particular, existe una necesidad adicional de investigación para desarrollar macrofilaricidas (fármacos capaces de eliminar o esterilizar de manera definitiva al parásito *O. volvulus* adulto), herramientas para el monitoreo del apareamiento de resistencia a la ivermectina y mejoras en los métodos de diagnóstico.

Conference Organization and Opening Remarks

The Conference on the Eradicability of Onchocerciasis was convened by The Carter Center and WHO and supported by the Bill and Melinda Gates Foundation from 22–24 January 2002 at The Carter Center in Atlanta, Georgia. Over 64 experts from a variety of disciplines attended and examined the theme “Is onchocerciasis (River Blindness) eradicable with current knowledge and tools?” Presentations were made by invited expert speakers (Appendix C) and four working groups deliberated on assigned topics (Appendix D). Conclusions and recommendations from the working group deliberations were discussed in plenary to formulate the main conference conclusions. Former President Carter participated in part of the plenary session on January 24.

The conference was co-chaired by Dr. Donald Hopkins, Associate Executive Director, The Carter Center and Dr. Maria Neira, Director, Control, Prevention and Eradication, Communicable Diseases Cluster, World Health Organization. Dr. Yankum Dadzie was appointed rapporteur. In his opening address, Dr. Hopkins urged conference participants to critically review available knowledge and evidence on the theme in order to make an informed judgment on whether or not onchocerciasis is eradicable with current knowledge and tools and to make recommendations on which actions need to be taken in the future. Dr. Maria Neira, in her remarks, stressed the importance of considering the cost complications of any recommendations made by the conference and to make sure that these were consistent with the broader public health agenda.

Introduction

Onchocerciasis, or river blindness, is caused by the filarial parasite *Onchocerca volvulus*. It is transmitted by the black flies of the genus *Simulium* that breed in fast-flowing water. Manifestations of onchocerciasis include eye lesions that can cause visual loss culminating in blindness, and skin lesions (severe itching, disfiguring skin changes, and subcutaneous nodules). A WHO Expert Committee in 1995¹ estimated that over 120 million persons are at risk with some 17.6 million infected, 99 % of whom live in Africa with the rest found in six countries of the Americas, and Yemen in the Arabian Peninsula. Onchocerciasis is a disease of remote, rural, poor populations. In Africa, onchocerciasis has been found to cause serious socio-economic problems; populations have in the past abandoned fertile land along the rivers that harbor the breeding sites of the *Simulium*, for fear of going blind, whilst persons with unsightly skin lesions have been socially marginalized.

Progress made in the last quarter century in the control of onchocerciasis, both in Africa and the Americas, has generated much interest and also raised questions about the feasibility of eradicating onchocerciasis using available tools. The Atlanta Conference on the Eradicability of Onchocerciasis was convened with the following purposes: 1) to review previous discussions and judgments on the eradication of onchocerciasis, 2) to discuss and evaluate the current knowledge base regarding the ability of existing interventions to interrupt parasite transmission, 3) to assess the status and prospects of new tools for treating, preventing, tracking, and diagnosing the infection, 4) to discuss evidence related to potential for emergence of resistance in *O. volvulus* to ivermectin, 5) to consider the scientific, operational, economic and political/social feasibility of eradicating onchocerciasis, using currently available tools; and 6) to propose future research needs and their implementation.

The feasibility of eradication of onchocerciasis was first examined during the meeting of the International Task Force for Disease Eradication (ITFDE) in 1992,² which concluded that onchocerciasis could not be eradicated, but could be controlled to a point at which it would no longer be a public health problem. An international meeting on Global Disease Elimination and Eradication as Public Health Strategies, held in Atlanta in 1998,³ concluded that “reconsideration” of the perceived barriers to onchocerciasis eradication “is now appropriate, given the considerable progress” in morbidity control in West Africa and the Americas. The subject of eradication was again reviewed during a WHO meeting in September 2000,⁴ where the prevailing opinion emerged that eradication of onchocerciasis in Africa was not possible with the existing tools, but evidence suggested that onchocerciasis could be eliminated in the Americas. A second ITFDE meeting on the subject of OEPA concluded in 2001 that eliminating ocular

¹ WHO. Onchocerciasis and its control: report of a WHO Expert Committee on onchocerciasis control. WHO Technical Report Series 1995; No. 852; 103 pp.

² Recommendations of the International Task Force for Disease Eradication. MMWR Recommendations and Reports 1993;42 (RR-16), 38 pp.

³ Goodman RA, Foster KL, Trowbridge FL, and Figueroa JP (eds). Global Disease Elimination and Eradication as Public Health Strategies. Bulletin of WHO 1998; 76 (supplement 2): 162 pp.

⁴ Anonymous. (2000) Guidelines for Certifying Elimination of Human Onchocerciasis, including a Discussion of Critical Issues (September, 2000, Geneva. WHO/CDS/CPE/ CEE/DIP/00.008).

morbidity and interrupting onchocerciasis transmission in the Americas, using currently available tools, was scientifically feasible.

The deliberations of the Atlanta Conference on the Eradicability of Onchocerciasis ('the Conference') reported herein used the definitions of terms recommended by the ITFDE and endorsed by the Dahlem Workshop on the Eradication of Infectious Diseases in 1997.⁵ Thus:

Eradication is a permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures thereafter are not needed.

Elimination is reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate intervention efforts; continued measures to prevent reestablishment of transmission are required.

Control is the reduction of incidence or disease manifestations to a predefined point at which public health authorities declare the condition to no longer be a public health problem. Continued measures are needed to keep transmission or morbidity at or below this point.

It was noted that another meeting held in Atlanta in 1998 on Global Disease Elimination and Eradication as Public Health Strategies⁶ recommended use of the term "regional eradication" in lieu of "elimination".

⁵ Dowdle WR, Hopkins DR (eds). The Eradication of Infectious Diseases: Report of the Dahlem Workshop on the Eradication of Infectious Diseases. Clichester, John Wiley & Sons, 1998: 218 pp.

⁶ Goodman RA, Foster KL, Trowbridge FL, and Figueroa JP (eds). Global Disease Elimination and Eradication as Public Health Strategies. Bulletin of WHO 1998; 76 (supplement 2): 162 pp.

Summary of Conference Discussions

(See Appendix C for synopses of presentations submitted to the Conference by invited speakers.)

African Perspective

The first large-scale control effort against river blindness, the Onchocerciasis Control Program (OCP) in West Africa, was launched in 1974 as a regional program in seven West African countries with the objective to eliminate onchocerciasis as a disease of public health importance and an obstacle to socio-economic development. Its strategy was aerial application of insecticide to kill the larvae of the vector *Simulium damnosum s.l.* in their riverine breeding sites in order to interrupt transmission of infection for the period necessary for the adult *O. volvulus* worms in humans to completely die out (the longevity of the adult *O. volvulus* is estimated to be 14 years). Later with the donation of ivermectin, a safe microfilaricidal drug, by the pharmaceutical firm Merck & Co. Inc. to onchocerciasis programs, mass ivermectin treatment was applied broadly in OCP as an adjunct to vector control, or as the sole control measure. The OCP will formally close at the end of 2002.

The second major African regional program, the African Program for Onchocerciasis Control (APOC), was launched in 1995 to control onchocerciasis in the remaining endemic countries in Africa. The goal of APOC is to control onchocerciasis to a point where it is no longer a public health problem or a constraint to socio-economic development. APOC aims to establish effective and self-sustaining 'Community-Directed Treatment with Ivermectin (CDTI)' throughout the remaining endemic areas outside OCP. Using the 'REMO' rapid disease mapping methodology, APOC targets communities found to have an onchocercal nodule prevalence of $\geq 20\%$ for annual CDTI. In addition, APOC is charged, where possible, to eliminate the vector and hence the disease from carefully selected isolated foci, using environmentally safe insecticides.

APOC has not yet used ivermectin long enough to be able to generate data to assess the impact of treatment on morbidity or transmission of infection. A multi country study to measure impact has collected baseline data in 13 sites, which will be re-evaluated in 2004, and again in 2009, prior to the end of APOC (in 2010). Therefore, the best information available to judge the eradicability of onchocerciasis in Africa at this time comes from the OCP. Results of OCP surveillance data analysis from the central part of the original program area demonstrate that interruption of onchocercal parasite transmission has been maintained without any control effort for over a period of 12 years. This original program area underwent 14 years of effective vector control. Recently, a major review has been undertaken of the OCP evaluation data on the long-term impact of ivermectin treatment.¹ It was concluded that ivermectin treatment has been extremely successful in controlling onchocerciasis to the point where it is no longer a public health problem in all endemic areas of the OCP. Community Microfilarial Loads (CMFL), an index of intensity of infection, have dropped to close to zero. In areas where ivermectin treatment of populations has been the sole strategy and carried out in different river basins at

¹ Summary report of the OCP/TDR meeting on the impact of ivermectin on onchocerciasis transmission. World Health Organization, 2001, Document JPC22-JAF7/INF/DOC.2

different frequencies (quarterly, semi-annually and annually) for up to 12 years, there are not sufficient data available to demonstrate that parasite transmission has been interrupted. Further studies are required before a judgment can be made.

However, even when transmission is interrupted with ivermectin, it can recur if ivermectin treatment is stopped prematurely. For example, in the mesoendemic Coruba River basin in Guinea Bissau, civil unrest in 1997 resulted in the suspension of an intensive quarterly ivermectin distribution program after five years of operations. Despite prevalence levels having fallen in the basin to near zero in 1996 after 20 rounds of treatment, evaluation carried out four years after the disruption of the distribution program showed that recrudescence of infection has occurred. Thus, even in the setting where transmission may be interrupted, it will likely resume if interventions are halted before the entire duration of the lifespan of adult *O. volvulus* worms (about 14 years).

There have, however, been exceptions in the effectiveness of vector control in interrupting transmission in OCP. Vector control that was started in 1977 has not been effective in interrupting transmission in the area around the Oti tributaries (Kara, Keran and Mo Basins) in Togo. Reinvasion of *Simulium* from the southern part of the program area accounted for the initial poor results at interrupting transmission. The extension of vector control southwards of the Program area in 1987 to treat the source of re-invasion, together with adding annual ivermectin treatment of populations in the area was not sufficient to stop transmission. Factors explaining these poor results include very poorly accessible mountainous terrain that hinders good ivermectin coverage, dry season migration of people pursuing gold mining, and reinvasion of black flies from the head waters of the Oti river after vector control was stopped there in 1996.

Reinvasion by vector black flies has challenged vector control efforts from the very onset of the OCP. Vectors flying from as far away as 500 kms from Sierra Leone and Guinea, assisted by Monsoon winds, have compromised larviciding operations and necessitated an extension of OCP operations to southern Cote d'Ivoire in 1978, and to the Western and Southern OCP area from 1988 - 1990. In addition, dry season reinvasion of black flies cruising on Harmattan winds from the north has been blamed for the rapid dispersion of insecticide-resistant black flies to other river basins in OCP. Fly movements could potentially promote dispersion of ivermectin resistance too, if it were to occur.

Whilst fly movements can promote the spread of onchocerciasis from uncontrolled to controlled areas, incompatibility in vector-parasite complexes seems to work to limit the infection. Studies show that in West Africa, flies from the savanna region are less effective in supporting transmission of forest strain *O. volvulus*. The converse has also been observed. These phenomena are limiting factors to the extension of infection from the savanna into the forest and vice versa. Incompatibility in vector-parasite complexes is not absolute, as at least one vector species, *S. soubrense*, is capable of effectively transmitting both forest and savanna strains of *O. volvulus*.

American Perspective

Compared to Africa, the entomological and epidemiological characteristics of onchocerciasis in the Americas favor a strategy aimed at elimination. Many of the American *Simulium* vector species are inefficient vectors due to their having a 'cibarial armature' that destroys most of the microfilariae they ingest in a blood meal, so preventing the development of microfilaria to infectious larvae. The localization of American onchocerciasis foci is in large part due to the requirement of very high vector densities and a human population with high microfilaria loads in the skin to maintain a viable transmission cycle. Thus, human population movements in the Americas are less likely to introduce or reintroduce onchocerciasis, since there are few such 'permissive' transmission environments.

In Guatemala where the 'armed' vector *S. ochraceum* is the principal vector, it has been shown in community-based studies that ivermectin administered at 6-month intervals can maintain levels of microfilaria in skin so low as to interrupt transmission. The community studies indicated that transmission could only be interrupted if sufficient coverage (>80% of eligibles) was achieved. Later it was demonstrated in an operational setting in a river basin in Ecuador that *O. volvulus* transmission was interrupted after five years of semi-annual ivermectin treatment, an observation particularly interesting since the vector there was the 'unarmed' *S. exiguum*, which is as efficient as the African vectors *S. damnosum*.

The Onchocerciasis Elimination Program for the Americas (OEPA) was launched in 1992, following a resolution of the XXV Directing Council of the Pan American Health Organization in 1991 to eliminate new morbidity from onchocerciasis from the Americas by 2007. OEPA also aims to eliminate onchocerciasis transmission wherever feasible using a strategy of semi-annual mass distribution of ivermectin to at least 85% of the eligible population. Current epidemiological information shows that in the six endemic countries of the Americas (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela) there are some 440,861 persons who need treatment, living in 1,969 endemic communities. Over 90% of these reside in Mexico, Guatemala and Venezuela. In 2001, 84% of these persons were offered at least one dose of ivermectin by national programs operating in each of the endemic countries.

Recent entomological and serological evaluations in the Americas carried out with OEPA support have provided strong evidence that parasite transmission has been interrupted in 5 of 7 river basins in Ecuador, in the single Colombian focus, and in the Oaxaca focus in Mexico. Transmission continues in foci where semi-annual ivermectin coverage has not been optimal: southern Chiapas in Mexico, in Guatemala and Venezuela. Elimination of onchocerciasis from southern Venezuela and Brazil will be particularly difficult given the problems reaching the nomadic Amerindians (the Yanomami) in parts of the immense Amazonian forest. However, in 2001 the Brazilian program demonstrated that it could indeed reach 80% coverage of these hard to reach populations. The challenge is to help the American programs deliver ivermectin treatment with high coverage *twice per year*. If this challenge is met, the data indicate that it is possible to interrupt transmission of *O. volvulus* in all foci in the Americas by 2007, perhaps with the exception of southern Venezuela (which contains <1% of the total at risk population in the region).

Modeling of Onchocerciasis Control

Two mathematical models were discussed during the Conference, ONCHOSIM and SIMONa. The ONCHOSIM model was originally developed to help OCP decision-making with respect to duration of vector control; the model was subsequently modified to incorporate ivermectin treatment. ONCHOSIM has been used to predict impact on onchocerciasis transmission from vector control alone, ivermectin alone, or combined ivermectin/vector control, and its predictions have been continuously tested against the entomological and epidemiological evaluation data of the OCP. Its predictions show that vector control conducted optimally requires 14 years to interrupt transmission, but the addition of ivermectin to vector control can shorten the required duration of control to 12 years. Elimination of transmission by ivermectin treatment alone would require a relatively long time period and very high treatment coverage, especially in hyperendemic areas. The simulations of the impact of ivermectin treatment were for an ‘isolated system’ uninfluenced by human and fly migration. Although the original model predictions did fit the observed data for the first five years of ivermectin treatment, comparison with the latest results for 12 years of treatment suggests that ONCHOSIM’s predictions of the feasibility of elimination (even for an isolated system) are overly optimistic, probably because of the assumptions pertaining to the impact of ivermectin on *O. volvulus* fecundity. Further fine-tuning of ONCHOSIM is ongoing within the context of the detailed analysis of the OCP evaluation data on 12 years of ivermectin treatment.

SIMON was originally written to model forest strain transmission of onchocerciasis in Africa. It is a more ‘conservative’ model than ONCHOSIM in that SIMON does not include an assumption that ivermectin has an irreversible effect on the fecundity of adult *O. volvulus* worms. SIMON has been recently adjusted to parameters of American vectors (SIMONa) and used to simulate a single hyperendemic sentinel village in Ecuador. Baseline and surveillance data from that village with over 11 years annual and semi-annual ivermectin treatment (with dates and treatment coverage figures) were entered into the model. Model predictions for infection rates in flies, serologic rates in children, CMFL, microfilaria prevalence in skin, and ocular disease were compared with corresponding observations in the village over time. With one exception model predictions matched observations (the exception is ocular punctate keratitis, which was observed to be higher than predicted by the model). In the second stage of the analysis, SIMONa was used to project when transmission could be eliminated and treatment halted, assuming continued semi-annual ivermectin treatments at $\geq 85\%$ coverage of eligibles (and assuming there was no new introduction of *O. volvulus* infection from immigration of infected individuals). The model predicted that after 2004, ivermectin treatment could be safely withdrawn (without running any risk of recrudescence).

Future comparison and validation of these and other model predictions is important. For such validation, it would be useful to have a serological marker to measure presence of adult worms, since in the Ecuador example observed infection rates in black flies and humans are now undetectable, yet recrudescence risk in the SIMONa projection remains considerable until 2004. There is also a need to use models to predict if continued low levels of transmission have true biological significance to the survival of *O. volvulus* in difference ecological settings.

Ivermectin Resistance

There is no documented evidence for ivermectin resistance in *O. volvulus* (or any animal filarial species) despite intense use of ivermectin in mass treatment programs for many years. However, high-grade ivermectin resistance emerged relatively quickly in intestinal trichostrongilid nematodes of sheep, goats and cattle. The fact that onchocerciasis control will likely remain dependent for many years upon mass ivermectin distribution has led to the speculation that conditions are favorable for emergence of ivermectin resistant *O. volvulus*. Changes in genetic polymorphism with selection have been noted in *O. volvulus* specimens obtained from human populations exposed to multiple ivermectin mass treatments rounds, compared to worms examined from naïve human populations. A recent report from Ghana of human non-responders to ivermectin (defined as individuals with microfilaria (mf) counts in skin >10 mf/snip after nine or more rounds of ivermectin treatment) has prompted a detailed clinical study on the issue, the results of which are still awaited. Research is ongoing to develop tools for detecting ivermectin resistance that could be easily deployed in large-scale ivermectin treatment programs. This is based on the assumption that if resistance is detected early strategies can be devised to contain it before it becomes widespread.

If ivermectin resistance in *O. volvulus* were to develop, it is possible that these parasites would be at once cross resistant to moxidectin. This is due to the fact that the two drugs share the same 3-dimensional chemical configuration and so likely the same receptor and the same mode of action. However, it is not necessarily true that such cross-resistance would have the same impact because of the very different pharmacokinetics of the two compounds.

Sustainability of Ivermectin Delivery

Both African programs (APOC and OCP) embrace the strategy of Community-Directed Treatment with Ivermectin (CDTI) with the aim to sustain ivermectin treatment in the endemic countries in Africa. The philosophy of CDTI is to empower the communities to make their own decisions (such as selection and remuneration of distributors, time of distribution, method of distribution, etc.) about the distribution process. It is believed that ivermectin treatment will be sustained if the traditional structures of the people are respected, and the motivation of Community-Directed Distributors (CDD) is provided through their own kinsmen. Also critical to sustainability is a central and peripheral health care system that can provide health education, training, supervision and monitoring of the program, acting in support of the community and its decision, ideally through an integrated approach. Drug reporting, ordering, and supply are other critical functions that must be strengthened and sustained. Financial and technical support emanating from the OCP/APOC Program and partner NGDO's so far has resulted in the success of the CDTI approach. The immediate challenge is to maintain this performance record in the 11 countries of OCP when that program comes to an end in 2002.

OEPA's challenge in the Americas is to reach and maintain the highest possible ivermectin treatment coverage, twice per year, to first interrupt transmission, and then maintain program performance and coverage for the duration of the life span of the adult worms. This accomplished, the endemic focus will go through a three-year pre-certification surveillance period without treatment. Demonstration of continued interruption of transmission thereafter will entitle the endemic country to be 'certified' as having eliminated onchocerciasis. The UTG(2)

(twice the ‘Ultimate Treatment Goal,’ which is the number of eligible persons for treatment in the region) has been adopted to simplify the monitoring and motivate country programs to meet their coverage objectives. In 2001, the combined American programs treated 80% of the regional UTG(2) of 881,722. In the future, OEPA hopes to help country programs monitor information on coverage at the community level, so that health staff can target those communities failing to reach $\geq 85\%$ coverage for special interventions (such as additional health education, technical training, etc.) so as to assure that transmission interruption is simultaneously achieved within an endemic focus.

***Loa loa* as an Obstacle to Control or Eradication of Onchocerciasis**

Serious adverse effects (SAEs) related to the central nervous system, including several deaths, have occurred after mass ivermectin treatment, primarily in Cameroon. These SAEs have been observed where *Loa loa* is coendemic with onchocerciasis, at a rate of about 8 SAEs per 10,000 ivermectin treatments. The SAEs occur principally after the first or second round of treatment, with individuals having high-grade *Loa loa* microfilaremia ($>8,000$ mf/ml blood) being at greatest risk. Remote sensing and GIS studies have generated maps of overlapping endemicity of onchocerciasis and loiasis in Africa based on REMO and remotely sensed vegetation indices that correspond to the permissive sites for *Chrysops* (the *Loa loa* vector) breeding sites. Special measures for managing patients with SAEs are recommended for ivermectin distribution programs operating in these high-risk onchocerciasis/loiasis coendemic areas. Ivermectin treatments should be provided in such areas only after good medical supervision and referral systems have been put in place. Special training and medical supplies are made available to referral health facilities that are on alert during the treatment period. Lastly, village-by-village assessments for onchocerciasis are undertaken to ensure that mass treatments are only provided in communities where onchocerciasis is ‘a public health problems (i.e., communities with $\geq 20\%$ nodule rates). The latter recommendation indicates that *Loa loa* coendemicity would be an important obstacle to a goal of onchocerciasis eradication, since it precludes expansion of mass treatment to some hypoendemic onchocerciasis areas (where onchocerciasis morbidity usually is not observed, but where onchocerciasis transmission can occur).

A new community diagnostic procedure (called ‘RAPLOA’) based on a simple questionnaire, when validated this year, may simplify the process of determining areas at highest risk of *Loa*-associated SAEs. The use of this technique could facilitate the safe expansion of mass distribution programs in hypoendemic onchocerciasis villages in *Loa*-coendemic areas.

Human Migration, and Political and Social Aspects of Eradication

Considerable human migration, both voluntary and forced, occurs throughout many of the onchocerciasis endemic areas in Africa. An eradication effort would need to achieve the required coverage among migrants or transient groups in conditions where these groups are often marginalized from the healthcare system, or where that system does not exist due to conflict. Drug distributors willing to work under these conditions would need to be trained to reach migrants, or distributors from among transient groups would need to be identified and trained. Census figures for determining coverage would have to be adjusted to account for new residents or transient populations. In areas of conflict, security related challenges would include obtaining

access to the conflict area through negotiation with warring factions, and establishing periods of tranquility. Skilled negotiators familiar with the warring parties and the prevailing issues could promote health as a non-political issue, or ivermectin distribution as a peace tool, or as a means of providing other essential health services to care for more lethal conditions. Ivermectin distribution can be successfully undertaken within conflict areas. In Sudan, distribution activities have grown over the years through a strategy that employs two separate but well-coordinated programs, operating on both sides of the battle line (one in the government-held areas and the other in the rebel-held areas). However, tailored approaches appropriate to the nature of each crisis must be designed, which almost always implies increased costs.

Economic Aspects of Eradicating Onchocerciasis

Economic studies carried out for donors to APOC considered primarily the costs to be borne by those donors. These studies revealed a 24% economic rate of return to the donors' investment in that control program. However, further economic studies have not yet been done that incorporate the costs of all partners (donors, NGOs, countries, communities) to effectively compare the options of control versus eradication. To be thorough, such an analysis of onchocerciasis control should include the possible scenarios of a) continued donation and effective distribution of ivermectin indefinitely in order to maintain control of onchocerciasis to the point where it is not a public health problem, and b) possible future resurgence of onchocerciasis because of failure to maintain ivermectin coverage or due to ivermectin resistance. If, at some future date, it is determined that onchocerciasis could be eradicated, doing so is likely to include a greater benefit/cost ratio if mass treatments could be halted eventually, reduced risk of ivermectin resistance, and reduced risk of recrudescence of the disease.

Conclusions and Recommendations of the Conference on Eradicability of Onchocerciasis

Key Conclusions and Recommendations:

1. The Conference concluded that onchocerciasis is not eradicable using current tools due to the major barriers to eradication in Africa, which include: a) data that show that the principal tool, ivermectin, when used as a single intervention, cannot consistently interrupt transmission in the African setting; b) the programmatic challenges of an expansive endemic area with mobile vectors and infected human populations, poor health infrastructure, and political instability; c) the presence of co-infections with *Loa loa* in many onchocerciasis endemic areas (where adverse reactions can occur to ivermectin treatment); and d) inadequate funds and poor political support for the more expensive undertaking of eradication, which would require increasing the population receiving ivermectin treatment by also targeting hypoendemic areas to interrupt transmission. Although interruption of transmission of onchocerciasis cannot currently be achieved in most of Africa, the Conference noted that programs that use ivermectin have been successful in controlling onchocerciasis to the point of it no longer being a public health problem. The Conference recommended that ivermectin treatment in community based control programs should continue, albeit indefinitely, and that efforts be made to maintain the transmission free status of those areas now freed of onchocerciasis by OCP. In particular, there is need for additional research in developing safe and easily administered macrofilaricides (drugs which could kill the adult *O. volvulus* parasite) and thus reduce the time needed for the program to eliminate adult worms from an endemic area. The specter of resistance to ivermectin, which has not yet been identified, was considered a potential threat to global control of onchocerciasis, and research for a probe for resistance monitoring and for replacement drugs was recommended.
2. The Conference concluded that in most if not all the Americas, and possibly Yemen and some sites in Africa, transmission of onchocerciasis can be interrupted with current tools due to the characteristics of the vectors, and the geographic isolation of the onchocerciasis foci. The Conference recommended that programs in the Americas and other carefully selected sites aim not for mere control of the disease, but for the complete interruption of transmission, using all appropriate and available interventions, so that the parasite could eventually be eliminated and interventions halted. Research is needed to develop tools to guide decision-making related to the duration of these treatment programs aimed at elimination of onchocerciasis.

Other Conclusions and Recommendations from Working Groups:

(See Appendix D for the Working Group Presentations to the Conference)

1. Feasibility of eradication with ivermectin:

- In Africa, the use of ivermectin has not been shown to provide a conclusive, secure and consistent interruption of *O. volvulus* transmission. In contrast, in the Americas, where

ivermectin has been used effectively (good geographic and therapeutic coverage at semi-annual regimen), interruption of transmission has been achieved.

Recommendations

- More information is needed on the impact of ivermectin intervention (including frequency of distribution, seasonality, etc) on transmission in different settings in Africa.
- Research (including mathematical modeling) is needed to provide a better understanding of very low levels of onchocerciasis transmission on sustaining the parasite.

2. Drug Delivery and Distribution Strategies:

- There is no single global approach to onchocerciasis control or elimination efforts, but rather a need for flexibility of delivery strategies depending on goals (control versus elimination) and country/regional situations. There is however a need to share experiences across programs and countries/regions.
- Geographic coverage of hypoendemic areas will vary according to the objective of the program (control or elimination of transmission). In control programs more highly endemic communities may be chosen for treatment, while in elimination programs, all communities where transmission is likely to occur must be targeted. However the objective within such targeted communities should always be to reach and sustain the highest possible ivermectin treatment coverage of the resident population.

Recommendations

- Develop and test ivermectin delivery strategies that will ensure and sustain high levels of coverage in the many and varied sociological, cultural and epidemiological settings where onchocerciasis is endemic. Elements of treatment activities should be geared to reach immigrants.
- Tailor health education to existing knowledge or misconceptions in the communities, with the view to improve coverage and avoid systematic non-compliance (refusal by certain individuals to ever take treatment).
- Strengthen the health system centrally and at the periphery in order to improve its function in support of communities.
- Encourage community-directed treatment in Africa, where appropriate.
- In areas of conflict, use health to promote peace, and allow extreme flexibility in the implementation of health strategies, being sensitive to the needs and expectations of the people there. Annual cease-fires (such as weeklong cease-fires for immunization and mass drug distribution) should be encouraged.

3. Monitoring and Surveillance

- Depending upon whether the goal is disease control or interruption of transmission, surveillance activities will differ qualitatively & quantitatively in terms of frequency,

depth and duration of data collection and analysis. If transmission interruption and eventual parasite elimination is the goal, then additional resources will be required to maximize surveillance activities.

- Although there is as yet no evidence of ivermectin resistance in onchocerciasis, its emergence is theoretically possible given the wide and prolonged use of ivermectin in the setting of ongoing transmission. Resistance to ivermectin might be contained if detected early. Monitoring for ivermectin resistance is required in both control and elimination programs.

Recommendations

- Collect accurate data on geographic and population coverage that are subject to regular random audits. Programs aiming for interruption of transmission must target poorly compliant communities, as well as identify if systematic or repeated non-compliance to treatment occurs among individuals.
- Establish regular exchange of data, experiences, methodologies and approaches between the different programs in order to highlight similarities and differences.
- Develop better entomological surveillance systems and establish thresholds of infection rates in black flies below which no transmission occurs.
- Develop working surveillance definitions for “ivermectin non-responders” and clinical or laboratory ivermectin resistance. Examine “non-responders” from different countries following a standardized protocol. Develop surveillance and monitoring strategies for early identification of resistance within mass treatment programs.
- Develop a containment strategy to stem such resistance if detected.

4. Product Research and Development

- The progress and investments made to date to control onchocerciasis need to be protected through continued support of fundamental research. Such support should include work on basic biology of *O. volvulus* and related filarial nematodes (particularly pertaining to understanding potential mechanisms of ivermectin resistance) as well as new product development (drugs, vaccines, diagnostics).
- There is a need for drugs that will shorten the duration of the current prolonged treatment period required for ivermectin treatment. Ideally, these new drugs should kill or sterilize the adult *O. volvulus* parasites (e.g., a macrofilaricide) and be cheap, safe and easy to administer in mass treatment programs. A macrofilaricide might make interruption of parasite transmission in Africa possible and justify a future effort to undertake global eradication of onchocerciasis.
- There is a clear need for the identification of an additional drug(s) that could be used in the event of emergence of ivermectin resistance.

Recommendations

- Drug research: Fund pharmacological research for drugs targeting *O. volvulus* or the essential endosymbiont, the *Wolbachia sp.* Use new approaches to drug discovery, including high throughput screening and the use of genomic data to identify rational targets. Solicit pharmaceutical companies to include *Onchocerca* species in their veterinary screens to identify candidate compounds. Carefully consider data on moxidectin with respect to its macrofilaricidal and macrofilaristatic activity, safety profile, pharmacokinetics in humans, and cross-resistance with ivermectin.
- Essential support for candidate drugs and vaccines: Maintain the *O. ochengi* animal model and clinical centers of excellence so that candidate drugs or vaccines can be promptly evaluated.
- Diagnostics: Develop and deploy monitoring tools to assess the presence of viable adult worms (a macrofilarial assay) and to detect early (pre-patent phase), new infections in humans. These tools are needed by programs, which aim at elimination of transmission of onchocerciasis. They should, whenever possible, use rapid assessment formats that are ‘user friendly’, and have the ability to provide instant feedback.
- Resistance probe: Develop and deploy methods and tools to detect *O. volvulus* resistance to ivermectin. Work should continue on genotypic resistance assays.
- Vaccines: Build upon the infrastructure already in place from the \$21 million investment of the Edna McConnell Clark Foundation in vaccine research for *O. volvulus*. Research should pursue additional vaccine targets or employ newer techniques for proof of principal target identification.

Appendix A

Agenda

Conference on the Eradicability of Onchocerciasis
The Carter Center/Cecil B. Day Chapel
Atlanta, Georgia, USA
January 22-24, 2002

FINAL AGENDA

Tuesday, January 22, 2002

- 8:00am *Continental Breakfast* (Ivan Allen Pavilion Foyer)
- 8:45am Introduction: Conference Purpose/Expected Outcomes**
- 9:00am Impact of Existing Interventions on Onchocerciasis Transmission**
9:00-9:15 Impact of vector control in OCP—*Dr. L. Yameogo*
- 9:15-9:35 Impact of ivermectin treatment, including multiple dose per year regimens, and results of OCP/TDR conference—*Drs. B. Boatman and H. Remme*
- 9:35-9:45 Impact of ivermectin treatment in APOC countries—*Dr. A. Seketeli*
- 9:45-10:05 Impact of ivermectin treatment in OEPA countries—*Drs. R. Collins and M. Sauerbrey*
- 10:05am Discussion**
- 10:30am *Coffee Break*
- 10:45am Feasibility of Onchocerciasis Eradication Using Available Tools**
A. Vector-Parasite Aspects: Vector-Species Characteristics
- 10:45-11:00 Differences between vector-parasite complexes relevant to elimination
—*Dr. B. Duke*
- 11:00-11:15 Vector species and transmission efficiency, and frequency of ivermectin treatment—*Dr. E. Cupp*
- 11:15-11:30 Long-distance vector migration and onchocerciasis transmission—*Dr. P. Guillet*
- 11:30am Discussion**
- 12:00pm *Lunch* (Cyprus Room)
- 1:00pm Feasibility of Onchocerciasis Eradication Using Available Tools (cont'd)**
A. Vector-Parasite Aspects: Modelling

- 1:00-1:15 ONCHOSIM: prediction of feasibility of onchocerciasis eradication
—*Professor J. Habbema*
- 1:15-1:30 SIMON: prediction of feasibility of onchocerciasis eradication—*Dr. J. Davies*
- 1:30pm Discussion**
- 2:00pm Feasibility of Onchocerciasis Eradication Using Available Tools (cont'd)**
A. Vector-Parasite Aspects: *O. volvulus* resistance to ivermectin: is it occurring?
- 2:00-2:10 Predicting risk of resistance. How quickly might it be expected?—*Dr. W. Grant*
- 2:10-2:20 Evidence for resistance and resistance monitoring in the field—*Dr. K. Awadzi*
- 2:20-2:30 Lessons from the veterinary field, with thoughts on surveillance for resistance
—*Dr. R. Prichard*
- 2:30-2:40 Cross resistance among the avermectins—*Dr. W. Shoop*
- 2:40-2:50 Cross resistance among the avermectins —*Dr. U. Schwertschlag*
- 2:50pm Discussion**
- 3:15pm *Coffee Break*
- 3:30pm Feasibility of Onchocerciasis Eradication Using Available Tools (cont'd)**
B. Operational Aspects--Achieving and sustaining high treatment coverage
- 3:30-3:45 Experience of APOC—*Dr. U. Amazigo*
- 3:45-4:00 Experience of OCP and challenges for post OCP monitoring—*Dr. B. Boatin*
- 4:00-4:15 Experience of OEPA—*Dr. F. Richards*
- 4:15-4:25 Integration of ivermectin delivery in national health systems—*Dr. E. Tarimo*
- 4:25-4:35 Community participation—*Mr. M. Katarbarwa*
- 4:35-4:45 Mapping treatment areas in Africa—*Dr. M. Noma*
- 4:45-4:55 *Loa loa* issues—*Dr. S. Meredith*
- 4:55-5:45 Discussion**

Wednesday, January 23, 2002

- 8:00am *Continental Breakfast* (Ivan Allen Pavilion Foyer)
- 8:45am Feasibility of Onchocerciasis Eradication Using Available Tools (cont'd)**
C. Political/Social Aspects
- 8:45-9:00 Relevance of insecure endemic areas—*Dr. C. MacKenzie*
- 9:00-9:15 Long-distance human migration— *Dr. D. McFarland*

- D. Economic Aspects**
 9:15-9:35 Economic aspects of eradicating onchocerciasis—*Dr. A. Haddix*
- 9:35am Discussion**
- 10:00am Research Needs**
 10:00-10:05 Introduction to onchocerciasis work at the Hamburg conference—*Dr. A. Hoerauf*
 10:05-10:15 Update on existing drugs—*Dr. D. Buettner*
 10:15-10:25 Update on development of new drugs—*Dr. A. Hudson*
- 10:25am *Coffee Break*
- 10:40am Research Needs (cont'd)**
 10:40-11:00 Update on diagnostics—*Dr. G. Weil*
 11:00-11:20 Update on vaccine—*Dr. E. Ottesen*
 11:20-11:40 Update on drug delivery research—*Dr. H. Remme*
- 11:40pm Discussion**
- 12:30pm Charge to the Working Groups**
- 12:40pm *Group photo*
- 12:45pm Working Groups**
(Box lunches will be provided in each breakout room.)

The charge for the working groups will be:

- 1) To reach a consensus if possible; if not, to provide a reflection of the main opinions presented, and
- 2) To provide, based on this, draft recommendations for further actions to be discussed in plenary

1. Feasibility of eradication with ivermectin

Discussion to include:

- evidence on the impact on transmission after 12 years of ivermectin use.
- latest model predictions of feasibility of elimination
- principal determinants of feasibility
- favourable factors, obstacles and challenges

2. Drug delivery strategies

Discussion to include:

- options for delivery strategy (mobile, community directed, etc...)
- community roles

- political commitment by government
- funding
- areas of conflict
- any needed operational research

3. Monitoring and surveillance

Discussion to include:

- epidemiology, entomology, mathematical modeling and resistance monitoring;
- any needed operational research
- surveillance and recrudescence control in areas where onchocerciasis has been eliminated e.g. central OCP area, OEPA

4. Product Research & Development

Discussion to include:

- macrofilaricide
- new diagnostics
- resistance monitoring tools
- vaccines

6:00pm Optional Jimmy Carter Presidential Museum Tour (*self-guided*)

7:00pm *Conference Reception* (Carter Presidential Museum Lobby)

Thursday, January 24, 2002

8:00am *Continental Breakfast* (Ivan Allen Pavilion Foyer)

9:00am Reports of Working Groups

10:30am *Coffee Break*

11:00am Reports of Working Groups (cont'd)

12:00am *Lunch* (Cyprus Room)

1:00pm Reports of Working Groups (cont'd)

2:45pm *Coffee Break*

3:00pm Conclusions/Recommendations

4:00pm Adjournment

Appendix B

List of Participants



**CONFERENCE ON THE ERADICABILITY OF ONCHOCERCIASIS
THE CARTER CENTER 2002**



Conference on the Eradicability of Onchocerciasis
The Carter Center
Atlanta, Georgia, USA
January 22-24, 2002

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Appendix C

Papers submitted by Conference Speakers

		<i>Page</i>
1.	Dr. Laurent Yameogo	Impact of vector control in OCP 37
2.	Drs. Boakye Boatın and Hans Remme	Impact of ivermectin treatment, including multiple dose per year regimens, and results of OCP/TDR conference 40
3.	Dr. Azogoda S�k�t�li	Impact of ivermectin treatment in APOC countries (Paper Not Submitted)
4.	Drs. Richard Collins and Mauricio Sauerbrey	Impact of ivermectin treatment in OEPA countries 54, 58
5.	Dr. Brian Duke	Differences between vector-parasite complexes relevant to elimination 60
6.	Dr. Edward Cupp	Vector species and transmission efficiency, and frequency of ivermectin treatment 64
7.	Dr. Pierre Guillet	Long-distance vector migration and onchocerciasis transmission 66
8.	Professor Johann Habbema	ONCHOSIM: prediction of feasibility of onchocerciasis eradication 72
9.	Dr. John Davies	SIMON: prediction of feasibility of onchocerciasis eradication 79
10.	Dr. Warwick Grant	Predicting risk of resistance: How quickly might it be expected? 82
11.	Dr. Kwablah Awadzi	Evidence for resistance and resistance-monitoring in the field 86
12.	Dr. Roger Prichard	Lessons from the veterinary field, with thoughts on surveillance for resistance 91
13.	Dr. Wesley Shoop	Cross-resistance among the avermectins 93
14.	Dr. Ullrich Schwertschlag	Cross-resistance among the avermectins 95
15.	Dr. Uche Amazigo	Experience of APOC 96
16.	Dr. Boakye Boatın	Experience of OCP and challenges for post-OCP monitoring 99
17.	Dr. Frank Richards	Experience of OEPA 103
18.	Dr. Eleuther Tarimo	Integration of ivermectin delivery in national health systems 106

19.	Mr. Moses Katarwa	Community participation	109
20.	Dr. Mounkaila Noma	Mapping treatment areas in Africa	(Paper Not Submitted)
21.	Dr. Stefanie Meredith	<i>Loa loa</i> issues	112
22.	Dr. Charles MacKenzie	Relevance of insecure endemic areas	116
23.	Dr. Deborah McFarland	Long-distance human migration	119
24.	Dr. Anne Haddix	Economic aspects of eradicating onchocerciasis	(Paper Not Submitted)
25.	Dr. Achim Hörauf	Introduction to onchocerciasis work at the Hamburg conference	122
26.	Dr. Dietrich Büttner	Update on existing drugs	123
27.	Dr. Alan Hudson	Update on development of new drugs	127
28.	Dr. Gary Weil	Update on diagnostics	130
29.	Dr. Eric Ottesen	Update on vaccine	(Paper Not Submitted)
30.	Dr. Hans Remme	Update on drug delivery research	(Paper Not Submitted)

IMPACT OF VECTOR CONTROL ON ONCHOCERCIASIS TRANSMISSION IN OCP

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Y Bissan, L Toé, A Aké, and BA Boatin

Seven West African countries started the Onchocerciasis control in 1975 in the most blinding onchocerciasis area, a large savannah area (654 000 km²), after the launching of the Onchocerciasis Control Programme (OCP) in 1974. The area was hyper-endemic showing prevalence rates of about 70% and, in some villages, blindness rates up to 9%. Moreover, the frequency and level of evolution of ocular lesions and of onchocercal blindness were among the highest in the world.

To achieve its objective which was to eliminate onchocerciasis as a disease of public health importance as well as an obstacle to socio-economic development, the Programme put in place a strategy to interrupt the transmission of the parasite, *Onchocerca volvulus*, which consisted in destroying the vector at its most vulnerable stage, i.e., the larval stage, by spraying the rivers of the affected areas with insecticides. Taking into account the duration of the larval life of *Simulium damnosum* s.l., vector control was based on weekly treatment of the breeding sites, each time the hydrological conditions were favorable to the development of blackfly larvae.

However, vector control can only be effective if it is continued until the disappearance of the human reservoir of parasite, i.e., for some 14-15 years.

At the beginning, the size of the area under insecticide treatment was such that the regions located at its center, colonized by *S. sirbanum* were protected from any exogenous parasitic contamination (brought by human or blackfly populations). Insecticide treatments were conducted with temephos, a cheap and efficient organophosphorous insecticide with insignificant impact on non target aquatic invertebrates and vertebrates. The sprayings, carried out essentially by aircraft, started in 1975 and were completed in 1989 in most parts of the area, i.e., 14 years after the beginning of control operations. However, at the edges of the southern part of the area, reinvasion of flies from non-treated rivers was an obstacle to a complete success of the larviciding.

The ATP is the index most frequently used to quantify transmission. It is defined as the theoretical number of infective larvae that the same individual placed at this catching point during the same period of time would receive. Above 800 infecting larvae per person and per year, the ATP is associated with the clinical signs of hyperendemicity¹. Below 100, it is considered that onchocerciasis transmission has virtually been interrupted and that the disease is no longer a major public health problem. The infectivity rate is a way of expressing the intensity of transmission. It is independent of blackfly density and corresponds to the number of infectious females (carrying infective larvae) per 1,000 females caught. This index will be mostly used to evaluate the residual transmission after the complete cessation of insecticide spraying because

the collection of field data entails fewer operational constraints compared to that for the calculation of the ATP.

In the central zone of the original Programme area, transmission of the parasite has been interrupted all along the vector control period. At Loaba on the Nakambé river and at Ziou Zabré on the Nazinon river, the ABR fell down from 6 090 and 11 879 in 1975 to 238 and 1 465 between 1976-1989 respectively. At the same time, the ATP at the same catching points were also reduced from 309 and 880 to zero between 1982-1989. A similar trend was observed at Bagre on the Nazinon and at Bitou on the Nouhao, a tributary of the Nakambé river.

The infectivity rates of flies caught 10 years after the cessation of larviciding indicate a better situation than the results obtained only two years after the stopping of larviciding as shown in Table 1.

Table 1: Infectivity rates recorded at Ziou Zabré and Loaba before the beginning of insecticide treatments and then 2 and 10 years after stopping treatment.

	infectivity rates (in brackets: blackflies caught)		
	1975	1991	1999
Ziou Zabré	33.05 (2,239)	0.25 (44,000)	0.05 (18,600)
Loaba	37.48 (1,574)	0.17 (6,000)	0.00 (8,500)

In certain zones at the limit of the initial Programme area (Oti tributaries in Togo, Leraba/Comoe in Burkina Faso, Baoulé and Sankarani rivers in Mali, White Bandama in Côte d'Ivoire, Lower Black Volta in Ghana), the effectiveness of the vector control measures was not as good as in the central part referred to above. It was demonstrated that reinvasion of flies from outside the treated areas was the obstacle to the success of the control operations. The origin of the invading blackflies was identified and, in 1979, larviciding was extended to the rivers in the south of Côte d'Ivoire then, in 1988, to the south of Togo, Benin and Ghana and, in 1989/1990, to Guinea and Sierra Leone. The impact of these extensions on the entomological results of most of the reinvaded areas was quite good. The ABRs and ATPs were strongly reduced at Pont frontiere on the Leraba for example (from 26 314 and 1263 in 1975 to 3 418 and 4 at the cessation of the larviciding period in 1989 respectively). However, even though an improvement of the entomological situation was observed on the Oti tributaries, the results are not as good as expected. Many factors such as the involvement of different vector species in the transmission, the complexity of the area, human population movements, the suspension of larviciding on neighboring rivers and therefore contamination of flies from those untreated rivers explain this situation.

Nevertheless, even without a complete elimination of the parasite in the Programme area, it is quite obvious that transmission has been virtually interrupted in some areas through larviciding alone, based on the results of prevalence and ophthalmological studies.

Some hyperendemic areas of the Onchocerciasis Control Programme in West Africa (OCP) have had, for the past twelve years, both ivermectin treatment and vector control through larviciding. In comparing the impact of this combined control strategy with an exclusive vector control approach, the evolution of transmission in two quite similar study areas in terms of entomological, parasitological and epidemiological situations have been monitored. The parameters used to quantify the transmission were the number of infective females per 1000 parous female flies and the number of infective larvae of the parasite *Onchocerca volvulus* per 1000 parous females. The study area with the combined treatment is situated in the humid savanna zone of Guinea, in the Upper Niger basin. That with the exclusive larviciding is situated in the Upper Sassandra basin in Côte d'Ivoire, also in the humid savanna zone ("guinean" savanna). In these two areas, *Simulium sirbanum*, a savanna blackfly species, is present all year round. The forest species, mainly *Simulium squamosum*, are well represented during the rainy season with a predominance over the savanna species from July to October. In comparing the data on evolution of transmission in the Upper Niger and Upper Sassandra basins it is found that: before larviciding began, in Guinea, transmission levels were around 14.5 infective females and 18.8 infective larvae per 1000 parous females respectively (averages over two years period). Combined larviciding and ivermectin distribution had an immediate impact on transmission which fell by about 90% after only two years of intervention. In Côte d'Ivoire, transmission levels before the beginning of operations was around 13.8 infective females and 31.2 infective larvae per 1000 parous females respectively (averages over a five year period). Contrary to the preceding case, it took six years for transmission to drop down to fairly comparable levels with those of the Upper Niger basin. These results clearly show that ivermectin "maximizes" the effect of vector control by reducing transmission more rapidly (90% reduction in two years instead of six). In operational terms, this impact of ivermectin contributes to the reduction in the total duration of control operations, now estimated at twelve years or so. On this basis but taking into account the entomo-epidemiological evaluation results mainly, the larviciding operations in most of the basins of Guinea stopped at the end of 2001.

Vector control is therefore the most powerful and definite tool for oncho elimination. Combined with ivermectin, its effects are enhanced allowing for a shorter duration of control activities. This latter point needs nevertheless to be confirmed by surveillance results after a complete cessation of control measures in the OCP extensions' areas.

Drs. Boakye Boatin and Hans Remme
**Impact of ivermectin treatment, including multiple dose per year regimens,
and results of OCP/TDR Conference**

**SUMMARY REPORT OF THE OCP/TDR MEETING ON THE IMPACT OF
IVERMECTIN ON ONCHOCERCIASIS TRANSMISSION**

Held at the Dept. Public Health, Erasmus University Rotterdam, Rotterdam, the Netherlands
3-5 October 2001

Summary

A comprehensive analysis has been undertaken of available data on the impact of more than a decade of ivermectin treatment on onchocerciasis infection and transmission. Relevant entomological and epidemiological data from 15 river basins in the OCP and one basin in Cameroon were reviewed. In all of these river basins, ivermectin treatment has been extremely successful in eliminating onchocerciasis as a public health problem. However, elimination of transmission has proven more difficult. In some basins significant transmission is still ongoing after 10-12 years of ivermectin treatment. In other basins, transmission may have been interrupted but this needs to be confirmed by in-depth evaluations. In one meso-endemic basin, where 20 rounds of treatment had reduced the prevalence of infection to levels as low as 2-3%, there was significant recrudescence of infection within a few years after interruption of ivermectin treatment. The implications of these findings for the feasibility of elimination of onchocerciasis transmission by ivermectin treatment are being investigated further in computer simulation studies.

Introduction

The ivermectin trials that were undertaken a decade ago demonstrated the effectiveness of ivermectin treatment for morbidity control. Transmission trials also showed that mass treatment with ivermectin resulted in a major reduction in transmission in Africa. However, after the first three rounds of treatment there still remained a significant level of transmission. Simulation models that were calibrated using these early trial data predicted that interruption of transmission by ivermectin treatment alone would be difficult to achieve and that ivermectin treatment needed to be planned for a period of decades. Hence, ivermectin treatment programmes were established with a long time frame in mind, the exact duration to be determined on the basis of further evaluation on the long-term impact of mass treatment on transmission and the parasite reservoir.

Ivermectin has now been in operational use for more than a decade, and the question of the required duration of treatment is receiving renewed attention. During the meetings of the Joint Programme Committee of the Onchocerciasis Control Programme in West Africa (OCP) and the Joint Action Forum of the African Programme for Onchocerciasis Control (APOC), held in Yaounde in December 2000, this question was also raised. It was noted that the main experience with large-scale ivermectin treatment over a long period of time in Africa was in the OCP. It was recommended, therefore, to undertake an in-depth analysis of the relevant OCP data, and to

update on the basis of the results the ONCHOSIM model predictions of the long term impact of ivermectin treatment on onchocerciasis transmission and of the feasibility of onchocerciasis elimination with ivermectin treatment alone.

Early this year, this process was started. A detailed analysis plan was developed during the annual internal operational research meeting of the OCP in March 2001, and the Centre for Decision Sciences in Tropical Disease Control of the Erasmus University Rotterdam was contracted to undertake the analysis and the corresponding ONCHOSIM simulations. The data analysis has now been completed and the results were discussed during an OCP/TDR sponsored meeting of onchocerciasis experts that was held from 3-5 October 2001 at the Erasmus University Rotterdam, the Netherlands. A summary of the results on the long term impact of ivermectin treatment on onchocerciasis transmission and the main conclusions of the meeting are reported in this document. A complete report of the analysis will be available shortly.

In the mean time, the second phase of the work has started. This will involve a re-calibration of the ONCHOSIM model on the basis of the observed epidemiological trends in the different river basins, and updated predictions of the feasibility of elimination of *Onchocerca volvulus* under different operational scenarios.

Results

During discussions with OCP and WHO staff, 14 areas from within the OCP programme were selected on the basis of their history of ivermectin treatment. Areas that only had larviciding done or were under ivermectin treatment for a too short period were not selected. Variation in the epidemiological background and treatment history was also important in selecting these areas. One area from outside OCP was included in addition, namely Vina Valley in Cameroon.

The 15 areas can be divided into three categories depending on the combination of control measures taken, namely areas that had ivermectin distribution only, areas that had ivermectin treatment after vector control, and areas that had ivermectin distribution and vector control in parallel. Epidemiological data (prevalence and community microfilarial load, CMFL) and entomological data (annual biting rate, ABR, and crude annual transmission potential, ATP) were taken from the OCP databases as available in June 2001.

Areas that had ivermectin distribution only

(A) Gambia (Mako). This basin is situated completely in the savannah area in the eastern part of Senegal and the northeastern part of Guinea Conakry. The area is entomologically relatively isolated. Only savannah vectors were present, mostly *S. sirbanum*. The area was hypo/meso endemic before onchocerciasis control with pre-control CMFL values > 30 mf/s in only two survey villages, and prevalences from 60-80%. However, these data were collected during a prolonged period of very severe drought that affected the area at that time, and data from before the drought indicate a much higher endemicity. Entomological studies were carried out for only two years in preparation of treatment. These studies showed ABRs around 15000, and highly variable ATPs around 3000. DNA probe identification of onchocercal larvae from flies collected during 1986-1992 showed 23% savannah strains of *O. volvulus* and 77% non-volvulus parasites

(mostly *O. ochengi*). Experimental larviciding was carried out in 1989 for 20 weeks during the rainy season. Large-scale ivermectin treatment started in 1989, with a 6-monthly treatment schedule.

The epidemiological indicators prevalence and CMFL show a dramatic decline in this area to very low values, although prevalence seems still a bit hanging in a few villages. This suggests that the parasite reservoir is nearly close to suppression. The entomological data is very limited. However, there is some very recent pool screening data wherein no infective flies have been detected. Therapeutic treatment coverage was high (around 80%). Factors that may have influenced results are: 1) there is important human migration from south to north and west, and 2) there is evidence that the increasing human population may have changed the environment in some places significantly affecting transmission.

These results suggest that ivermectin treatment may have interrupted transmission in this area. However, this needs to be proven by more proper detailed entomological studies with full dissection of flies. If interruption of transmission is confirmed in these studies, it should be considered to stop treatment after a few more years (when the prevalence in all villages has fallen close to zero), while still keeping the surrounding areas under control, and observe whether transmission remains interrupted. Further activities recommended for this basin are a reanalysis of existing records with a view to incidence, and getting a better insight in geographical coverage by making a complete map.

(B, C) Rio Corubal, Rio Geba. The main part of these two basins is situated in Guinea Bissau, very close to the Rio Gambia, Mako focus (A). Rio Corubal used to be a meso-endemic area with pre-control CMFL levels mostly < 30 mf/s, and prevalences varying from almost zero to 80%. Rio Geba had a very low pre-control endemicity, with CMFL < 5 mf/s and prevalence varying from almost zero to 30%. Vector control has never been done in these areas, but some capturing and dissection has been done for a period of two years in Rio Geba (1989-1990) and four years in Rio Corubal (1989-1992). DNA probe examinations of parasites in 46 infective flies from 1993 to 2000 showed 6.5% *O. volvulus* and 93.5% non-*O. volvulus*. In Rio Corubal, 3-monthly ivermectin treatment started in 1991, but this came to an end in 1996 because of civil strife in the area. In Rio Geba, 6-monthly ivermectin treatment was started in 1989.

Prevalence and CMFL in Rio Corubal show very favourable trends, reaching values close to zero in 1997, when ivermectin was no longer distributed. However, recently collected data strongly suggests that at least in some villages prevalence is increasing again from 2-3% in 1996 to values between 12% and 36% in 2001. ABR (around 15000) and ATP (around 500) were not extremely high, and seem compatible with a meso-endemic situation. Therapeutic coverage increased from around 60% at the start of the program to around 80% in 1996. Prevalence and CMFL in Rio Geba went down to values near zero in 1997, when the last available epidemiological data was collected. ABR (range 0-6000) and ATP (range 0-200) were quite low. Baseline ABR values may have been underestimated because of the period of severe drought in which they were measured. Therapeutic coverage was good (80%).

Despite the limited data available, it seems that in Rio Geba onchocerciasis is now eliminated. It is unclear whether this is the result of ivermectin treatment or whether onchocerciasis would have died out by itself in this low endemic area.

Rio Corubal seems very similar to River Gambia, but later follow-up shows evidence of significant recrudescence. This seems especially alarming after about 20 rounds of ivermectin treatments in a not very endemic situation.

No specific further activities were recommended for the Rio Geba. For Rio Corubal it was recommended to 1) construct a good map of geographical coverage, 2) investigate whether what happened in this basin can be explained with the current Onchosim parameterisation, or whether a new parameterisation is needed, 3) do a careful check of all individual records, and (maybe) 4) have a look at the possible development of ivermectin resistance.

(D, E, F, G) Faleme, Bafing, Bakoye, Baoule. These are very similar basins located across the borders between Mali, Senegal, and Guinea in the western extension area. The Faleme is a very complex river system with many tributaries. Vector control was planned for this area based on data collected in the 60's and 70's that indicated high endemicity. The whole area was badly affected by drought in the 70's and 80's. Subsequently, in epidemiological surveys carried out before the start of the western extension (when ivermectin was not yet available) an endemicity much lower than expected was found, and especially the blinding form disappeared from the north of the area. Annual ivermectin treatment was introduced in these four basins in 1989. Studies done in 2000, using DNA probe identification of parasites, found 21% *O. volvulus* savannah strain in the Falema basin, no *O. volvulus* savannah strain in the Bafing basin, 12% in the Bakoye basin, and 39% in the Baoule basin.

These are all mostly meso-endemic foci, with pre-control prevalences around 60% (range 10-80%) and CMFL values around 10 mf/s, with a small number of villages with higher values up to 60 mf/s on the Bafing, Bakoye, and Baoule. Epidemiological indicators show very favourable trends in all areas, with CMFL reaching values near zero in 2001 and prevalences coming down under 10%. Entomological data is only available for a short period between 1985 and 1990, with the exception of one capture point on the Bafing for which there is data up to 2000. ABR with values around 10000 was not very high, although there were a few places with values up to 50000. Now the period of drought is over, the entomological parameters may resemble those of the 60's and 70's. Therapeutic coverage was good with values about 80%. Geographical coverage, however, may not have been very good because these are areas far from urban centres with bad roads that make communication and treatment difficult.

From the point of view of morbidity control the whole area looks very good, and onchocerciasis is no longer a public health problem. The latest epidemiological results are similar to those for the Gambia basin in spite of the different treatment interval (annual vs 6-monthly). The lack of recent entomological data makes it impossible to state whether transmission has been interrupted. Stopping ivermectin distribution is, however, not indicated for the moment because prevalences are still close to 10% in some villages. Recommended further activities are 1) construct good maps of geographic coverage, and 2) perform a special entomological study on

transmission in a site that has a pre-control endemicity and a current situation comparable to Gambia.

(Cameroon) Vina Valley. This is the only basin outside OCP that is discussed in this report. It runs from the east to the west in the centre of Cameroon in a sudano savannah region close to the borders with Chad and the Central African Republic. The area along the river Vina is very isolated. The villages are all on the main road, which runs from east to west, roughly parallel to the river. Where the road approaches the river closely, there is a very high hyperendemicity, with CMFL's in excess of 200 or 300 mf/s. About 50% of the adult population have eye lesions. Pre-control ABR increased from 24250 at the upstream part of the river (Mbeing) to 47450 downstream at Touboro. Pre-control ATP also increased in the downstream direction from 1055 at Mbeing to 4190 at Touboro. Just over ½ to about ¾ of the infective larvae were *O. volvulus*. The Centre Pasteur started annual ivermectin treatment in 1987 in the most eastern part of the area. This area was expanded twice in 1988 to cover the whole basin. Since 1995 all north Cameroon is treated with ivermectin. The area is now part of APOC.

Factors that have to be taken into account when interpreting the results are 1) that there are herdsmen migrating into the country from the north with their cattle, and 2) that from 1985 on the area was invaded by refugees from Chad, who settled close to the river and were thus subjected to high infection rates.

Prevalence dropped from 80% in 1987/1988 to just over 20% in 1996/1997, after 10 years of ivermectin treatment. CMFL dropped from just below 50 mf/s in 1987/1988 to values very near zero in 1996/1997. ABR's were quite variable over the years with values between 10000 to 70000 in the period 1987-2001. Crude ATP was also quite variable and remained on a fairly high level (range 1030-2171). ATP due to *O. volvulus*, however, dropped from 1221 in 1987 to values between 504 and 29, while ATP due to *O. ochengi* remained on roughly the same but quite variable level around 600 with high peaks in 1996-1998 (1529) and in 2000 (1416). Herdsmen moving around the area might explain the variability in ATP due to *O. ochengi*. Geographic coverage was very high because all villages are on the main road. Therapeutic coverage was not so good, varying from 42% to 76% in one evaluated village along the river. No coverage data is available after 1994, but it is likely that values have remained approximately the same.

The main conclusion is that there was a significant decrease in transmission due to 12 years of ivermectin treatment but certainly no interruption. Recommendations made for further actions to be taken for this basin include a continuation of fly-catching for the next one or two years, and an effort to get more detailed treatment coverage data.

Area that had ivermectin treatment after vector control

(N) Bougouriba. The Bougouriba is a tributary of the Black Volta river, and is located in the south-western part of Burkina Faso, just on the border with Ghana. It is in the Sudano-Guinean savannah zone with forest galleries. The area has non-permanent medium sized rivers. The savannah vector species is predominant. The pre-control situation before 1974 was very highly endemic, with an ABR of more than 6000, an ATP > 600, a prevalence of 83.7% (at Mouvielo), and a blindness rate of 11.6%. There was regular larviciding done on the main river and on

important tributaries during the period 1975-1990. On some tributaries, and in particular on the Naimo, larviciding stopped in 1987. There was a complete cessation of larviciding in 1990, when the usual evaluation sites indicated good results or good trends in the previous two years.

In the period 1976-1991, there was an organised installation of populations in the basin by the government, in particular in the Naimo area. These migrants modified the environment and thereby created new artificial breeding sites. At the time when it was decided to stop larviciding, this new situation was not known.

Prevalence went down from around 80% in 1975 to low, but still not zero values in 1990. CMFL went down from very high values in some villages (> 90 mf/s) to values close to zero in 1990. In 1992, post-control entomological data turned out not satisfactory at Batie on the Bambassou river, a tributary of the Black Volta, very close to the Bougouriba. In 1994, newly infected children were found with an incidence > 1.8% in some villages.

In 1996, after this bad situation had been discovered, large scale ivermectin treatment was started in the Bougouriba basin for the purpose of recrudescence control. A 4-monthly treatment schedule was adopted. Therapeutic coverage was quite good (70-80%). Geographic coverage left much to be desired because it is not exactly known how many villages are to be treated, and, because after an initial strong effort to get a good coverage, the number of villages treated dropped from around 180 to values below 100 after 1998. Some ground larviciding was done to protect the population of a village on the Naimo, at the breeding sites created by this population.

After cessation of vector control in 1990, ABR rose to very high levels ranging from 30000 to 70000, and ATP rose to over 400 in one catching site in 1998. Because of the frequent ivermectin treatment schedule, very little epidemiological follow-up is available after 1996. Prevalence rose to values around 20% in some villages in 1996, but, in the few villages for which data is available, it was below 10% in 2000. CMFL remained near zero in all but a few newly included villages. There are some pool screening results from 2000 based on a limited number of flies caught by the local population. These rather uncertain results indicate that the situation is improving.

This is a very problematic area in which post-vector control recrudescence is going on, which went much faster than was anticipated from model simulations. Top priority here is to gather more entomological data on large numbers of flies to determine whether or not transmission has been interrupted. Also, there has to be a much better understanding of the geographical coverage, preferably in the form of a map.

Areas that had ivermectin and vector control in parallel

(H) Tienfala. This is a highly endemic area, situated in southern Mali on the river Niger, just on the border of the original Programme e area in Mali and the western extension. Aerial larviciding started in 1977 in the dry season, but was suspended in the rainy season because of very high river discharges. No larviciding was done from 1977 until 1985, and from 1986 until 1993 aerial and ground treatment were used, but there were also periods in which treatment was suspended. From 1994 up to now only ground larviciding was used. Because of the huge size of the complex

of breeding sites vector control is extremely difficult here, and the objective of larviciding was more to protect the people on the riverbanks against nuisance. Ivermectin treatment started in 1987. This was also an area of extensive nodulectomy that was stopped in 1988.

The trend in prevalence was very good with pre-ivermectin control levels varying from 10% to 80% to values below 10% in 2000. The trend in CMFL is similarly good, with pre-control levels going down from 30-70 mf/s to near zero values reached around 1995. ABR was generally high and very variable (range from 0 to > 70000). ATP was below 1000 with a few exceptional years with higher values. The percentage of *O. volvulus* strain varied considerably between sites (5% to 32%) as determined in 2001, and, correspondingly, the ATP involving only *O. volvulus* was very low and in accordance with the epidemiological data. Therapeutic coverage rose from 60% in 1988 to 80% in 1998.

The dramatic decline in parasite loads in this holo-endemic focus is illustrative of very good morbidity control. It is unclear what the relative contributions of vector control and ivermectin distribution have been. But as the pattern of decline in epidemiological parameters was similar to that observed in basins where only ivermectin distribution was used, and as the main part of the improvement seems to have occurred after the introduction of ivermectin treatment, it seems plausible that the contribution of ivermectin was most important. Aside from this, it should be noted that there might have been an important contribution of nodulectomy.

(I) Bui Gorge. This area is located in Ghana on the lower Black Volta. The limit of the focus is not clearly defined to the south. Most of the flies in this area are savannah flies. Aerial treatment started in 1975 and stopped on 31 December 1996, after 22 years. Annual ivermectin treatment started in 1987.

Prevalence went down from around 60% in 1980 to values around 10-20% in 1997-2001. First CMFL values available were from 1980 and were not extremely high (range 5-25 mf/s), indicating that 5 years of larviciding might have had an effect. ABR was very variable and decreased from values in the range 10000-20000 in 1975 to rather low values in the period 1980-1985 and then increased again to be in the range 10000-20000 in 1996 with an occasional extremely high value (> 50000). Crude ATP declined from values around 1000 in 1975 to low values in 1996 (around 100). Therapeutic coverage increased from 50% in 1987 to > 80% in 1997. Many factors complicate the interpretation of these findings. In the first place, this area is the largest non-stop breeding site in the program. There is a continuous string of breeding sites from Tagadi in the north to Tain-Aboi in the south, and, consequently, this is a very difficult area to control. Then, there has been some nodulectomy done in a few places, but this does not seem to have had much effect. There is also evidence of human migration to and from the south and south-east.

There has been some effect of larviciding, but 22 years of vector control has not brought transmission under control. Ivermectin distribution has improved the epidemiological parameters but has also not interrupted transmission.

(J) Titira / Koupergou. This is a meso- to hyperendemic area located in the eastern part of the program in Togo. The core area consists of the Oti, Keran, Kara, and Mo river basins. It is a

mountainous area with many huge breeding sites in the rainy season. Most of the flies are of the savannah species. Thousands of goldiggers migrate during the dry season from Ghana, Togo, Benin, and Nigeria to the Keran. There are also possible migrants from the south of Togo. Larviciding started in 1977, but results were poor until in 1987 larviciding in the south was started. Aerial treatment was suspended from 1993 until 1996 on the Oti, Keran and Kara rivers. Annual ivermectin distribution started in 1988.

Prevalence came down from very high values (between 50% and 90%) in 1977 to still high values (range: 0-50%) in 2000. CMFL has declined substantially from values around 30 mf/s to very low values, but is in some places not yet zero. ABR has risen considerably in recent years to values around 15000, but this observation was based on data from two capture points only, that had high values throughout the whole period. Crude ATP came down from values around 1000 in some villages to much lower values, but remained still above 100. Only in the last two years there may be an improvement in ATP. It is unclear as to what extent this improvement is attributable to vector control or to ivermectin treatment. Therapeutic coverage was reported to be good (80%) with equally high geographic coverage (96%), but it was noted that this evaluation was made only in static villages and did not include the migrants. Furthermore, distribution of ivermectin is very difficult in this mountainous area. This casts doubt whether geographic coverage is really good enough.

It is clear that there is still a problem in this area. The entomological data suggests that there may be improvement in the last two years. The epidemiological data are far from satisfactory, and there is still significant transmission going on. Recommended further activities are 1) to perform a study of the various fly populations using micro satellites and 2) to perform a study of the effects of population movement with special reference to the impact of ivermectin on transmission.

(K) Milo / Sankarani. The Milo and Sankarani basins are located in the eastern part of Guinea Conakry, and while the Milo is entirely within Guinea, a small part of the Sankarani extends to Cote d'Ivoire. The medium and lower parts of the basins are in the sudano-guinean zone. The lower parts are mountainous with more vegetation. Maximum discharge is reached in September/October. The human population is engaged in agro-pastoral activities, fishing, and mining activities (diamond and gold) the latter mainly during the dry season. These used to be hypo to hyperendemic areas with pre-control prevalence ranging from 4.4% to 88.1% in villages evaluated from 1985 to 1987. There is much migration of flies in these basins. In the lower Milo basin there is a predominance of savannah vectors throughout the year, in the medium part there is a predominance of savannah vectors in the dry season and of forest vectors in the rainy season, and in the upper part forest vectors are predominant throughout the year. In the lower part of the Sankarani basin there is a predominance of savannah vectors throughout the year, while in the medium and upper parts savannah vectors predominate during the dry season, and forest vectors during the rainy season. In the Milo basin, anti-reinvasion and experimental larviciding was done in 1987 and 1988. Full-scale larviciding started in 1989, as was large-scale ivermectin treatment. In the Sankarani basin anti-reinvasion and experimental larviciding was done from 1984 until 1988. In 1989, full-scale larviciding and ivermectin treatment was started. The proportions of parasite strains in infective flies from 1993 to 2000 on the Milo were 52% *O. volvulus* savannah, 14% *O. volvulus* forest, and 32% non-*O. volvulus* (35 infective flies). On the Sankarani, these

proportions were 47% *O. volvulus* savannah, 11% *O. volvulus* forest, and 42% non-*O. volvulus* (36 infective flies).

Prevalence went down from very high values around 80% in 1985 to values < 10% but not yet zero in 2001. There was an enormous pre-control heterogeneity in CMFL values ranging from < 10 mf/s to 70 mf/s. CMFL went down to values very near zero from 1993 onwards. ABR was very high (around 10000 in 1985) and increased to around 20000 in 2000, with extremely high values (> 50000) occurring in some villages. These high values may be the result of reinvasion or of treatment failures. The rise in ABR may be partially explained by the suspension of larviciding in the northern part of the OCP program. ATP values were more favourable, and went down from values between 100 and 2000 in 1984 to below 100 in 2000. Therapeutic coverage went down from 75% in 1989 to around 20% in 1997, which can be explained by the fact that only positives were treated. There seems to be no information on geographical coverage.

There are good trends in the epidemiological data in these basins. The entomological data seems consistent with this, despite the high ABR's in some places. The only logical conclusion seems to be that this is the result of the additional effect of ivermectin treatment. It is recommended as a further action to stop vector control in a good basin in 2002 and implement very good monitoring. This will allow OCP to test whether the strategy of 12 years of combined vector control and ivermectin treatment is indeed sufficient to eliminate the risk of transmission.

(L) Asubende. This is a hyperendemic focus located in the eastern part of the southern extension on the Pru River in Ghana. There is a continuous string of breeding sites along the river with the village Asubende in the centre. Larviciding started in the southern extension in 1988. On the Pru in 1988 and 1989, it was suspended in the rainy season, because of xenodiagnostic studies and because of studies of the impact of ivermectin on transmission. From 1990 until now the lower part of the Pru river was normally treated. From 1994 until 2000 almost all flies caught were of the savannah strain. Very few flies were forest flies (<1%). In the period January 1993 until December 2000 the proportions of flies infected with the various parasite strains were: 48% *O. volvulus* savannah, 20% *O. volvulus* forest, and 32% non *O. volvulus*. Annual ivermectin treatment was started in 1987.

There were favourable trends in the epidemiological data. Prevalence went down from > 90% in 1987 to 20-35% in 1997. CMFL declined from very high values around 75 mf/s to very low but not yet zero values in 1997. The ABR was very variable over the years with maximum values above 40000 in 1978 and 1999, and minimum values around 500 in 1986 and in the period 1991-1994. ATP dropped from values above 3000 in 1978 to values around 200 in about 1991, and remained at that level until 2000. Therapeutic coverage was high (> 80% in 1977). Geographic coverage was good. A new recent evaluation resulted in a therapeutic coverage of 76%, and a geographic coverage of 80%.

It is not clear what happened in this area. Entomological studies indicated that there was little impact from vectors coming from outside. There is some evidence of people from outside coming to this area, but it is not known where these people come from. An important point is how effective vector control has been here. At the moment, the biting rate is similar to pre-control values. There are therefore quite some vectors around.

The entomological data clearly indicate that there is still significant transmission going on. It is therefore impossible to stop ivermectin treatment. The parasite population and prevalence are declining nicely but slowly, and this is probably consistent with significant transmission in addition to treatment. It is difficult to determine what effect ivermectin has on transmission.

(M) Dienkoa. This is a quite limited but severely affected focus, located in the south-western part of Burkina Faso near the border with Mali. It is on the upper part of the Black Volta River and in the sudano-guinean zone with perennial medium sized rivers and savannah vector species. The area is very fertile and characterised by intensive migration and numerous hamlets. Before control started, it was a hyperendemic focus with an ABR of more than 9000, an ATP of 1200, a prevalence of 68% (Pendie), a rather low CMFL of 13.9 mf/s, and a blindness rate of 2.8%. Larviciding started in 1976. There were difficulties in selecting good catching sites representative of the epidemiological situation. The regularly visited sites were changed with time and the network was restructured in 1978/1979. New good sites were selected in 1985, 1986 and 1988, and three of these were regularly visited from 1986 onwards. From 1979 to 1989, larviciding was very difficult, and was done irregularly. This resulted in a resumption of transmission and the detection of a number of newly infected children in 1983 and 1985. No larviciding was done in the period 1987-1988 because of studies on the impact of ivermectin on transmission. Ivermectin distribution started in 1988 with mobile treatment, and was switched to CBTI in 1996, and finally to CDTI. Systematic and widespread ground larviciding was started in 1990, because of the poor results and new infections found, and because some catching points indicated that transmission was still going on. Better epidemiological results were obtained from 1994 up to now.

Over the whole period, prevalence went down from high values in 1975 (around 60%) to values near zero in 2000. CMFL ranged from less than 10 mf/s to just over 30 mf/s at the start, and went down to values near zero around 1993, after which this level was maintained. ABR went down after the start of the Programme in 1974 from values around 2000-4000 to quite low levels, with a sudden increase in 1986 when larviciding was stopped. When vector control was resumed it went down again, but in some places problems with high values remained. ATP followed the same pattern, and was generally low during the period of vector control, but with a recent small rise in one village. Geographic coverage was very poor at the start of ivermectin treatment (about 5 villages treated) but gradually improved until it was over 60 treated villages from 1997 on, but with a serious relapse in 2000 (31 villages). Therapeutic coverage was 50% at the start in 1988 and rose to 85% in 2000.

The situation in this basin is very complex, involving many factors outside vector control and ivermectin treatment. It is therefore not particularly well suited to answer the main questions posed in this report. With all the changes in catching sites, poor geographical coverage, migration, and so on, the impact of ivermectin on transmission is very difficult to ascertain.

Conclusions

The main results in the 15 study areas are given in Table 1, where for each basin the impact of ivermectin on four aspects of the disease problem have been summarised. The first of these aspects is its impact on the intensity of infection as measured by the Community Microfilarial

Load (CMFL). The CMFL is an index of the public health importance of the disease, and onchocerciasis is considered a public health problem when the CMFL exceeds 5-10 mf/s. The second is its impact on prevalence of infection. The third aspect concerns whether or not ivermectin distribution has interrupted transmission. The fourth and last aspect is whether elimination of the parasite has been achieved to the extent that control can be stopped without risking renewed transmission.

All evidence from these study areas clearly shows that ivermectin treatment has been everywhere extremely successful in controlling onchocerciasis as a public health problem. CMFL values are everywhere zero or very near zero, and prevalence of infection is generally quite low.

The difficult questions are coming up when interruption of transmission is considered. There are some areas where it is certain that transmission is still going on after 10-12 years of ivermectin treatment. There are also a few areas where transmission may have been interrupted, but there are still many uncertainties, and further monitoring and research is required to remove all doubt. There is also an important step from the third to the fourth column of Table 1, because stopping ivermectin distribution when low levels of infection, and low but not yet zero prevalences are attained may result in very serious problems. This is illustrated by the results from the Rio Corubal area where the latest data show a serious and unexpected recrudescence. So, even if interruption of transmission has been achieved for some time, if the parasite reservoir is not entirely eliminated, it is a big question whether ivermectin treatment can really be stopped.

A final point is noted regarding the frequency of ivermectin distribution. As far as elimination of onchocerciasis as a public health problem is concerned, annual treatment has done it and there is no need for shorter treatment intervals. The question was raised whether annual treatment should continue or that less frequent schedules should be considered, because when interruption turns out to be impossible, treatment should be maintained for a long time. However, implementing other treatment schedules, and especially less frequent ones, may have important operational consequences as well as implications for the development of ivermectin resistance. This should be further investigated, e.g. by incorporating ivermectin resistance in the simulation models.

Table 1: Impact of ivermectin distribution on four aspects of onchocerciasis infection and transmission.

River Basin	Intervention strategy	<i>Impact of ivermectin treatment</i>			
		(Status in 2001)			
		CMFL \approx 0 (PH problem eliminated)	Prevalence of infection very low (< 10%)	Transmission interrupted (R_x ongoing)	Elimination (control ceased)

Ivermectin only:

R. Gambia (A)	Ivm. 6-monthly since 1989	✓	✓	?	
R. Corubal (B) (up to 1996)	Ivm. 3-monthly 1991-1996	✓	✓	?	
R. Corubal (B) (from 1996 onwards)	No ivm. treatment since 1996	✓	Increasing prevalence	Transmission ongoing	
R. Geba (C)	Ivm. 6-monthly since 1989 and no treatment since 1996	✓	✓	?	?
R. Faleme (D), R. Bafing (E), R. Bakoye (F), R. Baoule (G)	Annual ivm. since 1989	✓	✓	?	
Vina Valley (Cameroon)	Annual ivm. since 1987	✓	Prev. mf ≈20% in 1999	Transmission ongoing	

Ivermectin treatment after vector control:

Bougouriba (N)	Ivm. 4-monthly since 1996	✓	✓	Transmission ongoing	
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Ivermectin + vector control

Tienfala (H)	Annual ivm. since 1987, and (ground) larv. since 1977	✓	✓	?	
Bui Gorge (I)	Annual ivm. since 1987 (3-monthly from 1994-1996), and larv. from 1975-1996	✓	Prev. mf up to 55% in 1998	?	
Titira / Koupergou (J)	Ivm. annual since 1988, and larv. since 1977	✓	Prev. mf up to 50% in 1998	Transmission ongoing	
Milo / Sankarani (K)	Annual ivm. since 1989, and larv. since 1989	✓	✓	✓	
Asubende (L)	Annual ivm. since 1987, and larv. since 1990	✓	✓	Transmission ongoing	
Dienkoa (M)	Ivm. since 1988, and larv. since 1976 (with interruptions)	✓	✓	✓	

Annex 1

Figure 1: Location of the 14 study areas.

[Map omitted]

Annex 2

List of participants.

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Chair TCC:	Prof M. Homeida
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Mectizan Donation Programme (MDP):	Dr Mary Alleman
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IMPACT OF IVR TREATMENT ON TRANSMISSION IN OEPA COUNTRIES
RC Collins

One goal in the Americas is suppression of L3 transmission over the long term, eventually leading to local eradication of the parasite. The magnitude of this task can be appreciated by comparing thresholds of ATP required for elimination of eye disease with that required for maintenance of an autochthonous transmission cycle, or endemicity (ATP is the annual rate of exposure to L3s per person). An ATP of less than 100 is generally associated with the absence of onchocercal eye disease. With *Simulium ochraceum s.l.*, the vector in Guatemala and Mexico, a minimum exposure rate of about 20 L3s is required to maintain an endemic transmission cycle. This number comes from pre-treatment transmission studies carried out in communities with a wide range of infection intensities, from hyperendemic to sporadic, and a force of infection model applied to Guatemalan field data. The important point here is the magnitude of the difference; 20 is 5 times less than 100, and so we will have to work at least 5 times harder, or 5 times smarter to eliminate parasite transmission than eye disease. We don't have good threshold estimates for other new world vectors, but we can expect them to be lower for the unarmed species such as *S. exiguum* than for *S. ochraceum*. Pre-treatment ATPs range from a low of 18 in El Jardin, Guatemala to 3888 with the unarmed *S. guianense* in southern Venezuela. Low pre-treatment ATP does not necessarily mean that transmission can be more easily suppressed. In northern Venezuela, the vector *S. metallicum* is a large unarmed fly with a painless bite that readily becomes infected while feeding on people with low mf skin density. In turn, community mf loads are low with little eye or skin disease so people do not feel sick and consequently are less interested in medication.

The impact of IVR programs on transmission can be assessed in relation to the two goals articulated by the PAHO resolution, elimination of morbidity and elimination of parasite transmission. All countries are on track for elimination of morbidity by the year 2007, our target date under the resolution. This is no small achievement. However, our subject here is eradication, and a country-by-country review on the impact on parasite transmission reveals a "good news, bad news" story. In all cases where parasite transmission has not been interrupted, it has been because some endemic communities within a focus have not received regular semi-annual treatment, or that the depth of coverage has consistently been under 85% of the eligible populations, or both.

The situation in Ecuador is "good news". In 1997, the results of the first, in-depth evaluations after 7 years of consecutive treatments on the Rio Santiago focus were published. In hyperendemic communities, children born after IVR treatment commenced had no infection compared to 64% biopsy positives in 5 yo born before IVR. Average coverage was 91.5%, and this increased from 82.5% in 1990 to 95.0% in 1996 indicating that the endemic communities were well prepared for the first dose, and that acceptance and popularity of the program (which include other health interventions) increased over time. The program was run by the Hospital

Voz Andes and the Catholic Church and financed by charitable foundations. The cost was about \$2 per treatment.

Last year, Ecuador again evaluated 3 sentinel communities in Rio Santiago after 11 yrs of IVR. Vector infection was assessed by PCR with split samples run both in Quito and a reference lab in UAB. A total of 594 pools of 50 flies each were run (29,700 specimens) and none were positive, either for heads (which would indicate L3 infection) or for bodies (which would indicate contact with a mf positive person). On the human side, untreated children born after IVR treatment started had no skin infection, no nodules, and no mf in the anterior chamber. Also, ICT test results on children under 11 yr old were negative. These data indicate that parasite transmission is suppressed in these communities and possibly throughout the Rio Santiago focus. A word of caution is required in extending these results to other areas. In Santiago, the most abundant vector is *S. quadrivittatum*, an armed species with low vector competence. Also, the cytospecies of *S. exiguum* on Rio Sanitago is less efficient than the Rio Cayapa cytotype.

The necessity for semi-annual treatments during the first years of a program was shown in follow-up studies of sentinel communities on the Rio Cayapas last year -- San Miguel, El Tigre, and Corriente Grande. This area started treatments in 1996, with one treatment in 1996 and 1997, semi-annual in 1998 and 1999, then one treatment in 2000. Coverage ranged from 84 to 94%. For El Tigre and San Miguel, we had pre-treatment infection data to compare with the year 2000. In San Miguel, percent of *S. exiguum* with L3s was 0.9 pre-treatment and zero in 2000; for *S. quadrivittatum* percent with L3s was 0.09 before and zero after. For El Tigre, percent infection in *exiguum* was reduced from 1.2% to 0.1, an 11 fold decrease; for *quadrivittatum*, it was 0.26 to zero. For Corriente Grande, we had no baseline, but infection intensity in the human population is greater than El Tigre and biting density of *exiguum* is higher, and percent of flies in the post-treatment evaluation in year 2000 was 0.02%, with no L3s in *quadrivittatum*. In terms of ATP, L3 exposure was reduced from 518 per year to zero at San Miguel, El Tigre from 743 to 34, and Corriente Grande to 17 L3s per year.

We can make some general statements from the Ecuador experience: (I) the coverage required for transmission suppression can be obtained in an operational program. The key to success was the use of local community health workers --- trained to take and update population census, follow-up people who for some reason missed treatment, and to educate the communities about the disease and the drug. While the dollar cost per treatment was relatively low, developing, training and assisting the community workers, however, took a large commitment of time by program managers, time spent in the endemic areas; (II) Suppression of transmission with an armed vector, in this case *quadrivittatum*, can be more readily accomplished than with an unarmed species such as *exiguum*. This confirms our hypothesis stated 1995, and bodes well for Mexico and Guatemala where the only vector is *ochraceum*, an armed species ---- provided, of course, that they can achieve the extent and depth of coverage required; (III) we need a better understanding of the biological significance of low levels of L3 transmission, for example, is 17 L3s per year above or below the threshold for endemicity. Stated another way, are 17 L3s enough to replenish the adult worm population and maintain the reproductive ratio (R_0) at > 1.0 .

Colombia has one endemic community with a total at risk population of 1400. Starting with the second treatment round in 1997, coverage has consistently been above 85%. Serologic and

parasitologic examinations carried out last year were all negative. A PCR evaluation for fly infection is scheduled this year. Based on reported coverage, however, we expect that transmission is suppressed in Colombia.

In the Amazon River basin areas of Brasil and southern Venezuela, the migratory nature of the human population and difficult access makes regular treatments hard to achieve. Brasil has contracted with the NGO coalition to distribute IVR. For the first year 2001, coverage was 76% and 80% of the eligible populations for the 1st and 2 rounds, respectively. Northern Venezuela commenced regular treatments during the year 2000. Their report to IACO 2001 indicates good coverage during the first round of treatment within the year, but poor coverage on the second. In addition, not all endemic communities within a focus were treated.

Mexico has been treating with IVR longer than any other country. The Oaxaca focus appears to be suppressed; ICT tests in children were all negative. Flies were collected during the last transmission season and will be processed by PCR. In the southern Chiapas, transmission is continuing despite reported high levels of coverage. The problem is that some communities do not allow the onchocerciasis brigades to enter at all, and in others that are being treated, certain groups refuse to participate. Reasons include bad experiences with the nodulectomy brigades, and they do not like being skin snipped or palpated for body nodules. Another method of IVR distribution must be developed to get the coverage required for suppression of transmission.

It's ironic that in Guatemala where we have the best understanding of transmission, an armed vector with low competence for developing L3s, and the central offices of OEPA, we also have the poorest record of coverage. Health services were decentralized in the mid-1990's and IVR distribution was disrupted for several years. The program reported about 241,000 treatments in 2001 with less than 1/3 of the communities getting coverage > 85% . In sentinel communities, infectivity in flies showed continued and in some cases increased L3 transmission. Like southern Chiapas, the perception of onchocerciasis control is unfavorable in some communities. MOH workers have many other responsibilities and onchocerciasis is low priority. They also need training in community-based health delivery, how to take and update census, health education, etc.

In addition to IVR, several characteristics of onchocerciasis in the Americas make us cautiously optimistic about elimination. *Onchocerca volvulus* in the Americas is an "island" species introduced some 500 years ago from Africa, and island species are more susceptible to the pressures of extinction because their gene pools and populations are confined geographically and not able to be replenished. When a mf reservoir came in contact with a competent vector, a transmission cycle was established and the disease became endemic. Although the parasite was introduced in many areas --- southern United States and Costa Rica, for examples, --- it became established only in 6 countries, and the endemic areas are relatively small and stable. Vectors in the Americas include both unarmed and armed species. The latter have relatively low vector competence and parasite transmission relies on high biting density. *Simulium ochraceum* is an example where despite its occurrence throughout Guatemala, it reaches population densities required for endemicity only on the western-facing slopes of the Pacific volcanos. New world vectors do not exhibit long-range migratory behavior, and generally stay within a few kilometers of their larval development sites, so re-invasion of infective flies from distant endemic foci is

unlikely. Also, transmission in the Americas is highly seasonal. In Mexico and Guatemala, transmission does not occur during the winter rainy season because the average life span of the vector population is less than the intrinsic incubation period for L3s maturation. In Ecuador, little transmission occurs during the dry season because the rivers drop below the line of trailing vegetation required for larval attachment. This means that IVR treatments can be scheduled for maximum effectiveness against transmission, the first at the beginning of transmission season and the second 4 or 5 months later. On the parasite side of the cycle, once transmission is suppressed and the parasite is eliminated from a particular focus, the probability of re-introduction of a new reservoir is also low.

Finally, all endemic countries have IVR programs up and running and OEPA is filling a pivotal role with a regional perspective. Proof that the strategy works and that semi-annual treatments can be delivered by an operational program can be found in Ecuador and Colombia, but Mexico and Guatemala need a new operational strategy for IVR delivery to insure the coverage required for suppression of transmission.

IMPACT OF IVERMECTIN TREATMENT IN OEPA COUNTRIES

M Sauerbrey

The Onchocerciasis Elimination Program for the Americas (OEPA), headquartered in Guatemala, is the technical and coordinating body of a multinational, multi-agency coalition which acts under the 1991 Resolution XIV of the XXV Directing Council of the Pan American Health Organization (PAHO) calling for the elimination of all onchocerciasis morbidity from the Americas by the year 2007. OEPA has two primary goals, which are to eliminate new ocular morbidity due to infection with *O. volvulus* in the region by 2007. This is also stated as elimination of onchocerciasis as a public health problem by year 2007, and to eliminate parasite transmission in those countries or foci where feasible, for which no time limit has been specified, with the exception of suppression of transmission aimed for 2007. The program implementation is through a coordinated regional effort, which embodies multiple partners, namely the governments of the six endemic countries, PAHO, NGOs, (TCC, LCIF, CBM), industry (Merck), donors (IDB), universities and international agencies (CDC). The elimination strategy is based on semi-annual massive distribution of ivermectin to 85% of the eligible population in all endemic communities to suppress disease transmission and prevent new eye disease attributable to onchocerciasis. Once suppression has been achieved, it must be maintained for a period of 10-15 years after which the adult parasite population, unable to replenish itself, will have perished from old age. At that point, the parasite transmission would be interrupted and mass treatment could be halted without fear of recrudescence of the infection.

The geographic distribution of the disease in the Americas shows a peculiar patchy pattern among six endemic countries (Mexico, Guatemala, Colombia, Ecuador, Venezuela, and Brazil) and constituted by 14 different well circumscribed foci, which are stratified in three groups according to current transmission status: previously endemic where morbidity and transmission may have been eliminated or suppressed by ivermectin treatment, not endemic (suspected), and endemic where transmission still continues.

The majority of the endemicity is found among foci from Mexico, Guatemala, and Venezuela, corresponding to 93% of all regions, and the other 6% distributed among Ecuador, Brazil, and Colombia. Following intense epidemiological field assessment in recent years, the estimates of population at risk for onchocerciasis in the region have been reduced by 86% from 4,700,000 persons in 1995 (two years after the inception of OEPA in 1993) to 544,009 in 2001, with a corresponding Ultimate Treatment Goal (UTG) of 440,861 eligible persons to receive treatment, who are found distributed in 1969 communities of which 211 (11%) are classified as hyper-endemic, 566 (29%) as meso-endemic and 1,192 (61%) as hypo-endemic. A total of 701,873 ivermectin treatments were provided in 2001 in the region, representing a 952% increase over treatments in 1993, when the regional initiative was launched. This figure constitutes 80% of the regional goal of providing two treatments per year to all eligible people at risk. Treatments took place in all six endemic countries in the Americas but only Colombia, Ecuador, and Mexico reached the 85% of their treatment goals.

Monitoring of program impact is being accomplished by periodic in-depth evaluations in hyper-endemic sentinel communities. To document the elimination of morbidity, parasitological (Mf in skin), and ophthalmological (MfAC and PK) indicators are used. For suppression of transmission, Polymerase Chain Reaction (PCR) is utilized to detect parasite DNA in pools of black flies and lately, serology, measured by the oncho Immuno-Chromatographic (ICT) antibody card Test to the antigen Ov 16 in children less than 6 years of age.

Results obtained with the serological test during 2001 surveys in different transmission zones in six foci from Colombia, Ecuador, Guatemala, and Mexico, showed a strong indication that suppression of transmission is being achieved in Oaxaca and Colombia and continue suppressed, since initially declared in 1997 by Guderian et al, in the Santiago River in Ecuador. Suspected not to be endemic in both North Chiapas focus, Mexico as well as in the Huehuetenango area in Guatemala, and lastly, confirmed still ongoing transmission in the case of the South Chiapas focus.

As has been shown, regional treatment with ivermectin has reached a level were it is highly likely to halt new ocular morbidity attributable to onchocerciasis by 2007. However, considerable technical assistance to countries will be required to satisfactorily document this impact.

In preparation to carry out the task; it was resolved that certification of elimination must be done on an objective basis, according to internationally accepted criteria and therefore, specific guidelines required by the countries to monitor compliance of their programs, to document interruption of transmission and ultimately, the cessation of ivermectin treatments and Certification of Elimination were the subjects at a WHO conference celebrated in Geneva in September 2000 where the final guidelines and Criteria for Certification of Elimination of Human Onchocerciasis to rule of the process were finally established. The process comprises basically four well-defined phases: Pre-suppression, Post-suppression, Pre-certification, and Post-endemic surveillance phase, after final Certification is granted.

In conclusion, the goal of complete suppression of *O. volvulus* transmission throughout the Americas is feasible and ambitious; and success will depend largely on gathering the political will and financial resources for a sustained, high level of treatment coverage, twice per year, in all endemic communities.

ONCHOCERCA-SIMULIUM VECTOR-PARASITE COMPLEXES –
THEIR RELEVANCE TO ERADICATION
B Duke

A. The situation in Africa

The concept that there are different *Onchocerca-Simulium* complexes, each confined to a particular geographical or bioclimatic zone, originated in West Africa as a result of research into the reason why blinding onchocerciasis was much more prevalent in the savanna zone than in the forest zone.

In the Republic of Cameroon, when ‘forest’ *S. damnosum* s.l. (now known to be *S. squamosum*) were fed on carriers of *O. volvulus* microfilariae from the forest zone, the microfilariae (mfs) were ingested in large numbers and developed well into infective larvae; but, when ‘Sudan-savanna’ *S. damnosum* s.l. (now known to be *S. damnosum* s.s. and *S. sirbanum*) were fed on these same volunteers, although their mfs were ingested in large numbers, only very few or none of them developed into infective larvae. The reverse was true in feeding experiments on *O. volvulus* mfs carriers from the Sudan-savanna zone. Their mfs would develop well in the ‘Sudan-savanna’ species of *Simulium* but scarcely at all in the ‘forest’ species. In Cameroon the dividing line between the two bioclimatic zones was fairly sharp and coincided with the escarpment just north of Ngaoundere which descends on to the Benue Plain (Duke, Lewis and Moore, 1966).

Further work on the same lines was then carried out in forest and savanna sites at various places in Malabo, Nigeria, Sierra Leone, Burkina Faso and Senegal; and later by OCP workers in Cote d’Ivoire and elsewhere..

Later, work in experimental rabbits showed that the mfs of the ‘Sudan-savanna strain’ of *O. volvulus* were very much more pathogenic than those of the ‘forest strain’ when inoculated into the cornea (Duke & Anderson, 1972), whereas there was no detectable difference between the pathogenicity of the two strains when inoculated into the ocular fundus (Duke & Garner, 1976). Probably this was a major factor leading to the greater prevalence of anterior segment onchocercal blindness in the hot savanna regions of West Africa.

The above findings provided a certain impetus to the establishment of the Onchocerciasis Control Programme in the Volta River Basin, for they implied that control measures could be applied in the savanna zones of the proposed control area, where onchocercal blindness was a severe socio-economic problem, without any great danger of reintroduction of infection from the forest zones to the south.

However, it must be remembered that the division between the between the “severely blinding” onchocerciasis of the hot West African savannas and the “less blinding” onchocerciasis of the forest is neither absolute nor always very sharp. Although the identification of persons, communities and areas, in which the different strains are found, has been made much easier with the development of DNA probes and PCR techniques, which can distinguish between the two strains of parasite with a high degree of confidence (Zimmerman et al., 1992), we are not dealing with impenetrable barriers. This for four reasons:-

1. The inability of the mfs of one strain to develop in vectors of the other strain is not absolute. A small proportion of mfs can succeed in crossing the barrier and, in the presence of appropriate selection pressure, this proportion may increase.
2. There are some vector species, notably *S. soubrense*, which will permit the development of mfs of either strain.
3. The increasing development of West African countries over the last few decades has resulted in much more frequent migration of workers and their families between the savanna and forest zones, thus tending to break down the barriers between these two main parasite-vector complexes.
4. Destruction of the forest environment by agriculture and logging may lead to the spread of the savanna vectors southwards.

It must also be remembered that, at present, virtually all we know about *Onchocerca-Simulium* complexes is limited to West Africa. We have no knowledge of the complexes that exist in Central and East Africa, where there are many vectors of the *S. neavei* complex as well as other members of the *S. damnosum* complex and, in the Democratic Republic of the Congo, doubtless *S. albivirgulatum* will also have to be considered.

In the present author’s opinion, it is unlikely that our knowledge of different *Onchocerca-Simulium* complexes in Africa will facilitate either the zonal elimination or the ultimate continental elimination of the parasite to any useful extent.

B. The situation in the Americas

The early work on *Onchocerca-Simulium* complexes in Africa was later extended to the Americas by way of investigations first in Guatemala (De Leon & Duke, 1966) and later in Venezuela (Duke, 1970).

One remarkable thing about the Guatemalan vectors (*S. ochraceum* being the main vector, with *S. metallicum* and *S. callidum* as subsidiary vectors) is their ability, when taking a blood-meal, to attract large numbers of mfs (increased by a factor of X 10-25) of the Guatemalan strain of *O. volvulus* towards their mouth-parts. This attraction, which probably results from some attractant in their saliva, means that *S.ochraceum* can ingest sufficient mfs to counteract the loss of the large numbers of them which perish from damage when passing through the cibarial armature. *S. metallicum* and *S. callidum*, which have no armature, usually succumb to the vast numbers of mfs which they ingest as a result of this attraction.

By contrast, this salivary attractant is not effective on the mfs of either the West African ‘forest’ or ‘Sudan-savanna’ strains of *O. volvulus*. Very few mfs of the West African ‘forest’ strain ingested by *S. ochraceum* developed to infective larvae, and none of those of the West African ‘Sudan-savanna’ strain reached the L3 stage.

In northern Venezuela, the main vectors, *S. metallicum* and *S. exiguum*, both exerted a marked attraction on mfs of the Venezuelan strain of parasite and a reasonable proportion of the ingested mfs completed their development. By contrast the mfs of the two West African strains did not respond to this salivary attraction and no mfs of either African strain managed to develop to infective larvae in these vectors (Duke, 1970).

In terms of the effect of these findings on the Onchocerciasis Elimination Programme in the Americas (OEPA), I believe we may say as follows:-

1. The numbers of *O. volvulus*-infected Africans who are likely to travel to and settle in any of the onchocerciasis endemic areas in the Americas must be totally insignificant, as must any traffic in the reverse direction. Any infected Africans who did reach the endemic areas in the Americas today would not constitute a serious source of infection owing to their poor development to L3s. Thus there is little danger of re-infection from Africa.

2. It is probable that the complex in Guatemala and that in Chiapas, Mexico are the same, but they may perhaps be different from that in Oaxaca, and may well be different from those in South America. Likewise those in Ecuador, southern Venezuela and Brazil may be the same but different from those northern and eastern Venezuela. As far as I can ascertain, there has been very little work done on the compatibility or otherwise of the *Onchocerca-Simulium* complexes in the different infected countries in Latin America. Only the recent work of Basañez et al. (2000) indicates that there is little or no possibility of the strain of *O. volvulus* from north-eastern Venezuela, which is transmitted by *S. metallicum*, being transmitted by the main vector in the Amazonian region, *S. oyapockense*.

3. Further investigations to determine the identity and range of the various complexes in the Americas might be useful in the context of the OEPA. Elimination of the foci in South America might be feasible, one by one, with minimal risk of re-infection from adjacent foci; and the same might be true for Guatemala/Chiapas and Oaxaca in Central America.

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VECTOR SPECIES, TRANSMISSION EFFICIENCY,
AND FREQUENCY OF IVERMECTIN TREATMENT

E Cupp

Transmission of *Onchocerca volvulus* is greatly influenced by phenological factors which shape population size and activity of *Simulium* vector species. Rainfall and temperature are important and collectively regulate abundance and flight activity of vector black flies; temperature also influences rate of development of the parasite in the vector (extrinsic incubation period).

Intrinsic physiological and behavioral factors control vector competence and regulate *Simulium* infection and subsequent transmission efficiency. Host selection by local vector species is a key feature in determining the number of *O. volvulus* infective stage larvae (L₃s) transmitted per person per year. Many vector taxa in the *S. damnosum*, *S. exiguum* and *S. metallicum* species complexes are zoophilic and may blood-feed indiscriminately on humans and ungulates. This process often results in the transmission of *O. volvulus* L₃s to cattle (a dead-end host) and diminishes the annual transmission potential of the parasite to humans (zooprophyllaxis). Other vector species such as *S. ochraceum* (species A) are highly anthropophilic and feed recurrently on human hosts. The presence of a cibarial armature in some vectors is a critical morphological feature that serves to regulate the number of microfilariae ingested in a blood-meal that remain viable and can infect the thoracic musculature of the fly. This chitinous structure occurs in the foregut and is sharply toothed in several New World vectors, damaging a large percentage of ingested microfilariae as they pass posteriorly in the blood-meal. As a result, many microfilariae are killed or incapacitated and unable to penetrate the midgut. Important vector species that are “armed” (possess the cibarial armature) include *S. ochraceum*, *S. oyapockense* s. l., and *S. quadrivittatum*. For this reason, these species have a higher infection threshold than “unarmed” vectors and transmission is most readily affected when the community microfilarial load (CMFL) is altered by drug treatment. Black flies also have active immune responses which rapidly kill *O. volvulus* microfilariae as they enter the hemocoel. Clearance is rapid and killing presumably occurs as a result of secretions by hemocytes (“leucocytes”). While somewhat controversial, recent laboratory evidence has confirmed early field observations that black fly saliva contains one or more substances that serve to orient microfilariae to the bite site and enhance vector infection. Other salivary factors such as very powerful vasodilators may also cause microfilariae to be swept into the hematoma created by the vector where they are ingested in the blood-meal.

As a result of the interactions between these climatic and intrinsic factors, variation occurs in the natural infection rate (mean number of *O. volvulus* L₃s per vector species) in different onchocerciasis foci. In populations of forest species of *S. damnosum*, the mean number of L₃s per infective fly ranges from 4-6 depending upon the cytotype/cytospecies but just over 2 L₃s in the major savanna vectors (*S. damnosum* s. s. and *S. sirbanum*). *Simulium ochraceum*, the principal

vector in Guatemala and southern Mexico, typically has 1.5 - 2.0 *O. volvulus* L₃s per infective fly whereas *S. exiguum*, a vector in northern South America has 3 L₃s.

Introduction of ivermectin (Mectizan) into the community quickly alters this steady state system. Because of its rapid microfilaricidal properties, there are immediate changes in parasite uptake by the vector which subsequently down-regulate transmission of L₃s. In a hyperendemic savanna focus in Ghana, a single annual treatment reduced the CMFL by 68-78%, resulting in an initial reduction in transmission of 65-85% during the first 3 months after treatment. However, transmission resumed at an unacceptably high level after a year. In a forest focus in Liberia where *S. yahense* is the vector, two treatments were given at annual intervals, reaching 58 - 60% of 14,000 people in the study. The number of infective flies with *O. volvulus* L₃s was reduced by 81.7 - 89.3%. Two years following treatment, there was a 44.5% reduction in age-adjusted incidence of children 7-12 (from 16.4% to 9.1%).

Because the skin is re-populated with sufficient *O. volvulus* microfilariae to infect most vectors at roughly six months post-treatment, biannual ivermectin treatments of some communities in Latin America have been shown to suppress vector infection and interrupt transmission. In Guatemala, the effects of treatment at roughly 6 month intervals in 3 communities/transmission zones was followed over a 30 month period. Coverage averaged 80.7% of the eligible population and community microfilarial densities were reduced to levels considered to be at or below the infection threshold for *S. ochraceum*, the vector. Thus, this regimen affected a large segment of the population that had previously been infective for the vector population but was no longer able to infect flies. As a result, there were significant changes in transmission parameters, i. e. flies with infective stage larvae/number of L₃s per 1,000 parous flies, the mean infective biting density, and mean transmission potential. In one location (Los Andes), transmission was blocked. In the Rio Santiago focus in Ecuador, a strategy was used of giving ivermectin treatments biannually in hyperendemic communities and annually in meso- and hypoendemic communities over a 5 year period. Coverage levels were high, with 81.9% to 98.0% of those eligible receiving the drug at each treatment interval, resulting in a reduction in the geometric mean microfilarial density from 19.3 mf/mg of skin to 0 (as indicated by biopsies from 120 randomly selected individuals). The overall rate of infection of the vector population, a mixture of *S. exiguum* and *S. quadrivittatum*, declined from 1.1% in 1989 to 0.08% in 1996. No new nodules were detected in the population after 1994 and no children under 5 became infected over the observation period, suggesting that transmission of *O. volvulus* was interrupted in the study area.

LONG DISTANCE MIGRATIONS OF BLACKFLIES AND ONCHOCERCIASIS TRANSMISSION

P Guillet

Onchocerciasis control, elimination or eradication?

Long distance migrations of blackflies will be discussed in this paper in relation to transmission and to the possible elimination of *Onchocerca volvulus*. An effective control of onchocerciasis transmission by repetitive treatments with ivermectin has been achieved in few foci, both in Africa in the Onchocerciasis Control Programme area (OCP) and in the Americas, especially in isolated foci. By extension, the possibility of eliminating onchocerciasis through a massive effort on ivermectin distribution has been envisaged.

Elimination of onchocerciasis as a disease of public health and socio-economic importance has been the primary objective of the African Programme for Onchocerciasis Control (APOC). In the APOC strategy which is based on community directed treatment with ivermectin (CDTI), there is no direct attempt to control transmission of the parasite *Onchocerca volvulus* except in very few isolated foci where durable elimination of the vector(s) is being envisaged. Another Programme for Elimination of Lymphatic Filariasis (ELF) has recently been launched, also based on community treatment using a combination of two micro-filaricidal drugs, ivermectin and albendazole. Both APOC and ELF almost entirely rely on a drug delivery strategy with a clear objective of disease control. Although not clearly stated, it is felt that this strategy could lead to a complete interruption of transmission if it is systematically and long enough implemented and, as a consequence, to the elimination of the respective parasite populations. The operational objective of OCP when it was launched in 1974 was to interrupt transmission of *O. volvulus* long enough (at least 15 years) through systematic and uninterrupted vector control operations in order to achieve a complete elimination of the parasite reservoir in human populations in the Programme area and to ensure there will not be recrudescence thereafter. Elimination is also the objective of the Onchocerciasis Elimination Programme in the Americas (OEPA), based on ivermectin distribution.

Blackfly, a long range flyer

To be effective, a strategy based on transmission control of parasites such as *O. volvulus* and *W. bancrofti* has to take into consideration a number of essential factors relating to vectors, among which their flight range and in the case of blackflies, their ability to migrate over long distances. This is of key importance, especially in Africa with onchocerciasis vectors belonging to the *Simulium damnosum* complex. Soon after OCP started in 1975 in West Africa, it appeared that the objectives could not be achieved in treating only the Programme area because of seasonal migrations of blackflies and reinvasion of treated river basins by vectors coming from untreated surrounding areas. Migration of insects over long distances was already well known (Johnson,

1969), especially for adult stage simuliidae due to their strong flight and dispersive ability (Hocking 1953) and *Simulium damnosum s.l.* (Hitchen & Goiny, 1966, Ovazza *et al.*, 1967). This ability was later confirmed by lab studies on flight performances of *O. ornata*, a palearctic blackfly species (Cooter, 1982) and several species of the *S. damnosum* complex from West Africa (Cooter, 1983). Blackflies are characterised by the presence of strong and very developed thoracic muscles, important amount of abdominal fat body at emergence and ability to feed on plant nectar. These three attributes are in favour of long range flight capacity. Another important factor involved is their longevity since migrations take time. It was already estimated long ago that life duration of *S. metallicum*, a blackfly species from Central America was quite long (30 to 85 days, Dalmat, 1952). More recent data from West Africa have confirmed this figure (see below).

Seasonal migrations of blackflies are very difficult to detect in natural conditions. In practice, it is possible only if very large areas including several contiguous river basins are simultaneously submitted to systematic larviciding and if local production of vectors is fully interrupted. In these conditions, reinvasion by adult flies coming from outside these areas can be detected through exhaustive entomological surveys to ensure there is no local production of flies inside the treated area. This was possible only in the framework of large control programmes such as the OCP with adequate logistic. Some tools such as radio-labelled isotopes or molecular markers could not be used or have been available only very recently. It is unclear in the current state of knowledge whether molecular markers may be of practical help in investigating long distance migrations in blackflies considering complexity of migration patterns and long distances involved.

In the OCP area, a number of detailed studies over a 10 years period involving dozens of consultants and professional entomologists was necessary to document long distance migrations of blackflies, especially in the western area of the Programme. These studies were carried out with the objective to better document epidemiological impact of vector migrations, to identify the geographical origin of reinvading flies and to propose solutions to prevent this phenomenon. The origin of reinvasion was first investigated at the end of the seventies through comprehensive entomological surveys carried out simultaneously in different river basins and at regular intervals between the reinvaded areas and the suspected source of reinvasions. In Côte d'Ivoire and southern Burkina, because of the remarkable correspondence in time and space between blackfly "waves", it was shown that savannah species of the *S. damnosum* complex were able to fly over very long distances, up to 500 km, when assisted by winds (Johnson *et al.*, 1985). It was also assumed that flies were migrating by successive flights over a 4 to 5 week time. Most of the flies reinvading treated areas were very old with exhausted fat body and a remarkably high level of infestation by *O. volvulus* (Walsh 1977, Garms *et al.*, 1979).

In the north-western part of the Programme, another approach was developed in treating, progressively and westwards, all potential sources of reinvasion and closely monitoring the impact on fly populations and transmission in both treated areas and suspected sources. These investigations, again complex, long and costly, have unambiguously confirmed the very long flight range of savannah species of the *S. damnosum* complex, flies migrating from northern Sierra Leone to western Mali in about 4 to 5 weeks with an average of 15 to 20 km/day (a summary to be found in Baker *et al.*, 1990). Simultaneous investigations based on pteridine concentration in the head of reinvading flies confirmed they were very old, from 30 to 60 days

(Cheke *et al.*, 1989). The main reinvasion axis in the western part of the OCP was from the South West to the North East at the beginning of the rainy season, monsoon winds playing a major role in the dispersal of flies. Reinvasion occurred as well in the eastern part of the OCP but with different seasonal and geographical patterns (Garms *et al.*, 1982, Cheke & Garms, 1983).

Circumstantial migrations of blackflies based on climatic events also occurred at a smaller scale and different times in the year, implying different species, e.g. forest species migrating in 1986 from central Côte d'Ivoire to savannah areas of south-western Mali. Some migrations also occur in forest areas: *S. sanctipauli* migrated from southern Côte d'Ivoire to southern Ghana, importing insecticide resistance in river basins far from the OCP area which had never been submitted to any larviciding. Long range migrations in savannah areas also had a significant impact on the dynamics of insecticide resistance. Before OCP extensions, yearly massive introduction of flies free of resistance genes originated from non treated areas had an effect of “dilution” of resistance in vast treated savannah areas. When insecticide treatments started in the extension areas, resistance developed locally almost immediately although the vector populations were fully susceptible just before treatments started. The likely explanation found at that time was the occurrence of reverse migrations from the initial Programme area. This reverse migration was later confirmed when OCP stopped vector control operations in northern parts of the original Programme area. It was occurring mainly at the beginning of the dry season, bringing flies from non treated areas the north-east to treated areas in the south-west, assisted by northern cold winds (“Harmattan”). This phenomenon was also suspected when important populations of savannah flies were collected in evergreen forest areas of Liberia (Garms, 1987).

Migration over long distances is an essential adaptive phenomenon which allows blackflies to quickly colonise vast savannah areas where rivers stop flowing for several months during the dry season. The same monsoon winds which bring rains also bring blackflies more or less simultaneously, first females being detected the same day when first rains fall and rivers start flowing (Bissan, pers. comm.).

Operational significance of long range migrations of vectors in the OCP area

When migrating over long distances, onchocerciasis vectors bite humans either before migration started or on their way, getting infected with *O. volvulus*. The yearly and massive introduction of new young parasites in the treated areas through reinvasions made virtually impossible to eliminate the parasite reservoir in these areas. This is why OCP, originally planned for 15 years in 7 countries (654,000 km²) area, had to extend its vector control operations to 11 countries (1.2 million km²). These important extensions including all known and potential sources of reinvasion were treated with the same objectives and the same strategy as in the original area. This approach was the only realistic option for making the whole OCP area free of the blinding species of the parasite *O. volvulus* and to prevent reintroduction of this parasite by long distance migrating vectors. Instead of ending around 1992, OCP operations had to be extended over an additional period of 10 years, up to 2002.

Blackfly migrations and prospects for onchocerciasis elimination

In Africa, where *O. volvulus* and its vectors have long co-evolved, most of the vector belongs to the *S. damnosum* complex. The distribution of the disease corresponds to the distribution of the vectors. There are almost no areas colonised by vectors which are onchocerciasis free. This wide distribution and close overlapping of vectors and parasites might at least partly result from ability of vectors to disperse and transmit the disease to almost all riverine populations exposed to the bites of the blackflies. In contrast, in the Americas, introduction of onchocerciasis with slaves from Africa has been recent and distribution of the disease is very focal with a much wider distribution of the vectors. In addition, in comparison to Africa, vector species are more diversified.

Because of the very focal distribution of onchocerciasis in the Americas, the small size of affected communities, especially in Mexico, Guatemala, Colombia and Ecuador, migration of flies, if any, do not constitute *a priori* a potential problem in transmission control. With good coverage and timing in ivermectin distribution, interruption of transmission has already been achieved in some foci and prospects for onchocerciasis elimination in those foci are good. The situation might be more complicated in forest areas of Venezuela and Brazil. Due to inaccessibility to and dispersion of affected human communities, relatively little is known about transmission, the bio-ecology of vectors, their distribution and ability to migrate.

In Africa outside the OCP, because of the complexity, the logistic implications and cost of such studies (see above), it will be very difficult to study long distance blackfly migrations and to get a clear picture of this phenomenon and its epidemiological significance. Nevertheless, in all areas where vectors belong to the *S. damnosum* complex, it is reasonable to assume that such migrations do occur comparable to that observed in West Africa, especially in savannah areas. If a transmission control strategy is implemented with the long term objective of onchocerciasis elimination, it is essential to take into consideration migration factors and its epidemiological consequences, including the introduction of parasites in areas under control. The APOC strategy is almost entirely based on disease control through a yearly CDTI. This strategy, as it is implemented, is unlikely to result in effective and sustainable control of transmission. Some vector control interventions have been envisaged in areas where local elimination of the vector(s) appear to be achievable. When these vectors belong to the *S. damnosum* complex and in the absence of well documented migration studies, it will be difficult to assess the feasibility of this approach. E.g. Bioko island in Equatorial Guinea where possible elimination of the vector(s) is currently envisaged is located about 50 km from the main land, a reasonable flight distance for the local vector. Last, when assessing prospects for onchocerciasis elimination, blackfly migrations are not the only factor to consider since long range and sometimes massive human migrations do also occur throughout the whole of Africa (this aspect is not discussed in this paper).

In the OCP area, despite extensive entomological studies carried out during more than 20 years, it is difficult to assess precisely the respective role of vector and human migrations in the persistence of a number of residual parasite populations after more than 20 years of intensive and continuous vector control, combined for several years with a good ivermectin coverage. If a complete elimination of the parasite populations has not been achieved by the OCP, combining

massive vector control and good coverage of ivermectin treatment, it is very unlikely it can be achieved through ivermectin distribution alone, especially when implemented by national health structures struggling with shortage of staff and resources.

Long range migrations of blackfly populations in Africa are a good indication of their adaptive response to environmental changes, either seasonal or long term changes such as deforestation. It is also an important factor involved in the long term co-evolution of vector, parasite and human populations. The situation of onchocerciasis before any intervention could be seen as very “stable” in comparison to malaria. Controlling the disease at a continental level in Africa through CDTI is the ambitious but achievable objective of the APOC. Interrupting transmission and bypassing adaptive response of the vectors would be quite another challenge.

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**ONCHOCERCIASIS CONTROL: FEASIBILITY OF ELIMINATION AS A PUBLIC HEALTH PROBLEM
AND OF ELIMINATION OF TRANSMISSION**
JDF Habbema

Introduction

In order to improve our understanding of the epidemiology of onchocerciasis in the river basins of the OCP area included in this study, and to assess the impact of the interventions, both empirical data from river basins under long term (exclusive) ivermectin treatment and computer simulations using the ONCHOSIM simulation program were carried out.

A key question was whether ivermectin by itself could lead to elimination in the low to meso endemic areas covered by this study. Elimination would justify cessation of treatment after elimination has been reached. Thus, it is important to know whether recrudescence can be expected after cessation of ivermectin treatments. If so, control may have to be maintained indefinitely.

An additional advantage of the simulations is that it provides a further validation of ONCHOSIM. How do the ONCHOSIM predictions compare to the OCP experience? ONCHOSIM was developed on the basis of data from the Ivermectin community trial in Asubende, Ghana. A correct prediction of the course of epidemiological parameters under the impact of ivermectin treatment would provide additional credibility to this tool and improve its reliability in guiding post-OCP control measures.

Methods

The epidemiological data was taken from OCP databases. Basins controlled by ivermectin mass treatment only were studied. These basins were: the Faleme, Bafing, Bakoye, and Baoule basins with a yearly ivermectin treatment, the Rio Gambia with a 6-monthly treatment, and the Rio Corubal with a 3-monthly treatment schedule (Figure 1).

The ONCHOSIM microsimulation program was used. The quantification of ivermectin effectiveness was based on the community trial in the Asubende basin. ONCHOSIM parameters defining the endemicity level were generally chosen to reflect both observed entomological parameters and observed epidemiological parameters. Ideally these should be consistent, i.e. when ABRs etc. as observed are used in ONCHOSIM, epidemiological output (prevalence, CMFL) should mimic observed values. However, discrepancies between biting rates experienced by fly catchers and inhabitants of villages may lead to apparently inconsistent results. Other factors that could lead to discrepancies between entomological and epidemiological parameters are vector properties and behaviour. While in Asubende *S. damnosum* s.s. dominates and zoöphily of vectors is generally low, this may not be the case in all of the basins included in this

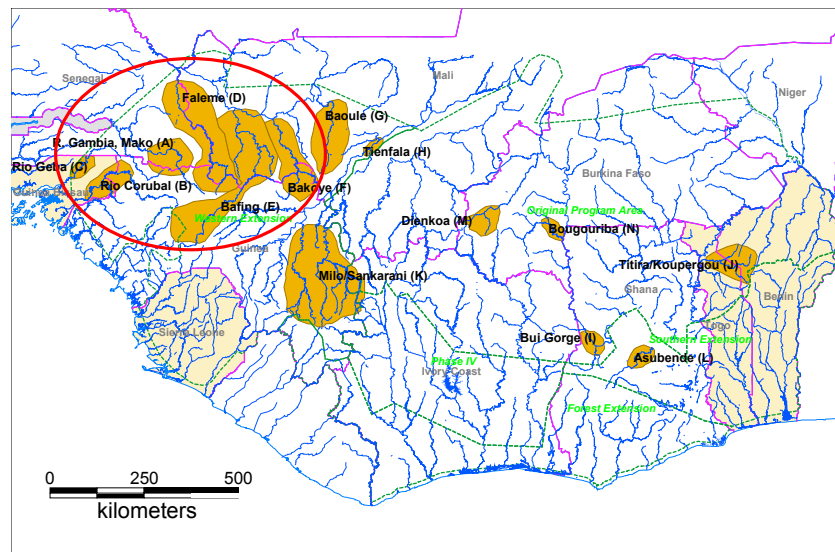
study. In fact, there are indications (differences between ATP and adjusted ATP) that zoöphily in the Gambia basin may be higher than in Asubende, and we have chosen to take a slightly higher value of this parameter in that basin. However, precise estimates of zoöphily appeared hard to come by as most pertinent entomological observations were made during the period that ivermectin was used. Use of ivermectin automatically increases the ATP / adjusted ATP ratio, as human bites should infrequently lead to ingestion of mf, while animal bites can still be successful.

Our approach was not to simulate all available data points in all basins, but rather select a ‘typical’ village from each of the basins included in the study. Coverage rates of ivermectin treatments were taken as reported. Generally, therapeutic coverage rates were taken as ‘the’ coverage rates, but adjusted slightly downwards when geographical coverage was poor. This choice was motivated by the assumptions that 1) villages with epidemiological data should generally have been included in the geographic coverage, and 2) first line villages presumably have a high probability of being covered, and a low geographic coverage is presumably due to the omission of second and third line villages. We have no hard evidence that these assumptions are correct, but they seem reasonable.

This model which uses the Asubende quantification adapted to reflect the trends in epidemiological parameters in the different basins studied in this report, is called the ‘basic’ model.

Where uncertainty regarding coverage levels existed (e.g. geographical coverage variable or low), simulations were repeated with different coverage levels. This was also done to explore whether recrudescence in the Corubal focus might have been caused by unduly optimistic reported ivermectin coverage rates. Another uncertainty factor was the macrofilaricidal effect of ivermectin when ivermectin was used more than once annually. Thus, instead of a 35% macrofilaricidal effect per treatment, simulations assuming a 19% macrofilaricidal effect were also done. As the four basins of Faleme, Bafing, Bakoye, and Baoule were very similar in terms of epidemiology and intervention strategy; they were treated as one basin from the point of view of ONCHOSIM simulations.

Fig. 1: Map showing the locations of the basins studied within the area covered by the OCP. In vitro predictions of elimination (Winnen et al, Bulletin WHO, 2002, in press)



Recrudescence occurred in the Rio Corubal focus. This appeared hard to attribute to ‘endogenous’ recrudescence, i.e. due to residual infection in the communities for which epidemiological data were available. Thus immigrating infected flies were assumed. These flies could have become infected in nearby villages that had poor coverage or have migrated from non-local foci. This is not clear

Graphs of observed prevalence of mf, and of observed CMFL both plotted against time are presented, with the simulation results superimposed. The thick lines at the top of the graphs indicate the period over which actual ivermectin treatment was implemented; the extra tickmarks on the inside at the top and at the bottom of the plots indicate the times at which ivermectin treatment was given in the simulations.

The purpose of this study was to estimate, using ONCHOSIM simulations, the duration of ivermectin mass treatment programs achieving elimination of infection with a .99 probability under different pre-control endemicity and coverage levels. To this end, a very large number of simulations were performed (based on the standard Asubende quantification) for an equally large number of combinations of endemicity levels, coverage levels, and durations of treatment. For each simulation it was noted whether elimination was achieved or not. This last variable was then used as the outcome variable in a logistic regression model, having endemicity level, treatment coverage, and treatment duration as predictors. This model allowed us to estimate the conditions (i.e. specific combinations of endemicity level, treatment coverage and duration of treatment) under which it is possible to achieve elimination with a .99 probability.

In Figure 2, an example of the output of an ONCHOSIM run is shown. In Figure 3 it is shown how the required duration of ivermectin mass treatment varies with pre-control CMFL level, and with treatment coverage.

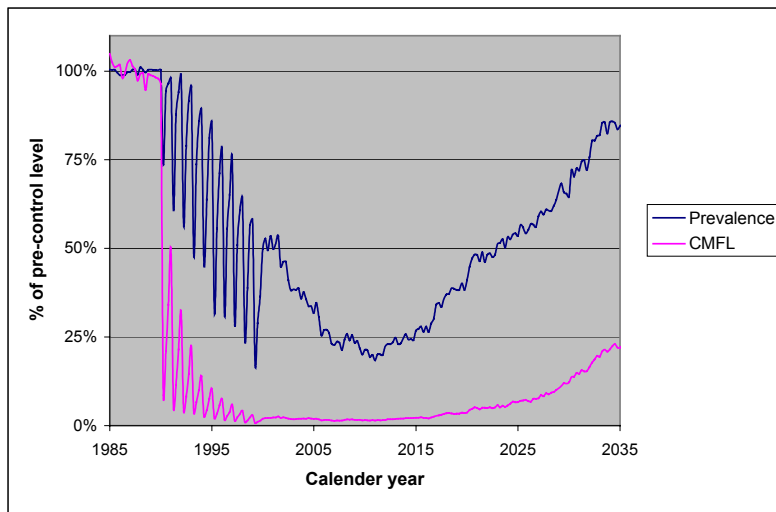
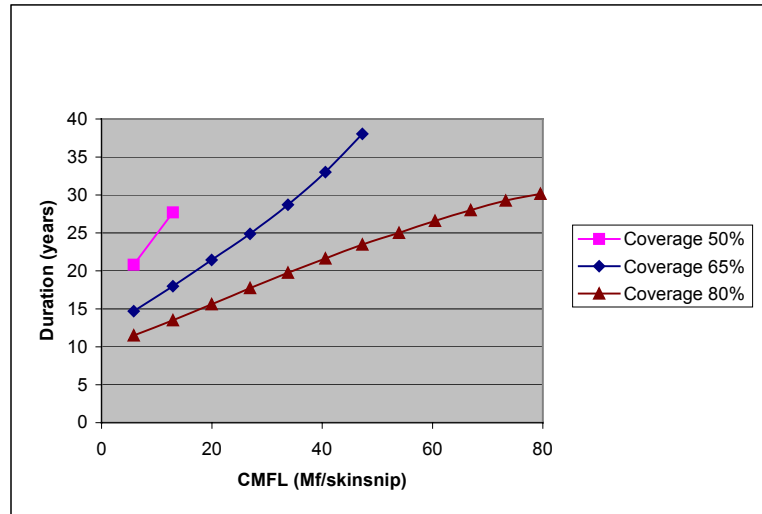


Fig. 2: Output of an ONCHOSIM simulation run. Results of 10 annual dosages with a coverage of 65% in a village with pre-control CMFL of 30 mf/ss (Winnen et al, Bulletin WHO, 2002, in press).

Fig. 3: Example of how the required duration for a .99 probability of elimination, varies with CMFL and coverage level. Annual treatment intervals and medium individual variation in biting rates were assumed (Winnen et al, Bulletin WHO, 2002, in press).



Results for the Faleme, Bafing, Bakoye, and Baoulé basins

These are very similar basins located in the Western Extension across the borders between Mali, Senegal, and Guinea. These were all mostly meso endemic foci with pre-control prevalences around 60% (range 10-80%), and pre-control CMFL values around 10 mf/s. Annual ivermectin mass-treatment started in 1989. The therapeutic coverage was around 80%. The geographic coverage may not have been very good. There were very favourable trends in the epidemiological indicators with CMFL reaching values near zero in 2001, with prevalences coming down under 10% (Figure 4). The ONCHOSIM simulations reproduced the average behaviour of villages in these basins accurately. Predictions for the years 2000-2002 were still positive (as was also observed in several villages) but even if ivermectin would be discontinued, elimination would still be achieved (according to ONCHOSIM). The actual response to annual ivermectin treatments, of prevalence and CMFL, in many villages, is striking.

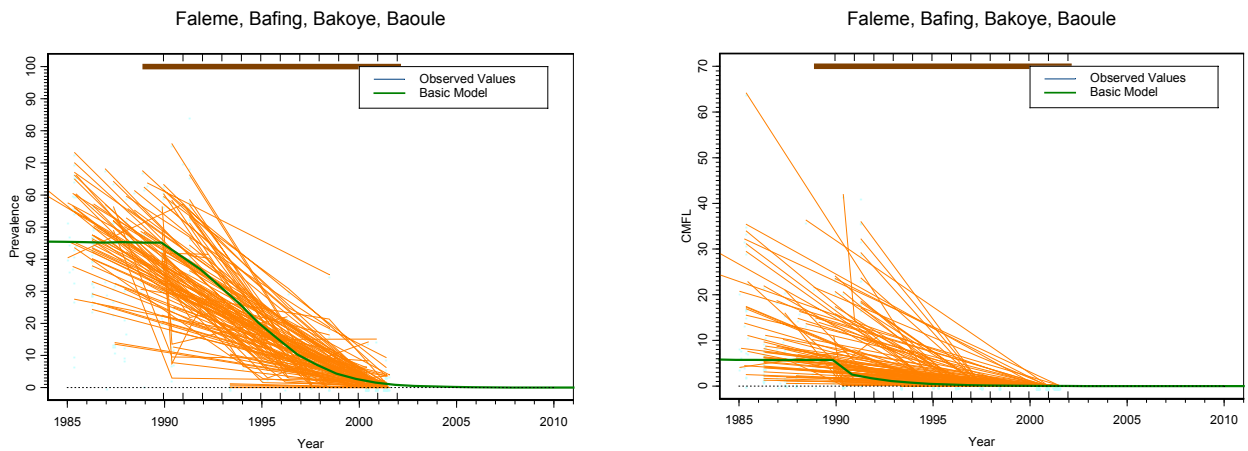


Fig. 4: Observed and simulated prevalence of mf (left panel), and observed and simulated CMFL (right panel) in the Faleme, Bafing, Bakoye, and Baoule basins plotted against time.

Results for the Rio Gambia Basin

This basin is located in the savannah area in eastern Senegal and northeastern Guinea Conakry. It was a hypo to meso endemic area, with pre-control prevalences ranging from 60% to 80%, and pre-control CMFL values > 30 mf/s in only two villages. 6-Monthly ivermectin mass-treatment started in 1989. The therapeutic coverage around 80%. There were favourable trends in the epidemiological indicators, although the prevalence seems to be hanging in a few villages (Figure 5).

In this focus the strategy of 6-monthly ivermectin treatments was tested. In the Gambia focus simulations tended to reproduce actual results in the ‘best’ villages, where prevalence tended to zero. Several villages however, had non-zero prevalence levels in 2000. It is unclear what differences there were between those villages and the ‘good’ villages where the prevalence tended to zero. Predictions made under the assumption of 19% macrofilaricidal effect did not differ materially (in terms of prevalence by the year 2000) from those made by assuming a 35% macrofilaricidal effect, so this could not be the explanation. An unduly optimistic ivermectin coverage rate also seems to be ruled out by our simulations. Simulations carried out assuming 10% and 20% lower coverage, also led to elimination. Nevertheless when a 20% lower coverage rate was assumed, elimination had not yet fully been achieved by the year 2000. Could it be that coverage is even lower in villages with residual prevalence of near 10%?

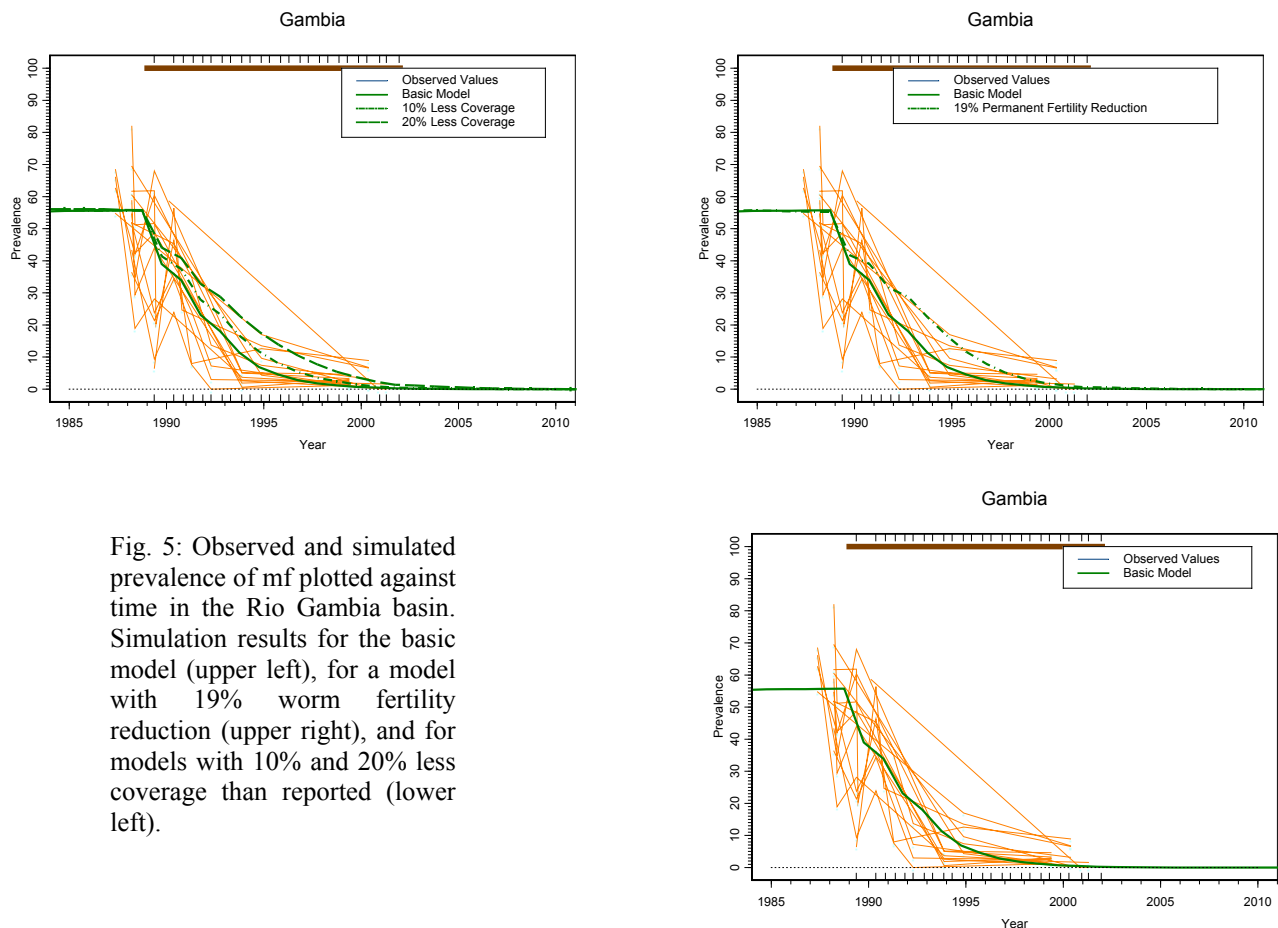


Fig. 5: Observed and simulated prevalence of mf plotted against time in the Rio Gambia basin. Simulation results for the basic model (upper left), for a model with 19% worm fertility reduction (upper right), and for models with 10% and 20% less coverage than reported (lower left).

Results for Rio Corubal Basin

This basin is mainly located in Guinea Bissau, close to Rio Gambia focus. It was a meso endemic area with pre-control prevalences from almost zero to 80%, and with pre-control CMFL values mostly <30 mf/s. 3-Monthly ivermectin treatment started in 1991, but stopped in 1996. Therapeutic coverage increased from 60% at the start to 80%. There were very favourable trends in epidemiological parameters until 1997, but recent data suggests prevalence is increasing again in some villages (Figure 6).

In the Rio Corubal, where 4-monthly ivermectin mass treatment was tested, ivermectin treatments were discontinued well before 2000 due to civil unrest. This ‘natural’ experiment in early cessation provides a unique opportunity to study elimination in practice. In fact, recrudescence appeared to occur after cessation of treatments. By contrast, according to ONCHOSIM, elimination should have been achieved, even when coverage levels would have been lower than reported, or the macrofilaricidal effect 19% instead of 35%. The same holds for the ‘extreme situation’ in which 30% of the population is permanently excluded from treatment. The only factor that could reproduce the observed recrudescence was immigration of infective flies. Of course, immigration of infected humans could have given the same result, but this was not simulated. Although, immigration of infected flies could account for the observed recrudescence, we don't know whether it did. What really accounted for the recrudescence is

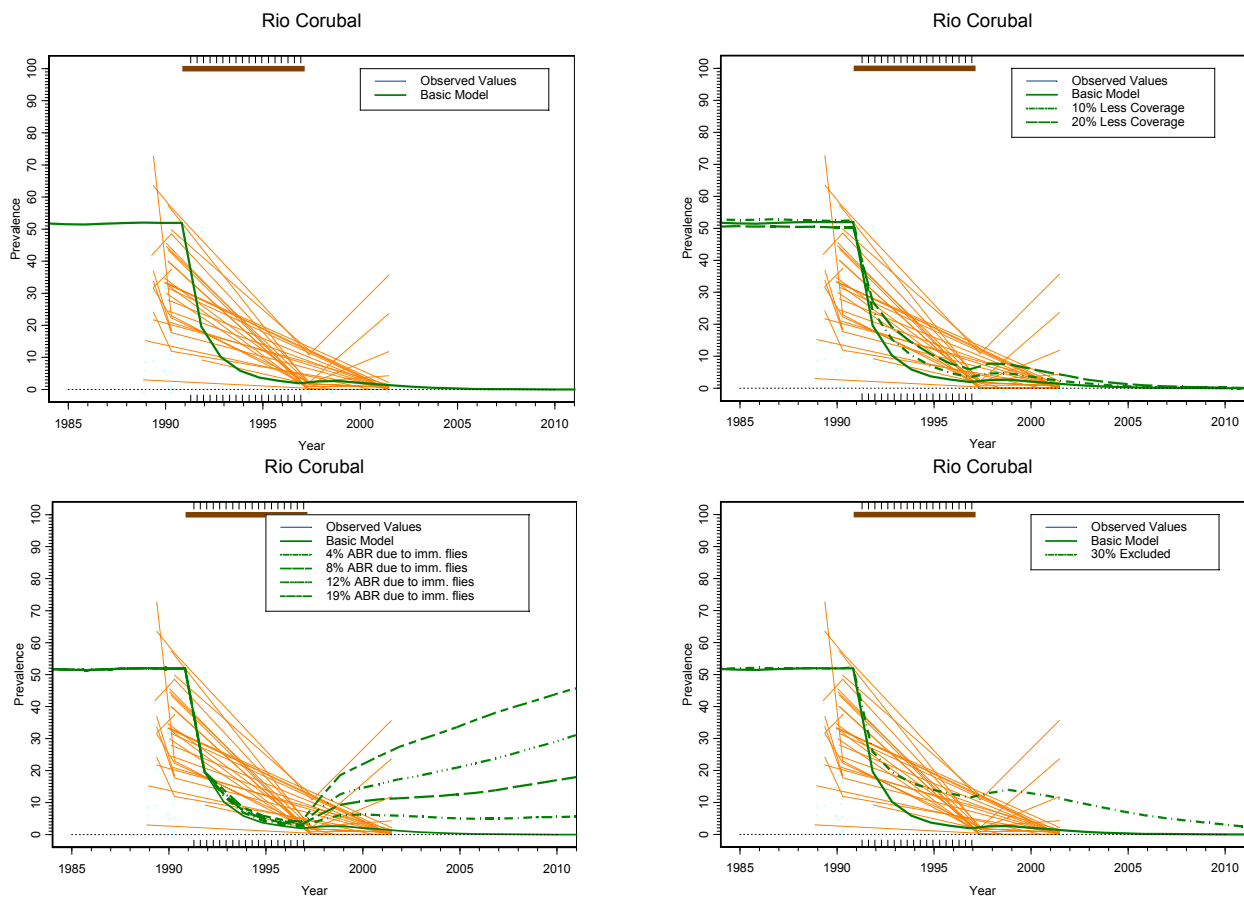


Fig. 5: Observed and simulated prevalence of mf plotted against time in the Rio Corubal basin. Simulation results for the basic model (upper left), for models with 10% and 20% less coverage (upper right), for models involving immigrating flies (lower left), and for a model in which 30% of the population was systematically excluded from treatment (lower right).

hard to establish.

Discussion

Both empirical data and ONCHOSIM simulations confirm that very low levels of prevalence CMFL and transmission can be reached. ONCHOSIM appeared to be broadly in line with empirical data in that it appeared to be able to reproduce observed trends accurately. On the basis of observations it is hard to distinguish macrofilaricidal effects (35% or only 19%?) or ivermectin coverage levels (as reported or 10% or 20% less) as predicted trends appeared to be somewhat insensitive to these choices. Despite this positive result, recrudescence was observed in the Rio Corubal basin following a cessation of treatment of several years as a result of the civil war. It is unclear what caused this recrudescence. ONCHOSIM was able to predict this phenomenon if immigration of infective flies was assumed. However, other factors not explored in our simulations may account for this phenomenon as well (e.g. immigration of infected humans).

According to ONCHOSIM, elimination of transmission from the basins included in this study is possible. However, the 'in vitro' predictions of ONCHOSIM are made under assumptions which are favourable for elimination (as regards geographical coverage, neighboring areas, and resistance). Experience in the Rio Corubal, not a highly endemic area, are a warning against undue optimism, nevertheless. Either, it may not be possible to eliminate all residual foci or prevent invasion of infective vectors or humans, or – alternatively, the biology of low level infections has not been modelled correctly in ONCHOSIM. This needs further exploration.

In view of these findings it would seem too optimistic to conclude that elimination of transmission is possible with ivermectin alone. The excellent results in bringing prevalence and CMFL down, do justify the conclusion that – provided no resistant strains emerge – morbidity can be controlled. Thus, elimination of onchocerciasis as a public health problem with periodic ivermectin mass treatments is definitely possible. For this objective, empirical evidence does not suggest that 6-monthly treatments have any advantage over annual treatments, provided that annual treatments have a high geographical and therapeutic coverage. The advantages of more frequent treatments as suggested by ONCHOSIM are partially based on an extrapolation of macrofilaricidal effects observed at annual treatments to 6-monthly treatments. It is unclear whether this extrapolation is justified. Thus, as yet, annual treatments seem totally adequate. Elimination of the infection will have to await the introduction of other control measures.

PREDICTION OF FEASIBILITY OF ONCHOCERCIASIS ERADICATION

JB Davies

SIMON-a is a microsimulation model designed to emulate the transmission dynamics of onchocerciasis with special regard to the situation in the Americas. It is intended to mimic any chosen community and the vectors associated with it and follow the progress of the disease in that community as it is subjected to variable regimes of ivermectin distribution.

To simplify the model's construction and to make its inner workings more transparent, it is built using an array of 45 columns by 80 rows using the Microsoft Excel® spreadsheet. Thus the information held on each person in the community is contained in a single cell, and the spreadsheet's built-in functions are used to accumulate totals and products such as prevalences that are used to quantify the state of the disease. It also simplifies the production of graphical output such as charts. Data is accumulated in tabular form so that the user can copy columns of information to other sheets to make any calculations required. Changes to the array which simulate the passage of time are driven by hidden instructions written in Visual Basic for Applications code (otherwise known as Macros).

SIMON-a operates in six-month time units called cycles or semesters. Two cycles constitute a year. At the start of each cycle there is the option to distribute ivermectin to a variable proportion of the human population, the effect of this on skin mf. densities is computed, and flies permitted to "bite" randomly selected members of the community in each of five age classes. Any infected flies and their mf are accumulated over each cycle and then placed in a separate "incubator" array which is updated every 6 month cycle until mature female *Onchocerca* have developed about 18 months later. Male worms are then rejected and the remaining female worms are then distributed randomly back to the human population. At the end of each cycle, numbers of worms, infected persons, mf loads and prevalences etc. are recalculated. At the end of each year all humans and the worms they carry are subjected to an annual probability of survival, and those that survive, are aged by one year, and new humans are "born" and enter the array.

Fig. 1

[figure omitted]

Data on each person in the community is held in coded form in a single cell of the array. Fig.1 shows the full information coded for a single female, aged 21 who is not pregnant, was first infected at age 3, and has received 7 out of a possible 8 doses of ivermectin. She is carrying 4 living female *O. volvulus* aged 4, 6 & 8 years, one of which is producing mf. She has one or more nodules and 1 mf/mgm of skin. She is negative for both punctate keratitis and mf. in the anterior chamber of the eye.

Objectives of the Current Project

1. To mimic the dynamics of onchocerciasis in a single hyperendemic Ecuadorian community which has received ivermectin regularly since 1991.
2. Compare the output from the model, such as prevalence, with data obtained from the field.
3. If SIMON-a predicts the field data with reasonable accuracy, examine the effect of various future scenarios.
4. Extend the use of the model to other communities in the Americas.

Assumptions and Limitations

In order to make the model manageable the following assumptions were made:

1. Human and vector populations are in a closed system with no migration in or out of either
2. Vector population size remains constant from year to year (could be changed later).
3. **Ivermectin has no long term effect** on survival or fecundity of female *O. volvulus*. A gradual recovery to pre-treatment microfilarial production levels takes place once ivermectin is stopped.

Subject Community

The community chosen was Corriente Grande, which had the following characteristics:

Location: On Rio Cayapas, Esmeraldas, Ecuador.

Population: c. 150

Pre- Ivermectin Biopsy +ve prevalence over 10 years old = 100%

Classed as **Hyperendemic**

First Ivermectin distribution 1991.

Annual and semi-annual regimes thereafter

Vectors: Primary; *S. exiguum* (unarmed cibarium). Secondary; *S. quadrivittatum* (armed cibarium)

Follow-up epidemiological surveys in 1996, and 2000-2001.

Initial Tests

Once SIMON-a had been set up with the parameters for Corriente Grande, including details of the semi-annual ivermectin coverage of the eligible population and estimated extent of annual nodulectomies, it was run for the equivalent of eleven years 1991 to 2001. The results obtained are compared with field data where it exists in Table 1. Correlation between the generated and observed values for skin biopsy +ve. nodule carriers, and larvae in flies were reasonably close (confidence limits could not be obtained from a single run).

SIMON-a tended to overestimate the number of infected under 6 year olds, and under estimate the prevalence of punctate keratitis. The model was therefore run with two treatments of ivermectin per year (coverage of eligibles; 85%) until the end of years 2001, 2003 and 2005. The predicted values for the Elimination Certification Criteria obtained are given in Table 2

The predictions suggest that by the end of 2003 all the human criteria would indicate that the disease had reached the point of elimination. However, infections in flies indicate that some persons are still infective. By 2005, no flies in a sample of 10,000 were found with larvae, and the criteria indicate that the disease can no longer be detected.

An examination of the numbers of L3 larvae transmitted to the whole Corriente Grande population each cycle (Fig. 2) shows that when ivermectin is stopped at the end of 2003, some 13s were transmitted into 2004 followed by a period 2005 to 2007 with no transmission. However, between 2008 to 2010 there was a brief resumption caused by the lifting of the suppressing effect of the drug on the remaining live female *O. volvulus*. Transmission finally ended in 2011, and by 2012 the whole population was negative.

Fig. 2

[figure omitted]

Conclusions

1. In its present configuration SIMON-a mimics the field data for Corriente Grande reasonably well
2. Prediction by extrapolation suggests that ivermectin might be stopped after 2003, although a few persons may continue to be infected until 2012 or beyond.
3. These predictions are based on single runs of the model. Multiple replications will be required to determine the degree of variation that might be expected.
4. Because SIMON-a assumes that ivermectin has no permanent effect on female *O volvulus* these predictions might be construed as pessimistic.
5. It is hoped to continue refining SIMON-a as more accurate information becomes available, and to apply it to other scenarios.

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HOW REAL IS THE THREAT OF IVERMECTIN RESISTANCE IN *O. VOLVULUS*?

W Grant

The answer to this question is dependent upon several related factors. Each of these factors needs to be considered in order to form a view about the likelihood that resistance to ivermectin (IVM) will lead to a failure of control or eradication of *Onchocerca volvulus* and the speed with which this could occur. I hope to indicate what some of these factors may be, how they may interact and what action could be taken to determine the risk of resistance arising. There are essentially no relevant data concerning IVM resistance in *O. volvulus* directly, so one of the major aims of this paper is to suggest what data need to be collected in order to make more reliable predictions concerning IVM resistance. The paucity of data also means, of course, that this paper is a starting point for discussion rather than a description of the real situation.

1. What is resistance? Resistance can be defined as the failure of control following a drug treatment that previously resulted in control. In the case of IVM and *O. volvulus*, defining resistance is more complex because IVM acts against at least two distinct stages of the life cycle to bring about 4 distinct effects. First, it causes the microfilariae to leave the skin and eventually accumulate in the lymphatics, where they are destroyed. What is the basis of this action of IVM on microfilariae? Second, IVM temporarily suppresses the production of new microfilariae by the resident macrofilariae. Third, it causes a permanent loss of ~30% of fecundity in exposed adult females once they have recovered from the acute effects of the drug so that repeated treatment will eventually result in permanent sterility. Fourth, there is some evidence that repeated IVM treatment reduces the lifespan of macrofilariae. Are the effects on macrofilarial fertility and longevity due to the action of IVM on a single target and is the target(s) in macrofilariae the same as the target in microfilariae. If not, on which target is resistance selection most likely to act and what will the resistance look like? This is an important question, because the manifestation of resistance is likely to differ depending on which of these drug effects is altered by the resistance allele (see Grant, 2000, for a more extensive discussion of this issue). Note that by using the singular “allele” I do not necessarily mean that resistance is monogenic. It is simply less cumbersome than “allele(s)”.

Briefly, there are two likely resistance phenotypes. A) If resistance acts to permit the survival microfilariae already present in the skin then resistance will manifest as a smaller than expected post-IVM decrease in skin microfilariae. This may be followed by a further slow decline of skin microfilarial numbers as natural attrition takes its toll before the macrofilariae recover and resume production of new microfilariae. B) If resistance acts to permit macrofilariae to continue reproduction or to resume reproduction more quickly following IVM treatment, then there will be the usual rapid post-IVM disappearance of microfilariae from the skin but a more rapid reappearance of new microfilariae. In the context of transmission (see below) both mechanisms will result in a period during which the only microfilariae available to blackflies will be either (A) the survivors of IVM-treatment or (B) the progeny of more rapidly recovering parents. In

either case, all transmitted worms will carry resistance alleles and will likely be related to each other but the “resistant” microfilariae will be present at different times post-IVM.

2. Emergence of resistance: Resistance can emerge through either the selection of a pre-existing allele present at low frequency in the sensitive population or through *de novo* mutation followed by selection. The former is compatible with polygenic inheritance of resistance but the latter is not (or it is very unlikely to be). Note that there is no necessity to postulate that a rare resistance allele that is maintained in a sensitive population is rare because it is deleterious. The frequency of an allele in a population is not necessarily a reflection of its adaptive value but can be the product of a range of other genetic factors (eg. population history, bottlenecks, founder effects, genetic drift etc). It is also obvious that the pre-existing resistance allele must be rare in an untreated, naïve population.

This is a restatement of one of the principles of evolution: selection requires phenotypic variation and that variation must be heritable i.e. due to underlying genetic variation. The genetic variability may arise via mutation or may already exist in the population. It seems almost certain that the necessary genetically determined variation in IVM sensitivity is already present in *O. volvulus*. That is, the IVM resistance allele is already present in *O. volvulus* populations.

What is the basis for this assertion? IVM resistance has arisen repeatedly in a wide range of parasites of veterinary importance following several generations of treatment and can be readily selected in populations of several species of free-living nematodes. The IVM resistant individuals in a naïve population have been directly observed in single step selection experiments in at least one species of ovine gut parasite. Thus it appears that the allele which confers IVM resistance is likely to be present in a broad range of nematode species and I am not aware of any reason *a priori* that it will be absent from *O. volvulus*.

3. Intensity of selection & refugia: The intensity of selection will have a major impact on the probability that resistance will emerge. The importance of selection intensity is illustrated by comparing two parasites of veterinary importance in which long periods of exposure to IVM have had very different resistance outcomes. *Dirofilaria immitis* (which is closely related to *O. volvulus*) has a long history of IVM treatment but no confirmed reports of IVM resistance. In contrast, gut parasites of sheep have had a similarly long history of IVM treatment and, in some cases, IVM resistance has arisen in the space of a few parasite generations. The key difference between these species is most likely the difference in the intensity of selection. In gut parasites the majority of the parasite population is in the host and is therefore exposed to IVM and subjected to selection. In *D. immitis*, only incoming L3's are exposed to the drug and these L3's are likely to represent only a small proportion of the total population. Simple models show that for a given resistance allele frequency, the intensity of selection is determined largely by the proportion of the total population that is exposed to selective agent or, conversely, the proportion of the population left untreated *in refugia*. In *O. volvulus* the proportion of the parasite population that is exposed to IVM is essentially 100% (assuming all infected hosts are treated) so that there are few or no worms of any stage *in refugia*. This is very similar to the ovine gut parasite experience where resistance has emerged quickly and where the speed of selection was largely a function of the proportion of the population that was treated. In the extreme case for *O. volvulus* (where there is complete treatment coverage) there are essentially no worms *in*

refugia and the only worms able to contribute to the next generation will be the survivors of the drug treatment i.e. be resistant. The majority of their progeny will carry the resistance allele and selection will be rapid.

4. The spread of resistance and transmission: The presence of a resistance allele in a population and intense selection pressure will ensure that resistance will emerge. Resistance will only cause control failure if it is disseminated through the parasite population, so it is not the emergence of resistance *per se* that is the key but rather its dissemination. This is especially true in *O. volvulus*, where the prevalence and efficiency of the blackfly vector will play an important role.

Envisage a situation in which there is one patient harbouring IVM resistant worms: the microfilariae in the skin of that patient post-IVM treatment have inherited the resistance allele but must be taken up by a blackfly, mature to L3 and then be transmitted to a new host and mature to reproductive adults in order for resistance to spread. There are several steps at which transmission may fail. This is especially true if any step in the transmission pathway is density dependent because it is likely that the numbers of IVM resistant microfilariae will be small and present only in a very small proportion of the host population. In particular, what is the effect of low microfilariae density on ingestion of microfilariae by blackflies and their maturation to L3's? These and other transmission related factors would have a major impact on the likelihood that resistance will be disseminated. How accurately can these be modelled? Even without modelling, it seems obvious that resistance is much less likely to spread in Central American foci with inefficient vectors than in Africa where the vectors are much more efficient.

An understanding of the timing of the reappearance or persistence of “resistant” microfilariae after treatment is also important for modeling the transmission of a resistance allele. The few “resistant” microfilariae present after treatment will be the only individuals available for transmission until susceptible microfilariae reappear as microfilariae recover. During this period the majority of parasites that make it through a blackfly to a new host will carry a resistance allele. Thus transmission of the resistance allele and resistance dissemination will be maximised if there is transmission during the period in which “resistant” microfilariae enjoy a monopoly. It is therefore important to know when this period occurs relative to IVM treatment and how long it persists. For example, coordinating IVM treatment with periods of low vector prevalence or localised post-IVM vector control where resistance is suspected will slow resistance dissemination.

The pessimistic prediction is, therefore, that the resistance allele pre-exists in the *O. volvulus* population and that following treatment there will be a period during which the only parasites that are transmitted will carry the resistance allele. The dynamics of transmission will be influenced by microfilarial availability (which is a function of the resistance mechanism), vector availability and vector efficiency. Thus, the threat of resistance will be influenced as much or more by the dynamics of parasite transmission as by the starting frequency and mode of inheritance of the resistance allele.

5. Detecting resistance: The likelihood that resistance will emerge in a population is the product of the resistance allele frequency in that population and the intensity of selection. We have seen that the intensity of selection is likely to be high in *O. volvulus* and that this will favour

resistance selection if the allele is present in the population. We are, however, unable to detect the presence of the resistance allele directly because we do not know what is. Nor is it likely that its presence can be detected indirectly by monitoring large numbers of patients after treatment, partly because we do not know how resistance will be expressed (see above) and partly because it is simply not practical to do so.

Intensive use of IVM to eradicate onchocerciasis in the absence of vector control should incorporate monitoring for IVM resistance. What form should this take? I favour a DNA based test that is carried out on the same blackfly samples that are currently used to monitor transmission. This ensures the critical linkage between emergence and dissemination of resistance is incorporated into the monitoring method, which is in turn based on a procedure that is already in place and accepted in the field. In the interim, current PCR-based transmission surveillance may be capable of detecting likely resistance: has already identified sites where transmission in the presence of IVM treatment has been detected. These sites warrant further investigation.

The key step in the development of a PCR-based assay is the identification of a suitable diagnostic or marker allele, a goal that still eludes us. Note that the “resistance marker allele” that is the basis of the assay need not be the gene that encodes the resistance determinant. It is sufficient that the marker is in tight linkage disequilibrium with the true resistance determinant so that there is an acceptably low risk of false negatives. The long lifespan of macrofilariae adds a complication to the development of a resistance diagnostic. Macrofilariae are not killed by IVM and may survive several years of IVM treatment irrespective of their ability to either produce resistant progeny (resistance phenotype A) or reproduce in the presence of IVM (resistance phenotype B). Thus the analysis of macrofilariae may not be informative in the context of defining or validating a resistance marker. It is the presence of microfilariae after IVM treatment (either due to differential survival of IVM treatment or an earlier recovery of microfilariae production) that is the most likely resistance phenotype. Consequently, the search for a resistance marker should be based on genetic analysis of microfilariae.

6. Conclusions: There is no direct evidence for an IVM resistance allele in *O. volvulus* but the existence of IVM resistance in other nematodes, the circumstances under which those resistances have arisen and the observation of apparent control failure in Africa all suggest that it would be prudent to include resistance monitoring in any IVM-based control or eradication program. The research requirements for the formulation and implementation of monitoring and intervention strategies are to define the resistance phenotype and likely genetic markers in *O. volvulus*. This research should be guided by careful consideration of the likely key aspects of IVM resistance biology in *O. volvulus*.

***O. VOLVULUS* RESISTANCE TO IVERMECTIN:
EVIDENCE FOR RESISTANCE AND RESISTANCE MONITORING IN THE FIELD
K Awadzi**

Introduction

Ivermectin is the only drug recommended for the control of onchocerciasis, the chronic filarial disease caused by *Onchocerca volvulus* (1). Although the parasite exists in the human host as infective larvae, pre adult forms, adult worms and microfilariae (mfs), current drug therapy is directed entirely at the mfs and adult worms. The mfs determine the major manifestations of the disease and are also the form taken up by the *Simulium* vector to complete the transmission cycle. The main importance of the adult worms lies in their production and release of mfs.

Ivermectin is supplied free of charge by the Mectizan Donation Programme to all residents of onchocerciasis endemic areas, for as long as they need it; the success of ivermectin based control programmes requires that ivermectin remains effective, however long it takes to control/eliminate the disease. The possibility that *O. volvulus* could develop resistance to ivermectin has been considered and a constant surveillance for this phenomenon has been advocated (2). WHO has urged that methods be established for detecting the development of this resistance and that possible underlying mechanisms be studied (1). Although the expectation was that resistance would develop following multiple treatments, it is just as important, if not more so, to examine for primary or 'first dose resistance' as selection of the resistant strain following treatment may occur more rapidly than with 'multi dose resistance'.

Treatment with ivermectin results in clinical (3-7), parasitological (8-16), clinical laboratory (17) and immunological changes (18-24); of these, the parasitological effects are the most readily reproducible and are used routinely for the evaluation of the effectiveness of treatment. The skin mf counts are indicators of microfilaricidal activity and surrogates for the effect on the adult worms. Reports from the field routinely use this indicator for treatment effectiveness in the individual and for deriving other indices such as the community microfilarial load (CMFL) and the prevalence of infection. Examination of the adult worms determines the effects on their viability and reproductive activity. Additional information is obtained from the uptake and development of mf in the vector.

The expected parasitological effects of a single, unique administration to a naive population and of multiple doses of ivermectin are well documented. The suspicion that *O. volvulus* has developed resistance to ivermectin is raised when observed results do not meet the expected. This needs to be fortified by the exclusion of other causes of inadequate response and confirmed by the demonstration of a plausible genetic basis for such resistance. It is essential to determine whether the abnormal response involves the mfs or the adult worms, as this determines the

optimum approach to the development of tools to detect resistance and the severity of the impact on resistance and treatment failures (25).

Resistance after multiple treatments

The suspicion

In 1987, the OCP initiated ivermectin distribution in the Lower Black Volta basin where aerial larviciding had started in 1975 and in the Pru basin where vector control was introduced subsequently in 1988. Both foci are located in Ghana. Communities were monitored for drug efficacy using parasitological and entomological indices. In 1997, the Ghana National Control Programme and the OCP identified 26 males and 5 females with persistent significant microfilaridermia. A concept of 'non response' (inadequate response) defined as a skin mf count ≥ 10 mf/snip after 9 or more treatments with ivermectin evolved. The need to exclude the development of resistance to ivermectin by mfs and/or the adult worms of *Onchocerca volvulus* following multiple treatments was indisputable.

Exclusion of patient factors

After obtaining informed consent, 28 male subjects were selected from the OCP database to participate in an open, case-control study at the OCRC. The 'cases' were the 'non responders'. They were matched with subjects from the same foci known to have become negative following treatment (responders) and with 14 infected subjects from an area without previous ivermectin distribution or vector control (The Tordzi basin). Matching was with respect to age, body weight, number of treatments and skin mf density, as appropriate. Prior to admission, a detailed history confirmed ivermectin consumption, documented the adverse effects to each dose and inquired about the use of agents that may adversely interact with the drug. Mf counts in skin snips established the category of the volunteer 3 to 4 years after the OCP investigation. In hospital, standard conditions were imposed on all participants (abstinence from alcohol, tobacco, herbs, non prescribed drugs and all had a common diet). Detailed physical, ocular and laboratory tests unearthed any underlying diseases. A single dose of ivermectin was given to each patient after an overnight fast, according to the Merck schedule. Multiple blood samples were taken over 72 hours to determine plasma levels and pharmacokinetic parameters.

Assessment of parasite response

Each patient acted as his own control and comparisons were made between pre and post treatment indices. The sensitivity of the mfs was determined on percentage reductions on initial skin mf counts and in mf uptake (VmfU) and larval development in the *Simulium* on fly feeding as at day 8. The sensitivity of the adult worms was determined from embryogrammes and the return of skin mf at month 3. A final assessment will be done at 12 months.

Parasite factors-the genetic basis for resistance

Parasite material collected pre and post treatment were preserved. They include mf from skin snips, mf and developing larvae from the vector and adult male and female worms. Genetic profiling is in the early stages.

Current status of evidence on resistance

In all 3 cohorts (non-responders, responders and ivermectin-naïve) we have observed responses that differ from the expected. The significance of these findings await data from other aspects of the investigation.

First dose Resistance

In an unrelated study, we have observed one ivermectin-naïve patient who, after treatment, achieved only a 42% reduction in the initial skin mf count at day 30 (expected 99-100%). There was no underlying disease and exposure to ivermectin was more than adequate, as determined from pharmacokinetic data. Here, 'primary' mf resistance is a plausible diagnosis. However, material is not available for genetic studies.

Concluding remarks

Ivermectin treatment has brought considerable benefits to all who reside in onchocerciasis endemic areas. The severe consequences of visual impairment, blindness, disfiguring skin lesions and weight loss seem to be features of a distant past. Other indicators such as the elimination of skin mf and reductions in prevalence and the CMFL attest to the efficacy of the treatment regimens. There is at present no firm evidence that there are populations of *O. volvulus* that are resistant to ivermectin. However, whenever a single agent bears the responsibility of disease control, to be used on a long term basis in differing dosages in many countries, it is prudent to examine for any differences between the observed and the expected effects of treatment. Although this is more likely after multiple treatments, first dose resistance could involve the first pill given to the first patient.

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O. VOLVULUS RESISTANCE TO IVERMECTIN: IS IT OCCURRING? LESSONS FROM THE VETERINARY FIELD, WITH THOUGHTS ON SURVEILLANCE FOR RESISTANCE

R Prichard, J Eng and B Ardelli

Ivermectin resistance in veterinary parasites

Ivermectin (IVM) resistance occurs in several trichostrongylid nematode parasites of sheep, goats and cattle in various parts of the world. In *Haemonchus contortus* it is very common. Nevertheless, it should also be remembered that IVM has been used extensively against nematode parasites of horses and dogs and resistance has not so far been reported in parasites of these hosts. However, against nematodes in horses it is not very effective against larval stages in the tissues of the horse and thus selection pressure may be low.

***Dirofilaria immitis*: a model for *Onchocerca volvulus*?**

In dogs, IVM is used for prophylaxis of *Dirofilaria immitis*. This is a filarial nematode, similar to *O. volvulus*. *D. immitis* in the dog has been suggested as a model for possible IVM-resistance in *O. volvulus*. This may not be a good model for IVM resistance in *O. volvulus* for several reasons: (1) IVM is used at only 3 µg/kg in the dog, compared with 150 µg/kg against *O. volvulus*; (2) in the dog, IVM is used prophylactically to kill incoming L₃ larvae. It does not act against other stages of the life cycle. Most of the parasite population will exist in other life-cycle stages and IVM selection pressure will be very small. In contrast, in onchocerciasis, IVM is directed to existing infections, normally killing all of the microfilaria (mf) in the human and sterilizing the adult worms for several months. Most of the worm population will be subjected to IVM selection and only the very small fraction of the *O. volvulus* population in the vector will be exempted from selection; and (3) dogs are treated on an individual basis with most of the dog population in a region often not being treated. In contrast, IVM is given on a community wide basis for onchocerciasis. However, the long life cycle and longevity of *O. volvulus*, and vector control will delay selection for resistance in *O. volvulus*.

The genetic basis for ivermectin resistance in veterinary parasites

In parasitic nematodes such as *H. contortus* and *C. oncophora*, that we and others have examined, we have found that selection for IVM-resistance selects for specific alleles of (1) membrane transport protein genes such as P-glycoproteins^{a,b,c,d}, (2) β -tubulin^e, and in these parasites and the free-living nematode, *Caenorhabditis elegans*, (3) glutamate-gated chloride channel^{e,f,g} genes. We believe that P-glycoproteins act to efflux IVM out of the nematode cell membranes, and glutamate-gated chloride channels are the mode of action receptors for IVM. The function of β -tubulin in IVM action is not clear, although it may play a role in anchoring the mode of action receptors at interneurone or nerve-muscle junctions. We have been examining

these and other genes associated with IVM action for evidence of genetic selection in *O. volvulus* following repeated field treatment with IVM.

Changes in genetic polymorphism in *O. volvulus* associated with ivermectin treatment

We have so far compared populations of *O. volvulus* derived from people who have not been treated with IVM (2 groups from Ghana and Uganda, respectively) and *O. volvulus* from people who have had community IVM treatment 6 or more times. We have found significant differences in the genetic polymorphism of P-glycoprotein and another membrane transporter gene (ABC-3), and β -tubulin in the *O. volvulus* from the treated subjects compared with the two untreated groups. In these genes, the two untreated groups, from different parts of Africa, showed similar genetic polymorphism.

Surveillance for ivermectin resistance in *O. volvulus*: a diagnostic tool

These results suggest that IVM may indeed be imposing genetic selection on *O. volvulus*, possibly associated with selection for resistance. However, additional *O. volvulus* samples, from different regions and/or *O. volvulus* not responding to IVM, need to be examined to confirm this evidence for genetic selection by IVM. If this data is confirmed, a DNA-based diagnostic tool for IVM resistance in *O. volvulus* can be developed. It is intended that this diagnostic tool would be used on samples of *O. volvulus* mf derived from the vector or from skin snips.

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Dr. Wesley Shoop
Cross resistance among the avermectins

**IVERMECTIN AND MOXIDECTIN ARE CROSS-RESISTANT IN NEMATODES
AND THE RATE OF DEVELOPMENT IS THE SAME**
W Shoop

Ivermectin was introduced to the market in 1981. In 1985 the first case of an ivermectin-resistant worm was reported. Since that time, ivermectin-resistance has been identified in five trichostrongylid species from sheep and cattle.

Moxidectin was commercialized in ~1992. It was offered at the same dose rate and against the same spectrum of parasites as ivermectin, but with the notable exception that it could be used against ivermectin-resistant worms. Whereas ivermectin has balanced activity against the spectrum of nematodes and arthropods, moxidectin emphasizes greater activity against nematodes, most notably against the three trichostrongylids in sheep that have become ivermectin-resistant. This ability of moxidectin to kill some ivermectin-resistant worms mistakenly led some to think that moxidectin may have a different mode of action than ivermectin and that there would be no cross-resistance.

Careful titration of ivermectin and moxidectin against an ivermectin-resistant field strain of *Ostertagia circumcincta* in 1993 revealed that worms resistant to ivermectin were simultaneously resistant to moxidectin. For example, 4.7 ug/kg of moxidectin was required to kill 95% of the susceptible strain of *O. circumcincta*, but 148.0 ug/kg was necessary to kill the same percentage of the so-called ivermectin-resistant strain. It should be noted that this field strain had been selected for resistance by ivermectin and had never been exposed to moxidectin at any point in its history. Yet, the resistance factor for moxidectin was 31-fold. Significantly, although there was substantial resistance to moxidectin, it would have gone unnoticed in the field because the amount had not yet exceeded the use level of 200 ug/kg.

To the other side of the story, ivermectin required 22 ug/kg to kill the same susceptible strain of *O. circumcincta*, but 514.0 ug/kg was necessary to kill the same percentage of the resistant strain. This represented a resistance factor of 23-fold. Clearly, 1) these worms selected by ivermectin were cross-resistant to both ivermectin and moxidectin, 2) moxidectin was more potent which disguised the underlying resistance, and 3) the rate of their resistance was the same.

As important as these previous conclusions were, additional observations showed that this identical pattern was also observed when resistant *Haemonchus contortus* and *Trichostrongylus colubriformis* were examined. To date, every study in which titrations have been performed have confirmed that when there is ivermectin resistance there is also moxidectin resistance, and vice versa. No study contradicts this tenet. Resulting from these studies, fewer statements have been seen recently in the literature suggesting that ivermectin and moxidectin have different modes of action or that there is not cross-resistance between the two, but instead the drumbeat has now shifted to the ‘possibility’ that there may be different rates of resistance development.

For example, it would be unfair to suggest from the aforementioned study, where there was an ivermectin resistance factor of 23-fold and a moxidectin resistance factor of 31-fold, that there was a greater rate of resistance to moxidectin. The fact is that these are absolute numbers based on estimated dosages and are not statistically significant. The best that one can conclude from these data, or any like them, is that clearly there is cross-resistance between the drugs but the rates are the same.

When others see differences, an evolutionist sees similarities. Any suggestions that ivermectin and moxidectin differ fundamentally must take into account the following fundamental similarities: ivermectin and moxidectin are semisynthetic molecules derived from *Streptomyces* sp., they are structurally superimposable, they kill the same spectrum of parasites, they are given at the same dosage, they have the same mode of action, they competitively displace one another at the same chloride channel binding sites, worms resistant to one are resistant to the other, resistance develops at the same rate, and they show the same mechanism-based toxicities.

The reason for these similarities is because ivermectin and moxidectin share the same pharmacophore. A pharmacophore is the 3-dimensional, electronic configuration that will lock into a specific receptor and trigger a defined mode of action. That pharmacophore in ivermectin and moxidectin is virtually identical and is why their biological activities are so similar. Any statements suggesting that one does something fundamentally different than the other should be viewed with skepticism and should be accompanied with a high burden of proof.

**SELECTION FOR RESISTANCE TO MACROCYCLIC LACTONES
BY HAEMONCHUS CONTORTUS IN SHEEP**
S Ranjan, GT Wang, C Hirschlein, and KL Simkins

Abstract

An anthelmintic-sensitive *Haemonchus contortus* strain was selected for moxidectin and ivermectin resistance concurrently for 22 generations. Treatment with 0.002 mg moxidectin/kg BW or 0.02 mg ivermectin/kg BW produced >99% efficacy against the susceptible parent strain passaged for 22 generations without any anthelmintic exposure. However, to obtain similar efficacy the moxidectin-selected and the ivermectin-selected strains of *H. contortus* required 0.05 mg moxidectin/kg BW or 0.4 mg ivermectin/kg BW. These results indicate that development of resistance to one macrocyclic lactone, simultaneously, results in resistance to another macrocyclic lactone. However, rates of resistance development differ between compounds and occurs more slowly with moxidectin than with ivermectin.

ACHIEVING AND SUSTAINING HIGH TREATMENT COVERAGE: EXPERIENCE OF APOC

UV Amazigo, M Noma, and A Seketeli

The African Programme for Onchocerciasis Control (APOC) was launched in 1995 as a unique health development partnership with the objective to eliminate onchocerciasis from Africa, by establishing a sustainable ivermectin (Mectizan®) delivery system to free more than 56 million people living in endemic communities. The public-private sector partners of APOC are, 19 African countries, donors, foundations, non-governmental development organizations (NGDO), affected communities and Merck & Co. Inc., which undertook to provide ivermectin (Mectizan®) free of charge and for as long as needed.

In 1997, APOC adopted as a principal strategy for the control of onchocerciasis within the programme 's scope, community-directed treatment with ivermectin (CDTI). By the end of 2001, APOC had approved 59 CDTI projects in 14 of the 19 member countries. The target is to treat at least 65% of the total population and 100% of all hyper and meso-endemic communities annually for several years in order to achieve the Programme's objective.

The unique features of the CDTI strategy are that endemic communities are empowered to take full responsibility for the drug distribution process. They decide how and when and by whom treatment should be administered; they oversee the implementation of treatment, recording-keeping, reporting and referral of cases of severe adverse experiences (SAEs). This is presently being done in more than 62,000 endemic communities in sub-Saharan Africa. CDTI has also been seen as a stimulus for delivering health care services in remote and hard –to-reach endemic communities, a ready pathway for international community to deliver donated and other drugs to those most in need, thereby strengthen the health services.

Achieving high treatment coverage

With CDTI, geographical and therapeutic coverages have increased substantially, to the levels needed to eliminate onchocerciasis as a public health and socio-economic problem. The number of people now receiving treatment every year, over 20 million, is more than double the eight million it was when APOC was launched and as shown in the tables, therapeutic coverage in individual countries and projects has increased in excess of 65%. The independent participatory monitoring reports indicate that most likely APOC projects will continue to maintain high treatment coverages during the life of the programme. The findings of the independent monitors are corroborated by a five-year (1996 –2000) data on therapeutic coverages in Nigeria, Uganda, Malawi and Tanzania which show increase in treatment coverage. Evidence from countries technical annual reports, External mid-term Evaluation of APOC and independent monitoring reports show that some projects are likely to maintain good coverage levels (>65% of total population) even after the cessation of APOC support. So far the trend is promising. The

challenge is sustaining high treatment coverage for several years after the cessation of APOC support in 2010.

Sustaining high treatment coverage

Maintaining over 65% therapeutic coverage over a long period of time, especially when community interest has waned and the immediate health benefits of treatment are no longer obvious is a major challenge to APOC and constitutes the mainstay of its focus during the Phase II and Phasing-out Period (2002 – 2010). The experience of APOC show there are obvious deficiencies, which impact directly on treatment coverages. The deficiencies which need to be addressed are mostly managerial and technical, they include:

- (i) deficiencies in budgetary provision and inadequate release of funds by participating governments,
- (ii) inadequacy of front-line health facilities and a decline in the quality of health services which has negative impact on the supervision of ivermectin distribution and the activities of community directed distributors (CDDs) of ivermectin.
- (iii) Shortage and untimely supply of ivermectin to affected communities. As example, a comprehensive analysis of more than 14,900 household interviews in 26 projects showed that 29% of 669 communities studied surveyed experienced shortages in the supply of Mectizan®, and there is a significant inverse relationship between shortage and treatment coverage ($p=0.005$).
- (iv) High rates of absentees and refusals to treatment. In countries' technical reports, program managers attribute high rates of refusals to fear of severe adverse experiences (SAEs). As example, in areas where onchocerciasis and loasis are co-endemic in Cameroon, reports of SAEs abound and community members have voiced their skepticism about ivermectin from their experiences of severe side effects. There is a clear need for better tools for assessing SAEs, improving community knowledge of early warning signs and strengthening IEC and communication strategies in affected areas. This challenge is receiving priority attention among the partners of APOC.
- (v) Inadequate empowerment of communities in decision-making and participation within the context of primary health care (PHC) and drug distribution systems. The level of involvement of communities in CDTI programs' decision-making processes varies from country to country. The experience of APOC and reports of independent monitors of CDTI projects indicate, among other things, that of the three indicators of sustainability related to community participation, community meetings over the period of treatment are more likely to improve treatment coverage. Treatment coverage rates tend to increase when communities receive ivermectin at the period they decided for distribution.
- (vi) The motivation of CDD and provision of incentives by communities needs to be properly addressed to maintain desirable levels of both geographical and therapeutic coverages. About 34% of CDTI target communities currently provide their own support to the ivermectin distributors as part of their responsibility in the APOC partnership. The provision of financial incentives has remained a thorny issue for CDTI and several other community based health interventions. However, in the experience of APOC, the

monitoring data of 26 CDTI projects over a three-year period (1998 – 2000) provided no clear evidence to show that provision of financial incentives to CDD improves treatment coverage rates. The challenge for APOC is to advocate for a standard policy on incentives among agencies supporting community-based health interventions.

In summary, APOC partners have made significant progress in achieving high treatment coverages through the Programme's strategy, community-directed treatment with ivermectin (CDTI). To sustain the high levels of coverage in all sites, in particular, in conflict areas within the confines of the programme will be required to achieve the elimination of onchocerciasis as a public health and socio-economic problem and strengthen the health care systems.

Dr. Boakye A. Boatin
Experience of OCP and challenges for post-OCP monitoring

**ACHIEVING AND SUSTAINING HIGH TREATMENT COVERAGE IN THE FIELD.
EXPERIENCE IN OCP AND CHALLENGES FOR POST OCP MONITORING
BA Boatin and KE Siamevi**

Achieving and sustaining high treatment coverage

Until 1987 vector control was the only means of intervention against onchocerciasis in the Onchocerciasis Control Programme in West Africa. The registration of ivermectin for the treatment of onchocerciasis and the confirmation of its feasibility for large-scale distribution was a breakthrough for drug management of onchocerciasis.

The OCP undertook an extensive mapping based on skin snip examination to demarcate areas to be eligible for treatment. Eligibility for treatment was based on CMFL 5 mfs/s or more. Using this criterion ivermectin distribution in the Programme has evolved from mobile treatment, through community based treatment to the present community directed treatment with ivermectin CDTI.

The simple parameters for assessing the performance in ivermectin distribution have been the geographic and therapeutic coverage. Geographic coverage of 100% and therapeutic coverage of a minimum of 65% respectively have been the target for treatment. (Therapeutic coverage has been defined in the OCP, as the number of people treated as a proportion of the total population in the area (community) under consideration.

Geographic coverage in the OCP has varied from as low as 45 % to 100%. The average has been about 80%. Treatment coverage has however been consistently high in most countries with an average of about 77% with respect to the minimum expected. In the experience of the Programme, the following factors seem to have played a role in achieving and sustaining high treatment coverage in the field:

Sensitization: Before the introduction of CDTI each of the countries held a country-specific workshop, which implicated the authorities at the Ministry of health- as participants or fully informed of the installation of CDTI. Thus sensitisation of the Ministry of health was done early. This generated authority and support for the lower (Regional, district, health centre) level staff to embrace CDTI as part of their work.

Decentralisation: As part of the workshops each country decided on the level of decentralisation for oncho activities including ivermectin treatment, and hence at which level of the ministry of health financing and logistics for oncho activities would be included in the plan of action for health activities e.g. Regional level, district or zone. All the countries have already implemented this policy of decentralisation. In Benin, Burkina Faso, Cote d'Ivoire, Guinea and Senegal oncho control features in the plans of action and budget of regions and districts.

Direct involvement of peripheral staff: The district and peripheral health personnel were represented at the country specific workshops. District specific workshops on CDTI were also held. They were fully involved in the preparation for CDTI. The peripheral nurses themselves provided information on the number of villages and their populations in their respective areas and, in collaboration with the National teams planned for their training and that of the Community distributors (CDs).

Training and retraining where necessary has been pursued vigorously. These have served to keep awareness and interest in the campaign and as a form of motivation for the nurses as well as CD. Although no specific cash payment was given to trainees their transportation cost and overnight stay when training was done at a central point was to the charge of the Programme/NGO. A cycle of training helped to ensure that new nurses transferred to the oncho endemic areas got trained to enable them supervise the treatment.

Supervision of treatment by the health Centre staff has been financed by NGOS and OCP in addition to what the countries can rake together. The OCP encouraged and helped start the necessary supervision by providing fuel for some health centres whose budget did not yet cover the extra distances involved. This is deemed a temporary measure until the countries begin to have the cost reflected in their plans of action and budget. Benin, Burkina Faso, and Senegal and are self-sufficient already. In some countries nurses have received payment from other sources for a number of villages supervised and well treated.

Best coordinator and district awards. The Programme established an annual award for the best coordinator and district in the implementation of CDTI as an encouragement. This has been keenly competed for perhaps to the advantage of all. The process has continued in time and may need a new a proprietor to continue it when OCP closes.

Monitoring has been done through several levels. a) By OCP field staff of the vector control Unit. A very simple questionnaire that is a modification of what was developed in Kaduna through the TDR Task force for operational research on onchocerciasis is used. b) Periodic field visits by national team staff financed in most cases by OCP (Benin and Burkina Faso have financed this by themselves) and OCP staff and c) by periodic external independent evaluation financed by OCP have been done. Monitoring has not only served to inform the national teams and the Programme of field operational issues but also as a way of keeping staff in touch with the community and to keep the communities (nurses, CDs etc) interest in the endeavour.

Drug supply in the field has been crucial for the treatment. The previous experience OCP experience of long-term planning and schedule for ordering tablets ahead of time by meant that shortages of tablets in the field were rare. If they occurred it was only for a short duration. This experience has been passed on to, and adopted by, the Countries that now order their own tablets and in relatively reasonable time and in right quantities for the period of treatment.

Low coverage has usually come about because of the overstretching of the number of villages to be covered for expediency rather than eligibility. Some villages are simply not treated because they have not yet been attended to or just too scattered. A clear and adhered to Ultimate

Treatment Goal (UTG) in terms of villages notwithstanding political and, or social pressures should help.

In most of the communities there is at least one CD to a village. Difficulties in finding a CD in some villages (refusal, no interest, inability of chosen distributors to understand what is required of them) means a CD could find him/herself responsible for more than one village long distances apart. Distributors are thus unable or unwilling to cover the villages attributed to them. Akin to this problem is the presence of hamlets, which are not reached by the CDs. No specific solution has been found to non-availability of CDs in some communities, but sensitisation of communities to help provide transport to distributors is being done.

Motivation/incentives for nurses and CDs would appear to work against achieving high coverage and sustaining it. In a recent study on motivation of nurses and CDs, (Prozesky) it was found that more than 50% of nurses and CDs had low to moderate motivation towards CDTI. While some CDs would be willing to start ivermectin distribution they very soon will stop if they do not see any sign of a form of motivation or incentive -either in cash, kind or a recognition.

Challenges for Post OCP monitoring

The challenges for post OCP monitoring could be managerial and technical.

Planning and the periodicity for monitoring in the absence a coordinating body will require a discipline that needs to be well entrenched in the Ministries of health, given that treatment will continue for a long time and will no doubt see a rapid turn over of personnel.

Each country is at liberty to devise their own manner of monitoring but it will be necessary to maintain a common ground for future cross country evaluation. Financing to support monitoring will be a challenge. With the withdrawal of OCP's support, the countries will need to look elsewhere- external sources, NGO etc.-to supplement their own resources. Inability to raise these funds means a laxity in the monitoring cycles or not at all, with its consequences. The countries will need extra funding to be able to conduct external and independent monitoring.

The fact that the Participating countries belong to a regional Programme makes them in some way accountable to the group to undertake various activities of which monitoring is a part. This seemingly 'peer pressure' will be absent during the post OCP period. The Participating countries therefore will have to maintain interest in, and continue to place oncho control high on their agenda and, with that, the need to monitor the performance of ivermectin distribution.

Technical issues with monitoring that will appear will need to be resolved on a country-by-country basis initially. External support will be needed in reviewing guidelines for monitoring on a regular basis with the evolution of ivermectin distribution.

The main challenges therefore for post-OCP monitoring could be, the recognition of Participating countries of the need to continue with monitoring in the face of competing health issues, financing, maintenance of high standards for the process, updating of the guidelines for

monitoring in the light of possible changes in ivermectin delivery and the need of each country to accept accountability to a common purpose.

ACHIEVING AND SUSTAINING HIGH TREATMENT COVERAGE: EXPERIENCE OF OEPA

FO Richards, Jr.

The endemic foci for onchocerciasis in the six endemic countries in the Americas (Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela) have different characteristics from those in Africa that have given rise to stable foci amenable to focused attack and (theoretically) eventual elimination using ivermectin alone. The resultant elimination strategy of the Onchocerciasis Elimination Program for the Americas (OEPA) is to suppress transmission calls a high level of treatment coverage (>85% of the eligible population), two times per year, in all endemic communities where infection prevalence is likely to support transmission of the parasite. Numerous laboratory and field studies have demonstrated that twice per year treatment will keep microfilaridemia at low enough levels to suppress parasite transmission,²⁻⁵ even in areas with efficient vectors, such as Ecuador.⁵⁻⁶ If program function can achieve and sustain the critical coverage for 10-15 years, transmission will be suppressed, and the adult parasite population, unable to replenish itself, will perish from old age. At that point the mass ivermectin treatment programs could be halted without fear of recrudescence of infection or eventual evolution of ivermectin resistance.⁷

The goal of complete suppression of *O. volvulus* transmission throughout the Americas is ambitious; coverage success will depend largely on sustained 1) health education to promote the understanding and compliance of the affected populations, 2) excellent program function, guided by good surveillance, data management and instructive epidemiological and process indices, 3) political will at the highest levels, and 4) sufficient financial resources. This presentation will focus on item 2, and issues arising from monitoring the American programs over time to achieve full coverage and sustain them until that point in time when it can be documented to an international certification team that coverage has been achieved and sustained to interrupt transmission, and end mass ivermectin treatments.

Examples of Programmatic Set Backs in Coverage: Guatemala and Ecuador

In Guatemala, public health policy changes resulting in the decentralization of public health activities caused the interruption of ivermectin treatment from October 1994 to June 1996; the treatment program resumed in July 1996, but it was not until four years later, in 2000, that the same numbers of persons were treated as in 1993-4. In Ecuador, where the need to sustain semiannual treatment is particularly important since onchocerciasis is transmitted there by the most efficient vector species in the Americas, *Simulium exiguum*, only 70% of the needed treatment were provided in a hyperendemic village (El Tigre). The suppression of the ATP in that village from over 700 to 37 L3/year was dramatic, but not below the 20 ATP level the program believes necessary to indicate suppression of transmission. In both the cases (Guatemala and Ecuador), such programmatic failures make it necessary, under current

guidelines, to or reset the 12 year clock toward determination of cessation of treatments after years of investment in the programs activities.

Semiannual treatment: lower coverage in second round

Coverage indices have focused on a percentage of the Ultimate Treatment Goal (UTG), which is defined as the total number of persons eligible for treatment in the American region (429,920 persons). In the first treatment round of 2000, 367,619 persons were treated, representing a UTG coverage of 86%. However, it was also observed that only 59.6% of eligible persons (256,385) in the Region were treated in the second half of 2000. The lower rate of coverage during the second half of the year was observed in all six national programs. This phenomenon could be related to community fatigue (people don't like treatment twice per year) and/or programmatic failure (less importance given to a second round by authorities).

Monitoring

1) *The UTG(2)*. A single indicator of coverage, the UTG(2), to incorporate both first and second treatment rounds, was adapted in 2000. This indicator focuses on treatments needed rather than on the eligible population at risk (UTG). For example, whereas 85% of the eligible population in Ecuador received treatment during the first round in 2000, relatively few (14%) of these persons received a second dose. Consequently, UTG(2) coverage in 2000 was only 50% in Ecuador. Use of the new UTG(2) denominator of 859,840 (twice the UTG of 429,920), showed the overall 2000 UTG(2) treatment coverage for the Region was 73% in 2000, with only Colombia and Mexico achieving the goal of surpassing 85% of the UTG(2). It was agreed at IACO 2000 that all programs would aim to reach at least 85% of their UTG(2) in 2001, with the exception of remote Amazon foci in southern Venezuela and Brazil, which would aim to reach their UTG(2) in 2002.⁸

2) *Community Coverages*: The UTG(2) is still an agregagate mean value and does not provide information on the range of community coverages being achieved in the program area. OEPA has before it the challenge of developing coverage reporting systems that provide individual community coverage rates, per round or community UTG(2), for the 1969 endemic communities of the region. This would allow national programs to identify and focus tailored interventions in problem communities not reaching the required 85% coverage of eligibles.

Conclusion

The way forward in the Americas was best summed up by Dr. Richard Collins in his commentary during the September 2000 round table discussion at WHO Geneva "How Far Can We Go Towards Elimination Of Human Onchocerciasis?"⁷ He said (page 57):

"While the development of objective elimination criteria has been a useful exercise in programme planning, goal-setting and evaluation, OEPA and the national programmes must now turn their full attention and energy to establishing and maintaining high level coverage twice per year in all communities where there is a risk of parasite transmission. The "high-tech" methods of PCR, DNA probes and sophisticated computer models can be helpful in evaluating outcome,

but high- level sustained coverage requires community participation and the basic principles of “shoe-leather” epidemiology: - finding the endemic communities; making maps of the houses; census of households and families; tracking births, deaths and migration; treating and re-treating all eligible persons; following-up of absentees and people refusing the drug; learning why people refuse and making adjustments.“

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STATEMENT BY E TARIMO

I would like to thank the organisers of the Conference for providing me an opportunity to share my reflections on the Eradicability of Onchocerciasis. My observations are limited to two interrelated areas on the agenda namely, Integration of ivermectin delivery in national health systems and community participation. These two areas feature prominently in APOC policies. I would like to say a word or two on their implementation in APOC countries and then very quickly raise five issues that are relevant to “Feasibility of Onchocerciasis eradication”.

1. Integration of ivermectin delivery

Table 1, essentially reminds us of the different dimensions and parameters of integration. The parameters relate to different levels and areas. Many APOC countries have made considerable progress in integrating CDTI with other services. The biggest achievements relate to establishment of community level coordinating mechanisms. But integration at higher levels needs to be intensified.

2. Community Participation

The term community participation has become overworked, it is always important to indicate the content and level of participation. Community participation in the CDTI projects it not either zero or hundred percent. Figure 1 shows Levels of Community participation as a continuum in different approaches of community treatment. Obviously decisions on level of participation for a particular programme will largely depend on the technology used, in this case ivermectin treatment, requires strong community participation for success. Other programs might not require such a high level of participation.

Strong community participation in CDTI in APOC countries is evidenced by high levels of leadership, planning and decision making by communities; Knowledge of communities on onchocerciasis and its treatment; Involvement of the local infrastructure including, religious institutions, schools, Traditional midwives, Traditional healers, Farmers co-operatives, women’s organizations, youth clubs, Town criers, Red Cross and Scouts and community contribution and community satisfaction.

3. Issues:

(i) Is CDTI under or over integrated?

Independent vertical programs are unable to benefit from economies of scale. Thus costs are high and benefits are low. Integration increases benefits and lowers costs. Increase in benefits, however, does not continue indefinitely. As the number of programs integrated directly under one direction increase, costs begin to rise because the bureaucracy is too large to be managed efficiently. At some point costs begin to outweigh benefits, See Fig 2, below. The point being

made here is that integration is not an end in itself; the form it takes at different levels of the health system has to be defined and made clear.

(ii) Entry point potentials of Ivermectin treatment

In many of the onchocerciasis endemic areas, no functional primary health system exists. Introduction of ivermectin treatment in these disadvantaged communities creates community awareness and mechanism on which other essential care can be added. There are many examples of this happening. Is this not a matter that should be taken into consideration in discussions on the issue of providing treatment to hypo-endemic areas?

(iii) Lessons from previous eradication programs

- ◆ **Learning from doing** One thing that does not come out clearly in the ten lessons from previous eradication lessons is the importance of learning by doing. Smallpox eradication and OCP are good example. People did not wait until all issues were resolved They started with scarcity of tools. Experiences in the use of existing tools, including organizational arrangements were the basis for deploying newer tools leading to success. Debate on issues such as 6 monthly treatment will be resolved in the field by ongoing studies and others.
- ◆ **Eradication programs require a vertical approach.** One of the ten lessons from previous eradication programs is that eradication requires a vertical approach. May be the full paper will provide some clarification. The term integration, like community participation has become overworked and can be misleading. Are the current policies of APOC, which favor integration an obstacle to eradication? And would they have to be changed if eradication is envisaged? As far as I know, failure of the malaria eradication program was essentially due to the fact that the program was organized vertically. The attack phase consisting of environmental reconnaissance, house to house spraying with residual insecticides to kill mosquitoes, was successfully carried out in many countries. The maintenance phase, during which new cases of malaria should be diagnosed and treated as they occurred, was a failure because basic health services did not have adequate coverage or capacity. There had been no concurrent effort to improve basic health services.
- ◆ **Time framework for eradication.** What lessons can we draw from previous eradication programs? Is a period of 10-20 years too long? Lessons outlined in the conference documents are silent on this point. Looking at time required for smallpox eradication, I would answer with a “NO”!

(iv) Participation in development of CDTI strategies

Clearly issues such as Ivermectin resistance, finding effective macrofilaricide for *O. Volvulus* and assessing impact of treatment need to be addressed by experts. But there are other issues such as whether effective community participation can be maintained for 5, 12 or 20 years; Achieving and maintaining high coverage rates and treatment in war and conflict situations, where extensive consultation and participation of communities is essential. I am not sure that there is adequate participation on these issues. We need to strengthen what APOC preaches, participation, participation. If we don't will make big mistakes. One example-medicated salt,

Mto wa mbu Tanzania will do. Villagers may be illiterate but they are not stupid. If I were asked to add another lessons from eradication effort I would say More faith in people.

COMMUNITY PARTICIPATION

MN Katarwa

Community participation implies:

- a) a “critical mass” of community members having access to vital information regarding the task to be undertaken;
- b) respect and utilisation/discussion of their local knowledge;
- c) a “critical mass” taking part in making decisions on who
 - should carry out community/household census,
 - collect ivermectin and
 - distribute ivermectin,

Individual community members in a general community meeting decide also on the time and place where distribution takes place and changing methods of service delivery to one that is convenient and less costly to all etc;

- d) responsibilities are identified and shared amongst individual community members and programme staff or /donors especially where external resources/skills are involved.

The involvement of appropriate community structures (Uganda situation) resulted into:

- a) zoning communities into kinship zones (respected traditional community structures) ensured equity and accessibility of health services delivery, a high level of transparency and accountability which resulted into individual members trusting the community-directed programme.
- b) selecting as many as possible community-directed health workers (CDHW) by their relatives/neighbours (hence ratio of CDHW: households is equal or less than 1: 4-6);
- c) community members or CDHW walking short distances to where the treatment services are provided;
- d) vulnerable groups such as elderly persons, children; pregnant mothers or those lactating within a week of delivery and sick persons being catered for;
- e) mass treatment being completed within a short time (mostly within 2 days); and
- f) promotion of active involvement of women in ivermectin distribution.

Potential for sustainable ivermectin distribution

Understanding community participation within the accepted community social structures and their social legal systems ensured:

- a) trust and respect of health care services delivered;
- b) a “critical mass” of community members attending health education and being involved in other community-directed activities such as selection of distributors, location of treatment centres, period of distribution, and mobilisation of other community members for treatment.
- c) equity and accessibility of services;
- d) compliance, attainment and sustaining of a desired coverage (at least 90% of the ultimate treatment goal);
- e) support of service providers such as CDHW, and community supervisors and health workers;
- f) involvement and service delivery to vulnerable groups such as the elderly, women youth and children;
- g) elimination of the concept and demand of external/monetary incentives as a prerequisite for service provision;
- h) transparency and accountability during health care delivery;
- i) development of skills at the community level required for disease control and prevention; and
- j) appropriate allocation of responsibilities and strengthened the partnership between communities, the public health care delivery services and donors.

Challenges for sustained and beneficial community participation:

- a) synchronising public health delivery systems with traditional structures and systems;
- b) empowering policy and decision makers with skills for enhancement of community involvement;
- c) timely generation and dissemination of valid information through research, on-going monitoring exercises and evaluation etc;
- d) aggressive promotion of dynamics of well researched and tested community-directed initiatives/interventions; and
- e) inadequate or lack of capacity to support services such as health education, training, supervision and monitoring for enhancement of community-directed initiatives by upper levels of public health care delivery services run by local governments.

Benefits of community participation:

- a) it is cost efficient;
- b) it equips community members with confidence and skills to manage CDTI activities as well as other health and development challenges;
- c) promotes equity, accessibility and trust in health care delivery; and
- d) it improves performance and sustainability of health programmes.

TREATMENT WITH MECTIZAN IN *LOA*-ENDEMIC AREAS

SEO Meredith

The Mectizan Donation program is in its 15th year and more than 200 million treatments have been administered in some 34 countries in Africa and Latin America. Mectizan is generally a very safe drug with few post treatment effects, and those that occur are related to the effect of the drug on the parasite and diminish with successive treatments as the parasite load is reduced.

As of January 2002, only 187 cases of Serious Adverse Events (SAEs) have been reported to the MDP and Merck since 1989. However in 1994 a cluster of serious CNS events was reported from Cameroon and it is now clear that there is a risk of encephalopathy in patients treated with Mectizan for onchocerciasis but who also have high *Loa loa* microfilaraemias. This syndrome has been termed “loa-related encephalopathy (temporally related to Mectizan administration)” (MDP, unpublished document, 1996).

Out of the 187 SAEs reported, 159 have been from Cameroon, and the others have all been from Loa-endemic countries, although the majority of those SAEs were not related to infection with *Loa loa*.

The countries endemic for Loaisis are generally known to be in the humid forest belt of Central Africa, with the most westerly focus in Benin and the eastern limits in Southern Sudan, though there is a report of patients with “sheathed microfilaria” resembling *Loa*” from Ethiopia (White, 1977). Currently, the precise distribution of the disease is not known and the best proxy indicator for loaisis distribution is based on the satellite mapping of the humid forest habitat of the *Chrysops* vector (Thompson et al, 2000.)

To date, the SAEs associated with infection with loaisis have mainly occurred in Cameroon with two possible cases from the DRC. The Mectizan Donation Program (MDP) organized a special consultation in 1995 to review and assess the cases, develop a working case definition and better define the known risk factors. When some of the treatment programs on Cameroon started to expand into new districts in 1999, another cluster of Loa-associated SAEs occurred and the MDP organized a second special consultation. This consultation addressed the management of cases and the SAE treatment guidelines were assessed and revised.

There is little doubt that the occurrences of the Loa-associated SAEs have impacted the community-based Mectizan treatment programs in Cameroon. Therapeutic and geographic and treatment coverages were reduced and compliance was very low.

The few known risk factors for the Loa-related encephalopathy temporally related to Mectizan administration are as follows:

- Living in a loa-endemic area

- The intensity of infection with *L.loa* > 8000 mf/ml blood (Gardon et al 1997)
- The prevalence of loasis in the community
- Males appear to be more at risk

In particular, the following issues have important implications for policies regarding Mectizan treatment in Loa endemic areas

- The need for better information on Loasis distribution, endemicity and intensity of infection.

Until recently, there was no reliable means of assessing the prevalence or intensity of infection with Loasis. However the new Rapid Assessment for Loa (RAPLOA), (TDR 2002) is a promising tool for mapping and defining the distribution of Loasis.

Recently, Boussinesq et al. (2001) have reported evidence of a direct relationship between the intensity and community prevalence of Loa infections, which will also be important for defining high-risk communities.

- The need for training of all levels of health personnel in the risk, recognition and management of SAEs following treatment with Mectizan
- The need for assessment of the training of the health workers
- The status of health care facilities and infrastructure
- The communication and transport infrastructure and facilities
- The inclusion of the non-governmental health care providers in the training and communication round Mectizan treatment in Loa endemic areas

A set of recommendations were developed by the MEC and Technical Consultative Committee of APOC (TCC) and distributed to Loa-endemic countries. These recommendations can be summarized as follows.

- Where 2 or more annual treatments with >60% coverage and no CNS events reported - community-based or CDTI treatment.
- No previous treatment, fewer than 2 rounds of treatment, <60% coverage, cases of serious CNS events reported – Rapid Epidemiological Assessment (REA) to be carried out to determine oncho endemicity.
- Mass treatment only for hyper-or meso-endemic communities with enhanced surveillance, training and health education.
- In hypo-endemic communities, individual or clinic based treatments should be offered to infected people following health education.

The implementation of these treatment policies clearly would have some implications for the treatment programs, the national authorities and the NGDO partners.

If all TCC/MEC recommendations were implemented, there would be

- Lower therapeutic coverage in many areas
- Safer treatment,
- Improved capacity of health centres and staff
- Increased cost to programs
- Some remote communities will not be treated

In Cameroon, there are two different situations to be considered when discussing treatment in areas hypo-endemic for onchocerciasis and endemic for Loiasis.

- 1) Communities that were previously under mass treatment with Mectizan for onchocerciasis, but with the REA, are now defined as hypo endemic and thus not eligible for mass treatment.

In general, previously treated people should be offered annual treatment with Mectizan (as long as no adverse effects have been experienced) through clinic, individual or other means. In certain situations the epidemiological situation e.g. the number of hypo-endemic communities/meso-hyper endemic communities, should be taken into account. It may be more cost effective to continue mass treatment as long as the enhanced health training and surveillance is in place.

Additionally, access to the communities and health care facilities needs to be considered.

- 2) New program areas with hypo-endemic communities
Hypo-endemic communities should not have community directed treatment with Mectizan (CDTI), but clinic or hospital based treatment. It is also recommended that all persons requesting Mectizan for the first time should have a calibrated thick blood film and should be treated with Mectizan only if negative for Loa or with >8000 mf/ml blood

To answer the main question of this meeting, can onchocerciasis be eliminated?

This is unlikely to happen in Cameroon, the DRC, Southern Sudan (Congo, CAR) unless considerable resources are made available to build the capacity of the Ministries of Health and improve health care infrastructure, country communications etc.

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**THE IMPLEMENTATION OF MASS DRUG ADMINISTRATION IN AREAS OF CONFLICT
OVERVIEW OF PRESENTATION**

CD Mackenzie, MA Homeida, I Mueller and M Ali

A. INTRODUCTION

Internal conflicts are depressing shadows hanging over mass drug administration programs for diseases such as onchocerciasis. It is easy to become depressed about the challenges of political unrest and its dampening or blocking effect on Mass Drug Administration of Mectizan® for onchocerciasis, or in fact any health problem. Indeed, one could reflect on the number of people still not fully covered by the treatment program in countries such as such as DRC, Rwanda, Sierra Leone and elsewhere. It is also perhaps all too easy to not address the needs of such countries, and to ignore the challenge of finding ways to get treatment active in these countries now; there is a tendency to wait until there is no conflict.

This presentation will highlight a positive approach taken by the Sudanese and their partners in the onchocerciasis program and the successes they have had. It is vital to address each situation of internal conflict individually, to do this now, and to develop logical approaches to their specific challenges to effective local MDA.

B. CONFLICT

- Definition of conflict
- Onchocerciasis endemic countries suffering from internal conflict
- General effects on health programs

C. THE PROBLEMS CONFLICT CAUSES TO ONCHOCERCIASIS PROGRAMS

- Mobility of the target population
 - *MDA is based on a sedentary population*
- Lack of commitment willing people
- Loss of trained personnel
- Movement of drugs to the areas is difficult
- The situations continually subject to change
- Communication and follow up assessment is problematic
- International negativity to such countries
- Financial implications
- Chronic diseases are not seen as the same as Acute Problems

D. A CASE IN POINT – The Republic of Sudan

- History
- Events in addressing the issue of “conflict & health”
- The Carter Ceasefire situation 1995
- Successes
- The principles applied in Sudan
 - *Two systems, but well coordinated*
 - *The role of NGOs*
 - *More verticality than other approaches*
 - *Trust must be build and fulfilled*
 - *Long term commitment*
 - *Endurance*
 - *Programme based on non-governmental organization*
 - *International support G2000, MSU, etc.*

E. SOME GENERAL PRINCIPLES TO APPLY IN CONFLICT AREAS

- The people’s view of disease versus the politician’s view
- Health as a non-political issue
- Role of women
- Role of the education & the family
- MDA as a “peace tool”
- Onchocerciasis is a “people” issue – not essentially a “political ball”
- Use it to develop health infrastructure
- Depends on the level of ferocity of the war

F. WHERE TO GO FROM HERE

- Where we need to focus
- Approaches made country by country
- Use opportunities for development
- Identify champions, dedicated people
- Communication outside the political arena
- What philosophical approach
- Be flexible
- NGDO are important
 - *G2000 & MSF examples*
- Establish formal connections at the United Nations level
- Need to identify and treat conflict countries differently – either informally or formally

- Give support
- What not to do!

G. IS IT A BLOCK TO TOTAL ERADICATION?

- Is rather a speed bump

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**FEASIBILITY OF ONCHOCERCIASIS ERADICATION: POLITICAL/SOCIAL ASPECTS
EFFECTS OF HUMAN MIGRATION ON DRUG DELIVERY, COVERAGE,
SUSTAINABILITY AND HEALTH SYSTEMS
DA McFarland**

Just as understanding the movement of the black fly vector is important to understanding the transmission of onchocerciasis, so appreciating the movement of people and populations is important for operational aspects of onchocerciasis control and elimination.

The reality is that people move. Migration is a fact of human existence. It has always been a key feature of people's survival and advancement strategies. This is particularly true of Africa. It has often been observed that there are few other regions in the world where the population is so mobile.

Internal migration accounts for most migration in Africa. Most people who move do so within their own country. Good data on migration patterns within countries are scarce.

Intra-regional migration is also important in Africa with people and populations moving into neighboring countries.

There are two major categories of migration – voluntary and forced. Voluntary migration is rarely a truly 'voluntary' activity. Certain people lacking resources such as money, information, and connections may not even have the choice to move.

Forced migration results in two categories of migrants – those who are internally displaced in their own country – IDP's – and those who are move across borders and thus become refugees.

Why do people move or migrate? They do so for a host of demographic, economic, social, political and cultural factors. These include:

- Migration is a way of life – e.g. nomadic populations
- Rapid growth in the population and the labor force
- Sharp rises in un-and underemployment
- Decreasing real incomes and growing costs of living
- Low agricultural production
- Food shortages
- Political instability
- Ecological disasters – e.g. volcanic eruption in Goma in last 2 weeks

Show three maps of APOC countries that indicate the movement of people within the respective country because of conflict or strife.

- Nigeria – large, recent population movements in highly endemic oncho areas, e.g. Taraba State, Kaduna State
- Guinea, Sierra Leone and Liberia – the nexus of these three countries, two OCP countries and one APOC country. Previously have looked at the migration of the black fly in this area. Also have massive population movements
- Uganda – less dramatic in terms of numbers, but a combination of IDP's and refugees, again in oncho areas.

The decision to migrate or move is rarely made by individuals acting on their own. It involves entire families as well as wider social structures and networks. This has implications for the kind of kinship structures that Katarwa has described as key to the selection of CDD's and for legitimate community directed programs. The decision to migrate concerns not just those who go, but also those who stay, and are closely related to the nature of the household economy. We need to understand the motivations and incentives of those who move and their economic status.

The implications of migration on the issue for this conference, i.e., the eradicability of onchocerciasis are:

- Drug delivery and coverage
- Census – who is where and when? The issue of what is the denominator is key for assessing coverage
- Selection of CDD's and integration into the community – migrants may be viewed as outsiders and not be party to the networks used to select CDDs and to determine treatment. Those migrants are more likely to refuse or to be absent during the treatment round.
- Underscores the need for segmented treatment strategies – those that are culturally and socially specific
- Security and access issues – well described by Charles MacKenzie in the previous presentation
- Increasing marginal cost of reaching hard to reach populations
- Continuity of a long term program over 12-15 years
- Migrants may be reservoirs of disease moving across areas where treatment coverage may not be occurring.

Implications for sustainability

- Government commitment and financing may be difficult to achieve for populations that are considered outsiders and not part of community fabric. Most obviously true at district, LGA level

- How to deal with IDP's versus refugees – different levels of support
- Poverty of communities – we must never forget that we are dealing with poor communities

Turning to a different area, but one critical to sustainability of oncho control/elimination is the issue of the effects of eradication programs on health systems. There is considerable controversy about this. Most of the evidence we have comes from the polio eradication program.

The positive effects of polio eradication appear to be:

- Strengthened management systems
- Improved social mobilization
- Increased surveillance laboratory capacity
- Increased confidence in the health system and politicians to deliver something tangible

The negative effects of polio eradication are:

- Missed opportunities for other preventive strategies with the exception of Vitamin A distribution
- Disruptions in health care delivery
- Mixed signals to communities regarding incentives for community workers
- A top down, global priority rather than a community priority

Importance of health systems highlighted by WHO in the World Health Report, 2000, that ranked the performance of health systems around the world.

Maps show that poor countries spend a significant proportion of their GDP on health expenditures. Need to ensure that the money is “well spent”. There is not a direct relationship between performance and resource allocation. Some of the poorest countries rank in the middle range of health systems performance. And some of the richest countries, e.g. U.S., rank lower than far poorer countries.

Conclusions

- Migration of populations, either voluntary or forced, is inevitable presenting difficult, but not insurmountable challenges for operations of oncho programs
- Biggest challenge is sustaining the political will of donors, national governments and communities to keep on keeping on
- Health systems and health delivery infrastructure, already fragile, cannot and must not be ignored in designing elimination and eradication strategies.

Dr. Achim Hörauf
Introduction to onchocerciasis work at the Hamburg conference

**RESEARCH NEEDS: INTRODUCTION TO ONCHOCERCIASIS WORK
AT THE HAMBURG CONFERENCE**
A Hörauf

September 19-23, 2001 saw the Bernhard Nocht Institute for Tropical Medicine and WHO/TDR host an international conference in Hamburg, Germany to review recent achievements in research and control of onchocerciasis and lymphatic filariasis. More than 100 scientists representing 22 countries provided a unique assemblage of expertise in filariasis gained both “from the field and from the laboratory.” At a time when "Global Alliances" have been formed to eliminate lymphatic filariasis and onchocerciasis as public health problems, this meeting focused on both, recent research advances and future research needs required to sustain these programmes and achieve their goals.

With regard to updating on research advances, the Hamburg conference which was made possible to a large extent by a contribution of the German Ministry of Health to the WHO/TDR, can be seen as standing in a series of other conferences over the last decades such as the conferences on onchocerciasis research to develop a vaccine, funded by the Edna Mc Connell Clark Foundation, or the Wellcome Trust series of conferences on filariasis research. The latter were continued at the Bernhard Nocht Institute on a bi-annual mode and finally resulted in the European Filariasis Conference held in September 2000, celebrating the 100th anniversary of the Bernhard Nocht Institute.

Major topics at the Hamburg Conference 2001 have been summarized in a conference report in *Trends Parasitol.* (2001) 17:566-7 (abstracts can be downloaded as a PDF file from the BNI homepage, <http://www.bni-hamburg.de> ->Willkommen -> Aktuelle Mitteilungen und Veranstaltungen -> Archiv -> Mitteilungen 2001 -> Internationale Filariasis Konferenz). They comprised research in both, onchocerciasis and lymphatic filariasis, and also in loiasis. Despite cancellations (the conference took place one week after the World Trade Centre attack) many of those who had to cancel still managed to give important input through e-mailed presentations which were held by their colleagues.

Prior to the conference, after discussions between the organizers of the Atlanta conference and the WHO/TDR co-organizers of the Hamburg conference, it was considered that the Hamburg conference would provide an excellent opportunity for a review of the state of the art in chemotherapy, diagnostics, immunology and drug development, since many of the leading experts in these topics would be present. Accordingly, the last day of the Hamburg conference was reserved for break-out into discussion groups whose task was to provide reviews of these topics including further research needs, with special emphasis on onchocerciasis, for presentation at the Atlanta conference. In the following presentations, the rapporteurs will give their summaries that are based to a large part on the results and reserach needs identified during the Hamburg Conference 2001.

RESEARCH NEEDS: UPDATE ON EXISTING DRUGS FOR ONCHOCERCIASIS
DW Büttner and A Hörauf

Introduction

Chemotherapeutic mass treatment of human onchocerciasis needs drugs effective against microfilariae (mf) or juvenile or adult female or male worms. Because of the rather short life of infective (L3 a few days) or fourth stage larvae (L4 a few weeks) these are no good targets for chemotherapeutic mass treatment. They would demand either a drug depot or frequent administrations. A final conclusion on the efficacy can only be based on studies on human patients. The results of tests on *Onchocerca volvulus* in vitro or in laboratory rodents are only preliminary and experimentally infected chimpanzees are almost not available. Therefore, existing drugs are those that have shown their efficacy in human onchocerciasis patients. The number of these drugs is limited and most of them are considered to be not suitable for mass treatment. Some of them are presently not produced. Regarding the costs and the time needed for development the research should focus on drugs that have already been registered for use in humans.

Overview of existing drugs

Both **macrofilaricidal** drugs, melarsoprol (trimelarsan) and suramin are used for the treatment of African trypanosomiasis. Because of their toxicity and the mode of administration demanding repeated injections they are presently no longer considered to be suitable for mass treatment of onchocerciasis patients. The macrofilaricidal activity of amocarzine is doubtful and it is toxic. Its development has been stopped before registration.

Among the **microfilaricidal** drugs, ivermectin is presently the drug of choice for onchocerciasis. Diethylcarbamazine (DEC) was previously widely used for onchocerciasis and lymphatic filariasis, but because of its adverse side effects, it is presently not recommended for onchocerciasis patients. Metrifonate, an organophosphate, that had been used for human urinary schistosomiasis, is no longer produced by Bayer. Suramin, amocarzine and the benzothiazole CGP 20376 are probably too toxic. Extracts from the bark of *Cassia aubrevillei* containing chrysophanic acid, which are frequently used as a traditional herbal drug in Liberia have only been studied with limited numbers of patients. However, a careful search may reveal other traditional herbal drugs with antifilarial activity.

Embryotoxic drugs are ivermectin, the benzimidazoles albendazole and mebendazole citrate, and suramin. The embryotoxic activity of ivermectin and of the benzimidazoles does not cause sterility of the female worms, at least not as long as the presently used regimens are administered, and the female worms recover after a few weeks (benzimidazoles) or after about 8-12 months (ivermectin). A combination of ivermectin with albendazole did not show a better

efficacy than ivermectin alone. A long lasting inhibition of the embryogenesis has so far only been observed after therapy with doxycycline, that eliminates the endobacteria of *O. volvulus*.

Concerning the mentioned existing drugs more research may be needed on ivermectin alone and its combination with other antifilarial drugs and on antibiotics eliminating the onchocercal endobacteria.

Ivermectin

The administration of ivermectin may need further research. Several results of previous studies on ivermectin and moxidectin suggest that the regimen of ivermectin administration can probably be designed more effectively. Can higher doses (400 microgrammes/kg or more) administered more frequently (every 3 – 6 months) for several years (2-5 years) prevent male worms from mating or cause sterility or kill the adult worms?

If the development and spreading of ivermectin resistant *O. volvulus* is considered to be a real risk, research may be needed to prevent this or to delay it, and a reserve microfilaricidal drug may have to be developed in time to replace ivermectin.

For the prevention a multidrug regimen combining ivermectin with another microfilaricidal drug may be suitable. DEC is no longer used for human onchocerciasis because of its adverse side effects. However, after elimination of most microfilariae by ivermectin the adverse effects caused by a few resistant microfilariae treated with DEC may be negligible. Alternatively Bayer or another company may be asked to produce at least enough metrifonate for clinical trials to study the effects of a single dose of metrifonate administered after ivermectin. Moxidectin is not mentioned here since it is not yet an existing drug for *O. volvulus*.

Antibiotics

Many filariae harbour endobacteria in the hypodermis, in oocytes, all embryonic stages and microfilariae. All *O. volvulus* worms from Yemen, Mexico, Guatemala, Brazil, and 8 African countries that were examined presented large numbers of endobacteria in their tissues. These endobacteria of the genus *Wolbachia* belonging to the Rickettsiales are sensitive to several antibiotics among which the tetracyclines have been examined most widely. The *Wolbachia* can be eliminated by antibiotics and the removal of the endobacteria has several effects on the filariae, which vary depending on the treatment regimen. Usually an interruption of embryogenesis was observed. The most promising result was seen in cattle infected with *O. ochengi*, where tetracycline showed macrofilaricidal activity. Some of the effects of tetracycline are probably independent of the antibacterial activity and they may have been caused by the antibiotic itself as prevention of larval moulting. Antibiotics that have shown *in vivo* activity against *Wolbachia* are so far tetracyclines, rifampicin and less effectively chloramphenicol. Further experiments may identify a few more antibiotics, e.g. azithromycin.

Doxycycline trial with onchocerciasis patients

Based on the promising results of the animal experiments, onchocerciasis patients have been treated since 1999 in hyperendemic villages in south-western Ghana along the Ofin river. The patients received 100 or 200 mg doxycycline per day for several weeks. The activity against the endobacteria and the filariae was evaluated by examination of microfilariae in the skin and of the adult worms in extirpated onchocercomas 2-18 months after the begin of the chemotherapy. Microscopy, immunohistology and PCR were used for the assessment. So far mainly the results of the treatment with 100 mg doxycycline per day for 6 weeks are available. The activity of doxycycline in human onchocerciasis observed was the following:

- Elimination of endobacteria,
- blockade of embryogenesis,
- decreased insemination of female worms,
- and with ivermectin given after doxycycline a strong and sustained (18 months) reduction of microfilaria loads to levels < 0.3 mf/mg.

This regimen was neither distinctly macrofilaricidal nor microfilaricidal and it caused no obvious inhibition of spermiogenesis.

Preliminary results achieved with other doxycycline regimens indicated the following:

- 100 or 200 mg doxycycline per day for 2 weeks did not eliminate the endobacteria or interrupt the embryogenesis.
- 200 mg doxycycline per day for 4 weeks may have the same efficacy as 100 mg for 6 weeks.
- Two or 3 additional weeks of treatment with doxycycline administered after intervals of 2 months do probably not enhance the efficacy significantly.

More research is needed since the present regimen of doxycycline administration is not applicable for general mass treatment because of the long duration of the therapy, the exclusion of pregnant women and of children less than 9 years old.

- The minimal duration of doxycycline treatment has to be identified.
- Periods of observation longer than 18 months may be needed.
- The efficacy of other antibiotics and of combinations has to be studied, e.g. of rifampicin and azithromycin.
- The optimal timing of ivermectin administration after therapy with antibiotics has to be identified.
- Regarding the results seen with *O. ochengi* one may search for a regimen that has a macrofilaricidal effect.
- (It has to be investigated which other research is needed due to legal implications.)

Preliminary indications

The preliminary indications for individual or group treatment of onchocerciasis patients with 100 mg doxycycline per day for 6 weeks followed by 1 or 2 doses of ivermectin may be the following:

- Patients who migrate from endemic areas to controlled areas.
- In controlled areas (OCP and America) remaining or newly arrived patients, microfilariae carriers and prepatent individuals.
- For such small groups of patients administration of antibiotics for several weeks plus ivermectin may be more advantageous than several years of ivermectin treatment, which does not eliminate all microfilariae thus leading to continued transmission.

DEVELOPMENT OF NEW DRUGS FOR ONCHOCERCIASIS
AT Hudson

The management of onchocerciasis is dangerously dependent upon the use of one drug, ivermectin. New medicaments are urgently required, primarily to act against adult worms – either by having a direct macrofilaricidal action or by effecting permanent sterilisation. There is also a secondary need for an oral microfilaricide which would not be cross-resistant to ivermectin. In this summary the immediate prospects for new drugs are reviewed along with the strategies which could significantly impact upon the earlier stages of the discovery research pipeline.

Drug discovery research is an iterative, multi-disciplinary process with an increasing rate of attrition as compounds pass along the pipeline into the clinical phase of testing. It consists of a number of distinct stages:

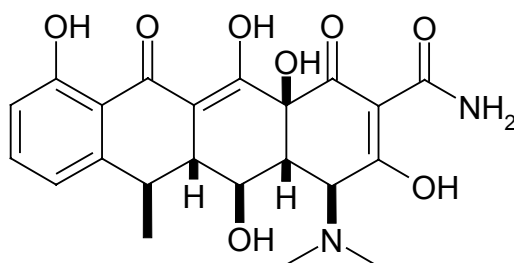
1. Target identification/validation
2. Assay development
3. Lead identification
4. Lead optimisation
5. Pre-clinical development
6. Clinical evaluation

In order to be sure of success the pipeline must be fed with a steady flow of active molecules - ‘hits’- identified from discovery screens and then modified through lead optimisation programmes into efficacious, metabolically robust molecules with healthy therapeutic indexes. Currently the onchocerciasis pipeline is grossly unbalanced with 2 compounds in the clinical phase of testing, doxycycline and moxidectin, and then virtually nothing else other than very early stage research programmes which have yet to yield credible lead molecules.

Compounds in clinical development

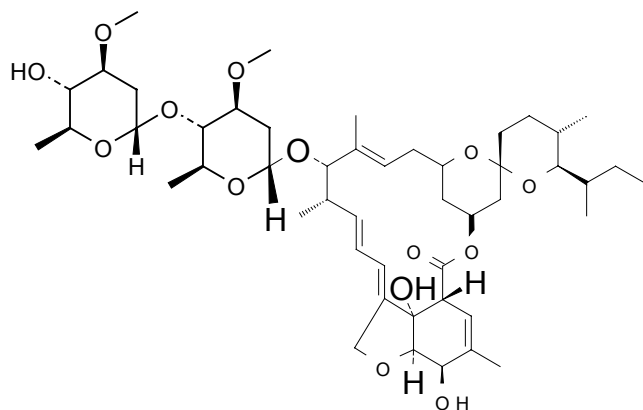
Recent *in vitro* and *in vivo* data have provided circumstantial evidence for the essential role of *Wolbachia* endobacteria in symbiosis with all the human filarial nematodes (for recent review see Taylor MJ, Hörauf A. A new approach to the treatment of filariasis. *Curr. Opin. Infect. Dis.* 2001; 14; 727-731). Various antibiotics show anti-filarial effects on *Wolbachia*-positive worms yet lack activity on the *Wolbachia*-negative species *Acanthocheilonema viteae*. Clinical evaluation of one such antibiotic, doxycycline, shows that in ivermectin-treated patients the drug causes long-term sterilisation of *O. volvulus* adults when 100mg per day are administered orally for 6 weeks. In addition to decreasing microfilariae levels, in support of an anti-*Wolbachia* mode of action, doxycycline virtually also eliminated the bacteria (Hörauf A, Mand S, Adjei O, Fleischer B, Büttner DW. Depletion of *Wolbachia* endobacteria in *Onchocerca volvulus* by doxycycline and microfilaridermia after ivermectin treatment. *Lancet* 2001 May 357;

9266; 1415-6.). Because doxycycline is contraindicated for children or pregnant women it will not be possible to use the drug with the current dosing regimen for mass treatments. Alternative dosing schedules, or other licensed antibiotics may offer opportunities for clinical usage beyond individual treatments, e.g. rifampicin – see Townson S et al. Antibiotics and *Wolbachia* in filarial nematodes: antifilarial activity of rifampicin, oxytetracycline and chloramphenicol against *Onchocerca gutturosa*, *Onchocerca lienalis* and *Brugia pahangi*. Ann. Trop. Med. Parasitol. 2000; 94; 801-816. More long term it should be possible to identify novel anti-*Wolbachia* agents. However, before investing too much in such work it would be prudent to provide more direct evidence at the molecular level for the central role of *Wolbachia* in the mode of action of the anti-filarial antibiotics.

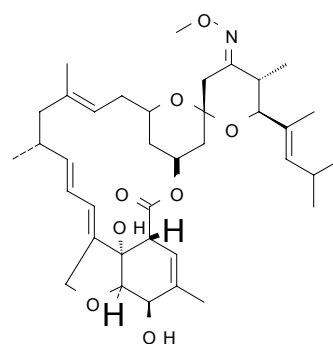


Doxycycline

Moxidectin, an analogue of ivermectin, is in widespread use as a veterinary anthelmintic. Promising data has been accrued on the potential of this drug in the treatment of human filariasis. Although the compound is little different to ivermectin when tested *in vitro* against microfilariae, *in vivo* it shows significant advantages being both more active and persistent (Tagboto SK, Townson S. *Onchocerca volvulus* and *O. lienalis*: the microfilaricidal activity of moxidectin compared with that of ivermectin *in vitro* and *in vivo*. Ann. Trop. Med. Parasitol. 1996; 90(5); 497-505.). In addition it has shown macrofilaricidal effects against *B. pahangi* in dogs, a single dose of 1000µg/kg giving complete clearance of adult worms (McCall J. et al. Poster presented at the Amer. Soc. Trop. Med. Hyg. Annual Meeting, Washington D.C, November/December 1999). The compound has now entered into the clinical phase of evaluation, initially being studied in healthy volunteers.



Ivermectin



Moxidectin

Pre-clinical research

In the last decade the early stages of the drug discovery research process have changed dramatically, driven by advances in molecular biology and automation which at the beginning of the 90's ushered in the era of high throughput screening (HTS). This in turn created an insatiable demand for compounds which was met by medicinal chemists devising combinatorial synthesis strategies which allowed large and diverse chemical libraries to be rapidly generated. Concomitantly, this demand for compounds led to the establishment of commercial suppliers of both proprietary and non-proprietary compound libraries. HTS coupled with a ready supply of test compounds is now viewed as the obvious strategy for attacking the flood of molecular targets which are starting to emerge from the huge investment in genomics. Increasing attention is also being paid to virtual screening as a cost-effective way of achieving far greater molecular diversity than can ever be attained by laboratory syntheses. The hits identified *in silico* are used as the basis for creating focussed libraries usually made up of 1, 000 - 10, 000 compounds as opposed to the more normal 100, 000 to 1 million used in 'real' HTS campaigns.

Unfortunately it is not been feasible until very recently to apply the modern pharma research paradigms to the discovery of new anti-*Onchocerca* agents. This is because of limitations in compound supplies and difficulties in carrying out HTS campaigns in non-commercial centres. However, it is now possible to purchase large numbers of compounds from the 40 or more commercial suppliers and also to commission specialist companies to develop protein-based assays suitable for HTS format. The latter can then run campaigns screening whatever numbers of compounds are thought necessary to identify credible leads. On-going work recently funded by the WHO include tRNA synthases from *Onchocerca* and secretory venom allergen-like proteins and nuclear receptor (NR) transcription factors from *C. elegans*.

Providing the appropriate finances are made available to allow purchase of compounds and commission screening, it should now be possible to harvest the most attractive of the molecular targets starting to emerge from analysis of the genomes of *Brugia malayi*, *Onchocerca volvulus* and *Wuchereria bancrofti*. However, it has to be recognised that such investment will lead to the identification of lead compounds, not drugs. Consequently there has to be funding and management strategies in place to facilitate progression of such compounds through the often most difficult and rate limiting stage of the drug discovery process – lead optimisation. It may well be that in order to achieve success a new management system might have to be instigated, for example along the lines of the recently established Medicines for Malaria Venture. The latter in the short space of several years has built, financed and is managing a complete anti-malarial drug discovery pipeline and there seems no reason why a similar filariasis-focussed organisation shouldn't be equally successful.

UPDATE ON DIAGNOSTICS FOR ONCHOCERCIASIS ERADICATION

G J Weil

Introduction: Any program for onchocerciasis eradication will need efficient means for identifying endemic areas to be targeted for intervention, for monitoring changes in infection rates and transmission during the course of the program, for determining whether the goals of the program have been achieved (“certification”), and for post-eradication surveillance.

Identification of endemic areas: Control programs such as OCP and APOC are aimed at preventing disease. Rapid assessment methods (e.g., leopard skin rates in men) were developed as surrogates for parasitology screening to efficiently identify areas at greatest risk for blinding disease. However, such low-tech rapid assessment methods are not sensitive enough for eradication programs. Eradication programs need to identify all endemic areas, not just those with high disease rates and risk. Diagnostic methods must be cost effective, reasonably sensitive, very specific, and acceptable to target populations.

Assessing progress toward elimination / eradication: In addition to information on the presence or absence of onchocerciasis, eradication programs also need to be able to document changes in infection rates and transmission over time. It will take many years to achieve eradication of onchocerciasis. Sponsors and other stakeholders will want to see objective data from time to time on effects of the program on infection rates and transmission. The keys here are selection of sentinel study sites and standardization. Tests and sampling methods must be standardized to permit “apples to apples” comparisons over time. Training materials and regional workshops will be needed to increase uniform implementation of the agreed-upon standards.

Use of diagnostic tests to define program success: Diagnostic tests will be critically important as tools for knowing when to declare victory in areas/countries. Clear goals need to be set early on to know when to stop treating formerly endemic areas and move on to post-eradication surveillance. Diagnostic tests for this purpose need to be focused on detecting current or recent transmission. Such tests need reasonably good sensitivity, but specificity is perhaps more important if we want to avoid needless prolongation of intervention activities. There is no current consensus on the optimal tools and targets for this purpose.

Available tests for human infection / exposure to onchocerciasis

Clinical examination (skin, nodules, slitlamp exams) is a start, but this is not sensitive enough for any stage of eradication programs. Also, disease is a poor indicator of ongoing transmission.

Skin snips for microfilariae (MF): Skin snips are insensitive for detecting early (prepatent) or low intensity infections. This test is inconvenient and somewhat invasive; some populations refuse skin snips because they fear transmission of blood-borne diseases.

Diethylcarbamzine (DEC) patch test: Filter paper with DEC cream is placed on the skin under a bandage, and the test is read after 48 hours. A papular skin rash indicates local death of microfilariae. This method was described many years ago and recently restudied by OCP in W. Africa (Toe et al, Trans Roy Soc TMH 2000). Briefly, the sensitivity of the test was only fair (56-80%) in people with positive skin snips. Patch test rates correlated well with MF prevalence rates in untreated populations, and the authors recommended the test as an alternative to skin snips. However, there are lingering questions about specificity, and some patients develop significant adverse reactions to the DEC cream. The direct cost of materials is only \$0.12 per test, but the need to read the test at 48 hours decreases its field applicability.

Parasite DNA detection by PCR: *Onchocerca* DNA can be detected by PCR amplification of a 150 bp repeated sequence in genomic DNA, the O-150 repeat. The method (described by P. Zimmerman and T. Unnasch) involves several steps: Isolation of DNA from skin snips or scrapings, PCR with genus-specific primers, and detection of amplified product with a species-specific oligonucleotide probe. This is the only method available that can distinguish forest and savannah strains of *O. volvulus*, and it is the most sensitive method developed to date for detecting *O. volvulus* parasites in human skin. PCR is also much more sensitive than dissection with microscopy for detecting *O. volvulus* larvae in flies, and it can easily distinguish *O. volvulus* larvae from related animal parasites in black flies. Pooled samples of flies can be tested to improve the cost effectiveness of this test, and the test has been successfully used for years in endemic country labs in West Africa and Latin America. However, this is still an expensive test, and it is very demanding in terms of laboratory infrastructure and skilled personnel.

Antigen detection: This option has been extensively explored by several research groups. *O. volvulus* antigen is sometimes detectable in sera or urine from infected patients, but the sensitivity of antigen testing is too low for it to be practically useful.

Antibody assays: Recent advances in this field have included identification of several *O. volvulus*-specific recombinant antigens and the demonstration that specificity can be improved by measuring IgG4 subclass antibodies. The recent success of a rapid format card test for lymphatic filariasis prompted us to explore this technology for onchocerciasis with recombinant antigen Ov16 (Lobos et al, Science 1991). Prior studies showed that an ELISA based on this antigen was sensitive and specific for onchocerciasis and that antibodies to Ov16 often developed in experimentally infected primates and naturally exposed children long before the first appearance of MF in skin snips. AMRAD ICT in Australia developed a prototype card test that detected IgG4 antibodies to the antigen in 15 minutes. The card test was first evaluated with selected sera in two labs (Weil et al., J Inf Dis 2000). The test had a sensitivity (vs. skin snips) of 90% and excellent specificity. Sensitivity was the same for sera from Africa and Latin America and also equal for sera from children and adults.

The next step in the evaluation was to try the card test in the field. The company modified the test for use with fingerprick blood samples and packed the tests in the “rapid assessment kit”

format. Field studies were performed in late 1999 in collaboration with the OCP in West Africa. These studies compared the sensitivity of the card test with skin snips in villages with differing levels of endemicity. Over 1,500 people were tested. The test was well accepted by the people (adults and children). Sensitivity compared to skin snip was 81% overall (75-95%). Higher values were seen in villages with low infection intensities following treatment than in untreated hyperendemic villages. As with the DEC patch test, many residents of endemic villages with negative skin snips had positive antibody tests, and antibody rates correlated well with MF prevalence rates in untreated villages. Sensitivity was equivalent in children and adults. Specificity results were reassuring. Only 2 of 160 people under age 20 in formerly hyperendemic villages where transmission had been interrupted for 20 years had positive tests, and these were recent migrants. Many older adults in these villages had positive antibody tests. These results emphasize the need to focus on young children when using the card test in eradication programs.

Over the past year, a number of groups have used the Ov16 antibody test in different settings in Latin America and Africa. Approximately 12,000 tests were used, with the greatest numbers being used by OCP and OEPA. In general, their results have confirmed our early field experience with the test. Sensitivity was fairly good, but variable (range 70 to 100 % for blood from people with positive skin snips). Perhaps more importantly, seroprevalence rates in children were consistent with expectations, with no unexplained positives in children borne in areas where transmission was interrupted and many positives in areas with ongoing transmission. Specificity was consistently excellent; studies by Drs. Brattig and Buettner in Hamburg showed that sera from patients with *M. streptocerca* were not reactive in the assay. They also found that the test worked well with sera from an area of Uganda with a high prevalence of HIV. The main advantages of antibody detection are simplicity and sensitivity for early infections. The card test is a very convenient means of detecting antibodies. People do not mind providing finger prick blood; this method is widely employed for malaria screening. The test provides a rapid result on the spot with a standardized format. It does not require extensive training, expensive equipment, or transportation of specimens to central laboratories for testing. One limitation of antibody tests for onchocerciasis is that they not provide proof of current infection with sexually mature *O. volvulus* parasites. Antibodies to Ov16 may indicate current mature infections, prepatent infections, past infections, or even heavy exposure to *O. volvulus*. Despite this caveat, these results suggest that the Ov16 antibody test should be useful in the clinical setting for confirming the diagnosis in individual patients suspected of having onchocerciasis. More importantly, the test has great potential as a tool for large scale efforts to eradicate onchocerciasis. First, antibody testing can be used as a primary surveillance tool for efficiently detecting infections and recent transmission in untreated communities. Second, the card test may be useful for monitoring the success of control programs that aim to interrupt transmission. For example, serial surveys of antibody prevalence rates in young children or studies of seroconversion rates in children may be practical and useful approaches to this pressing problem. Antibody testing should be especially useful for detecting ongoing exposure to the parasite in areas where MF rates have been reduced by ivermectin therapy. Finally, antibody testing of standardized samples of children may be valuable in the later stages of eradication programs as a tool for detecting residual foci of transmission or for documenting the absence of transmission.

Availability of antibody testing: The Ov16 antibody card test is not available commercially. Prototype tests used in field studies were manufactured in Australia by AMRAD ICT. AMRAD ICT failed financially, and a successor company in the USA has made a business decision that they are not going to produce the tests. This is because they believe the market is too small and uncertain for them to invest the money needed to develop the test and obtain regulatory approval. The antigen can be used in other formats; we have identified a company outside of the USA that is beginning studies that may lead to a new rapid antibody test based on OV16. But in the end, the market may fail us here. Just as ivermectin is subsidized, subsidies may also be required if we are to have diagnostic tests needed for eradication of onchocerciasis.

Which test(s) to use for eradication programs?: There is no consensus on this at this time. In my opinion, different tests may be needed for different phases of the eradication program. Antibody testing, skin snips or the DEC patch test could be used to identify endemic areas. I think that antibody testing of standardized samples of young children (3 to 5 years of age) would be an efficient way to go for monitoring progress and for certifying eradication. I also think that parasite DNA detection in *Simulium* vectors should be used as a second tool for monitoring progress and for certification.

Recap: Different diagnostic tools may be needed for different phases of an eradication program for onchocerciasis (primary surveillance or mapping, interim monitoring, certification, and post-eradication surveillance). Specificity is more important than sensitivity, especially in later phases of the program. New tools include the rediscovered DEC patch test, parasite DNA detection in skin and flies by PCR, and a rapid format antibody assay for use in the field. No eradication program will be successful without good diagnostic tools. However, more thought and discussion are needed to determine the best ways to use these tools and to develop standards for the program. Help is also needed to encourage commercial development of an antibody test for field use.

Appendix D

Working Group Presentations

	<i>Page</i>
1. Feasibility of Eradication with Ivermectin	135
2. Drug Delivery and Distribution Strategies	139
3. Monitoring and Surveillance	141
4. Product Research and Development	144

Working Group #1: Feasibility of Eradication with Ivermectin

Presented by DH Molyneux

Working Group # 1

FEASIBILITY OF ERADICATION WITH IVERMECTIN

FEASIBILITY OF ERADICATION WITH IVERMECTIN

- No evidence is available that onchocerciasis is eradicable with currently available tools and at current levels of resourcing.
- There is evidence from the Americas and some sites in Africa that transmission can be interrupted in isolated foci. This must occur before eradication can be achieved.

FEASIBILITY OF ERADICATION WITH IVERMECTIN

Evidence on the impact on transmission after 12 years of ivermectin use

AFRICA

- "use of ivermectin does not give a secure and consistent interruption of transmission"
- When ivermectin is used effectively interruption of transmission has occurred

AMERICAS

- "When ivermectin is used effectively interruption of transmission has occurred"

FEASIBILITY OF ERADICATION WITH IVERMECTIN

- There is no area where there is clear evidence that transmission has been interrupted with strategies based on only ivermectin.
- Areas where transmission interruption may have occurred but evidence (entomological data) is not available (Senegal 2 x 12 yrs; Mali annual 12 yrs).
- Despite high annual coverage over 12 years transmission has continued in several foci (Togo, Cameroon).

FEASIBILITY OF ERADICATION WITH IVERMECTIN

AMERICAS

- Semiannual treatment in parts of Ecuador, Mexico and Colombia has interrupted transmission.
- Foci in Venezuela, Brazil, Mexico and Guatemala transmission has probably not yet been interrupted due to low therapeutic and geographic coverage.

FEASIBILITY OF ERADICATION WITH IVERMECTIN

Latest model predictions of feasibility of elimination

AFRICA ONCHOSIM

- Onchosim model has predicted that in isolated foci ivermectin treatment could interrupt transmission.
- However in the African situation, migration coverage issues and fly migration perturb predictions.
- Onchosim for isolated foci is too optimistic in its predictions after 12 years treatment regimens.
 - 3 separate situations when modeled, did not fit data, especially after more than 5-10 tx rounds

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

AMERICAS

- SIMONa simulation of specific foci in Ecuador match available data following 11 years of semiannual Mectizan® and predict interruption of transmission and eventual elimination of onchocerciasis with this strategy. This could be extrapolated to most American foci.
- It is proposed that modeling should be applied to African and American data in a comparable way.

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Principal determinants of feasibility

- Complete geographical coverage and high therapeutic coverage (avoid systematic non compliance)
- Human migration/fly migration
- Continued efficacy of Mectizan®
- Available human resource capacity
- Endemicity levels

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Favorable factors, obstacles, challenges

- Political Will
 - Donors (\$)
 - Merck commitment
 - Host countries (stability, \$)
 - NGO community
 - International agencies
 - Sustained active and inclusive partnership
 - Regional collaboration
 - Disease of Poverty-poor people, poor countries, no threat to the West

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Favorable factors, obstacles, challenges

- Drug Issues
 - Merck commitment
 - Safety
 - Acceptability
 - Potential for resistance
 - Over dependence on single drug

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Favorable factors, obstacles, challenges

- Operational Issues
 - Migration
 - Human
 - Vector
 - Loa Loa
 - Conflict Situation
 - Seasonality of transmission in Americas and savanna sites in Africa

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Favorable factors, obstacles, challenges

- Health Systems Issues
 - Reform process
 - NGOs
 - Priority level/Burden of disease
 - Drug delivery systems
 - Human capacity
 - Potential for integration with other programmes
 - Disease of poverty
 - Regional collaboration
 - CDTI is driver for integrative intervention in Africa
 - Drug brings additional health benefits

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Why Oncho?

- Donors see endpoint
- Donated drug/safe efficacious/popular with communities
- Eliminable in isolated foci
- Disease of poor rural people

"If we cannot deliver one intervention once a year how can we have any functional effective health system"

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Success Factors

- Progress made
- Intervention works (prevents blindness, alleviate itching/skin disease)
- Research has had proven impact in ensuring cost effective control and appropriate change in strategies.

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Constraints

- Compliance in communities could reduce as symptoms recede hence elimination goal threatened
- Donor fatigue

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Recommendations

More information on impact of ivermectin (including frequency of distribution) on transmission in different settings

Extend and develop modeling using available data in both geographical area. Models should take account of lack of isolation of endemic communities; complementary and comparative studies between different models should be undertaken

Based on most current data and modeling predictions, it is recommended that programs aim for the interruption of transmission using all available interventions in isolated foci, which includes most if not all the Americas, and possibly Yemen and some sites in Africa.

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Recommendations

Need to develop and test drug delivery strategies that will ensure and sustain high levels of coverage in the many and varied sociological, cultural and epidemiological settings where oncho is endemic. Need research [field based and mathematical modeling] leading to a better understanding of very low levels of I_2 transmission on sustaining an autochthonous transmission cycle [endemicity].

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Recommendations

There is a need for R & D to optimize impact of an intervention which is "marginal technology" (Group 4) * However Group 1 endorses a need for diagnostic, chemotherapeutic and immunoprophylaxis research

Health system and operational research will continue to be required to optimize interventions

Biological significance of low level transmission

Drug delivery strategies

Loa Loa issues

Potential resistance to ivermectin

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Recommendations

Cost benefit of interventions are required and these studies should be linked to models.

Research agenda should include research on:

New strategies

Integration of oncho programs into the health structures and link with other disease control programs

New funding strategies

Implementation and program management

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

Recommendations

Review and strengthen new partnerships (to enhance communication, collaborations, share knowledge, accelerate application of effective interventions) that bring together:

Programs in all geographic areas

Researchers

Donors

NGOs

Corporations/Pharmaceutical manufactures

Governmental agencies

FEASIBILITY OF ERADICATION WITH
IVERMECTIN

- The group adhered to the definition of eradication as a global concept.
- The answer to the simple question: *is onchocerciasis eradicable with current knowledge and tools?* -No.

Working Group #2: Drug Delivery and Distribution Strategies

Presented by MN Katarwa

Drug Delivery and Distribution Strategies

- Drug Delivery
 - Good forecasting and communicating needs for drugs early enough to allow manufacturing packaging and shipping within good time
 - Accuracy of documentation
 - Governments should take responsibility for cleaning and exempting drugs from taxes
 - Merck & Co. reaffirmed commitment to supply ivermectin as required and as long as necessary

Political Commitment by Governments

- Through commitment of resources necessary for eradication/elimination of onchocerciasis
 - WHO and UNICEF offices could be used to enhance momentum for advocacy at the highest level of governments
 - Quantitative indices for country performance could encourage competition and advocacy for political commitment

Distribution Strategies: OEPA

- There is need to share experience across programs and countries/regions
- Need for flexibility depending on situation
- Objective should be attained at a high coverage of at least 85% of UTG and sustained
- Continued health education tailored to existing knowledge in the communities should be encouraged. This should be achieved through research

Distribution Strategies: APOC

- LF/Oncho areas where ivermectin/albendazole are distributed and that are hypoendemic need to be monitored as a natural experiment in order to see the outcomes
- This will include hypoendemic areas in OCP that are being subjected to ivermectin

Health System Structure

- Strengthen the health system at the periphery levels in order to improve its function
- CDT in Africa should be recommended to the nations involved as a complimentary system for strengthening health care delivery at the periphery
- Promote data-driven interventions as they will ensure better coverage and sustainability

Role of Community

- There is need to encourage communities to get involved in self-monitoring of their programs and providing feedback to the rest of their members and other relevant partners

Partnership

- Need to strengthen partnerships
- More partners are needed (both local and international)
- Partnerships are critical for planning, decision-making, joint advocacy and resource mobilization
- There is need to minimize unhealthy competition between partners

IEC

- Strengthen capacity at different levels for IEC
- Need for production of appropriate IEC materials

Areas of Conflict

- Aggressive advocacy for ceasefires in order to allow program activities to take place
- Use health to promote peace
- Allow for flexibility in implementation strategies of programs
- Highlight the importance of areas locked in conflict zones as reservoirs for infection
- Be sensitive to the needs of people in conflict areas
- Advocate for annual weeklong ceasefire for immunization and other disease control

Funding

- Need for better knowledge of the complete cost of the project/program incurred by all partners in order to sustain control or eradication of onchocerciasis
- Need to know areas where cost will be incurred by each country and region for planning and advocacy
- Need to know the cost to be borne by individual countries and what would be required for eradication

Operational Research

- Investigate seasonality of drug distribution where maximum benefits pertaining to interruption of transmission can be achieved
- Develop better strategies for marketing CDT in health delivery systems
- Investigate the frequency of distribution to obtain maximum benefits/effectiveness in respect to cost/operational difficulties and coverage related to eradication
- Studies/monitoring needed in areas where coverage is low

Operational Research (continued)

- In OEPA areas, there is need for identifying better strategies for ivermectin delivery which should include cost per capita by individual countries and at regional level
- There is need for capacity building for operational research at program level

Working Group #3: Monitoring and Surveillance

Presented by W Grant

General Comments

- Surveillance is in place in all current programs but there may be a need to strengthen the existing procedures
- Surveillance will differ qualitatively & quantitatively between control & eradication. Major differences are frequency, depth and duration.
- Monitoring period divided into pre-treatment, treatment, [pre-certification & certification]. Our discussion was mainly on pre-treatment and treatment phases

General Comments

- Some attempt to differentiate between Africa (OCP and APOC) and Americas but no input from OEPA and discussion tended to be more general
- Additional resources are required, especially if the goal is eradication
- Our conclusions are largely similar to Sept. 2000 but with some significant differences, particularly on the scale of monitoring required and the explicit inclusion of IVM-resistance as a factor

General Comments

- At all levels, new models should be considered based on new modelling tools (e.g. BSE and FMD)
- Report divided into operational (process/program), infection and disease and resistance monitoring

Operational Monitoring

- Need to establish systematic exchange of data/experience/methodology between OEPA, OCP & APOC to highlight similarities and differences
- Accurate data on geographic and demographic coverage are essential
- Migration a major problem: do existing procedures incorporate migration?

Operational monitoring

- Validation of records/databases: regular random audits of individual/village records and of links between village to district to region, etc.
- Village records to include any examples of systematic or repeated non-compliance
- Maintenance & sustainability of databases: motivation & morale of personnel, provision of equipment (e.g. computers) and training
- Models need to include coverage data

Infection and disease

- Pre-treatment
 - Elimination in Africa will require treatment of hypoendemic areas: are the current pre-intervention data adequate?
 - Particular concern about the entomological data. Are they adequate to permit estimation of ATP, f.o.i., L3/fly, L3 prevalence, vector species composition, etc.? These are required for accurate baselines to be established against which intervention can be measured (especially for eradication)
 - OCP has the most comprehensive data. How available is this?

Infection and Disease

- Pre-treatment (continued)
 - Is meta analysis of all entomological data feasible?
 - For eradication, the key estimate is the L3/fly or prevalence that is the minimum replacement requirement for the worm population. Can this be calculated?
 - What, if any, new entomological data are required? For example, PCR gives prevalence but dissection gives intensity. How equivalent are these?

Infection and Disease

- Pre-treatment (continued)
 - In the context of PCR, fly collection is the limiting step. Can this be improved? Artificial traps vs. human baits.
 - How widespread are novel Onchocerca genotypes that cannot be typed with existing probes (Democratic Republic of Congo)?

Infection and Disease

- Treatment
 - Large-scale monitoring essential, especially for eradication
 - DEC patch a qualified, preferred option from existing tools but with caveats
 - Major disadvantages of patch are that it measures transmission events that occurred >2 years previously and it requires time from application to readout
 - Entomological monitoring measures transmission potential in real time but not actual transmission

Infection and Disease

- Treatment
 - Development of a pre-patent period assay is desirable. Could the antibody test fill this niche? A test based on Wolbachia?
 - Is the skin snip really dead? Limited application to provide quantitative data at sentinel or problem sites?
 - Development for macrofilarial assay

Infection and Disease

- Treatment
 - Suggest a two-tiered system of monitoring
 - Patch & entomological (antibody) on a wide scale
 - Skin snip/nodulectomy on a small scale and in problem areas
 - On what basis will the criteria for transmission interruption and eradication be set? Geographic range and coverage depth of monitoring plus parasitological threshold

Resistance Monitoring

- Resistance monitoring is essential but it is not included in any current program. Additional resources are required
- No definitive criteria for resistance validation
- No means to validate resistance detection tool(s)
- Resistance modeling essential to help establish a conceptual framework
- Need to collect parasitological material widely to establish a pre-IVM baseline

Resistance Monitoring

- Resistance monitoring via control failure (patch/entomo) will require more intensive monitoring followed by detailed evaluation of apparent failures. Coverage data critical.
- Genotypic resistance assay desirable. Problem with validation criteria

Resistance Monitoring

- Incorporate PCR-assay into routine entomological monitoring or against skin-snip mf in suspected resistance foci
- Resistance could be contained if detected early because there are alternatives: localized vector control, antibiotics, nodulectomy, DEC in low doses, high IVM or MOX
- EARLY DETECTION BEFORE DISSEMINATION IS KEY

Working Group #4: Product Research and Development

Presented by SEO Meredith

Product Research and Development Group Report

Introduction - 1

- In order to protect the enormous investment made in onchocerciasis control and to insure continued success, significant funding for research and development is critical.
- The question remains, "is onchocerciasis eradicable with the tools currently available?"
- If the definition of eradicable is global, then no. However if elimination at regional /country level is considered:
 - For Africa, the simple answer is no
 - For Latin America, the answer is possibly
- Can the current approaches contain the problem of onchocerciasis and protect the existing health gains provided by the work of OCP/APOC/OEPA?
 - Again, the answer is probably not.

Introduction - 2

- It was noted that a relatively small proportion of the funds for OCP/APOC/OEPA were allocated to non-operational research, but that many of the existing tools relied on for onchocerciasis control were provided by basic research.
- Thus, there was a strong consensus that support of any eradication or elimination campaign would require extensive support of fundamental research not only on product development – be they drugs, vaccines, diagnostics or mechanisms of drug resistance – but also on the basic biology of *Onchocerca volvulus* and related filarial nematodes.
- For any program, ~ 20% of budget should be dedicated to research and development.

Drug Development - Macrophilicidal or static drugs

- Without additional drugs, it was felt that elimination will not be possible in Africa. Thus, there was a clear argument for the identification of an additional drug(s) that would target adult parasites;
- In addition, a drug that could be used as a microfilaricide in the event of ivermectin-resistance must also be considered.

Drug Development - Macrophilicidal or static drugs

- Given the emerging approaches to drug discovery - including high throughput screens and the use of genomic data to identify rational targets – new candidates can now be identified more rapidly.
- Because veterinary screens require anthelmintics with broad specificities, putting *Onchocerca volvulus* through industrial veterinary screens would be a cost effective way to identify specific compounds.

Drug Development - Macrophilicidal or static drugs Recommendations - 1

- Directed funding is needed for pharmacological research
 - a task force involved in reviewing specific requests for proposals could be one approach.
- For drugs (or drug combinations) targeting the Wolbachia, *in vitro* screens [e.g.insect cell lines] and/or *O. ochengi* model could be used prior to human trials. Early human trials with already registered drugs might also be carried out.
- Clinical trials to define regimens that would be both macrofilaricidal or –static and feasible for use in *O. volvulus*-endemic areas should be implemented as soon as possible.

**Drug Development - Macrocyclic or static drugs
Recommendations -2**

- Explore with pharmaceutical companies the possibility of including filarial species in their veterinary screens (as they regularly discard helminth-specific compounds).
- Assess carefully the data on moxidectin with respect to its macrofilaricidal and macrofilaristatic activity, safety profile, and pharmacokinetics in humans.

Diagnostics

- Progress on the diagnostic front has been formidable, although an antigen detection system for onchocerciasis diagnosis has not been feasible using currently available technologies.
- The only operational and available tool to support elimination/eradication is a PCR-based assessment of transmission using pools of black flies.
 - These methods have been standardized and there has been statistical validation of the methods
 - quality control methodologies have been put into place, and regional, centralized laboratories have established to provide the laboratory support for field collected samples.

Diagnostics

- What is needed are monitoring tools
 - for assessing the presence of viable adult worms in the absence of microfilariae
 - the early detection of new infections in humans to be used during eradication programs.
- Neither skin snips, PCR for microfilarial DNA (using skin snips or scrapings), nor the DEC patch test was felt to be sufficiently sensitive or field applicable to be considered ideal for detection of early (and prepatent) infections.

Diagnostics- Recommendations

- Support the development of antibody based tests for use as a monitoring tool. Rapid assessment formats are 'user friendly', have the ability to provide instant feedback, good advocacy tool, proven efficacy in other control programs.
- Support the development of sensitive tests for viable adult worms [e.g. stage-specific antigen/antibody tests].

Resistance Monitoring

- There are currently no tools available to monitor for resistance nor is there a workable definition of it for *Onchocerca volvulus* infection.
- Although there are theoretical reasons why ivermectin resistance might not get fixed in the population, the veterinary data would suggest that resistance at some level will likely occur.

Resistance monitoring

- There were 2 questions addressed:
 - How does one monitor for resistance; and
 - What would be the strategy if resistance were found?

Resistance monitoring- Recommendations

- Develop working definitions for "non-responders" and resistance
- Need to examine "non-responders" from different countries in a standardized fashion.
- Need to have surveillance and monitoring strategies in place if resistance is detected.
- Strategies for containment must be developed before resistance is detected.

Vaccines

- Progress in vaccine development against larval stages of *Onchocerca volvulus* has been great.
 - Small and large animal screening is in place
 - and 15 potential vaccine candidates have been identified with 8 having shown some promise in an *O. ochengi* cattle model under intense transmission.
- There was a some consensus that vaccines inducing even partial immunity against either the larval stages or the microfilariae could be an important adjunct toward elimination of *Onchocerca volvulus*.

Vaccines

- Building upon the infrastructure already in place (*Onchocerca volvulus* genome project, stage-specific gene identification, large and small animal models) additional vaccine targets could easily be identified. Newer techniques such as RNAi could be utilized in proof of principle target identification.

Vaccine - recommendations

- Vaccine development for L3, L4 and microfilarial stages should be supported
 - acknowledging the that testing of microfilarial stage-directed vaccines would be the most easily assessed for efficacy in humans
- Fund a field center for *O. ochengi* model for testing vaccines and drug development

Other recommendations

- A 'curated' database of all available data from the OCP, APOC and OEPA programs that could be accessed widely and used for models, etc. should be set up.
- It is important to support and maintain a regional clinical trial center