Criteria for certification of interruption of transmission/elimination of human onchocerciasis

REPORT OF A MEETING


World Health Organization
Communicable Diseases
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For further copies, please contact:

World Health Organization
Communicable Diseases
CDS Information Resource Centre
Office L. 52
1211 Geneva 27, Switzerland
Fax: +41 22 791 4285
E-mail: cdsdoc@who.int

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Design by A.M. Guilloux (WHO/CDS)
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MEETING
ON
CRITERIA FOR CERTIFICATION OF INTERRUPTION / ELIMINATION
OF HUMAN ONCHOCERCIASIS TRANSMISSION

WHO, Geneva
28 p.m. – 29 September 2000, Room M 105

LIST OF PARTICIPANTS

Dr M.-G. Basañez, Departmental Lecturer in Infectious Disease Epidemiology, The Wellcome
Trust Centre for the Epidemiology of Infectious Disease (WTCEID), Department of Zoology,
University of Oxford, U.K.

Dr R. Collins, University of Arizona, Tucson, Arizona, U.S.A.

Dr K. Y. Dadzie, Former Director OCP, Pazzallo, Switzerland.

Dr B. O. L. Duke, Emeritus Medical Director, River Blindness Foundation, 2 Hillside,
Lancaster, U.K. (Rapporteur)

Dr T. Mancero, Ministerio de Salud Pública, Quito, Ecuador.

Dr J. Méndez G., Director del Programa de Enfermedades Transmitidas por Vectores,
Secretaría de México, Mexico City, Mexico. (Chairman)

Prof. D. H. Molyneux, Professor of Tropical Health Sciences, Liverpool School of Tropical
Medicine, Liverpool, U.K.

Dr F. O. Richards Jr., Technical Director, Global 2000 River Blindness Program, The Carter
Center, Atlanta, U. S. A.

Dr M. Sauerbrey, Director, Onchocerciasis Elimination Program for the Americas (OEPA),
Guatemala City, Guatemala.

Prof. I. Tada, Emeritus Professor, Department of Parasitology, Kyushu University, Graduate
School of Medical Sciences, Fukuoka, Japan.

Dr G. van Oortmarssen, Department of Public Health, Faculty of Medicine and Health,
Erasmus University, Rotterdam, The Netherlands.

WHO/Regions

Dr B. Boatin, Director, Onchocerciasis Control Programme in West Africa (OCP).
Ouagadougou, Burkina Faso.

Dr J. Ehrenberg, HCT/P, PAHO, Washington, D.C., U.S.A.

Dr L. Yaméogo, Onchocerciasis Control Programme in West Africa (OCP), Ouagadougou,
Burkina-Faso.
Secretariat (WHO/HQ)

Dr M. Behrend, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS).

Dr D. Etya'ale, Prevention of Blindness and Deafness (PBD), Management of Non-communicable Diseases (MNC), Non-communicable Diseases and Mental Health (NMH).

Dr P. Guillet, Vector Control – Malaria, Strategy Development and Monitoring for Parasitic Diseases and Vector Control (PVC), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS).

Dr M. Karam, Certification of Eradication and Elimination, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS).

Dr J. Lazdins, Product Research and Development (PRD), Communicable Diseases (CDS).

Dr M. Neira, Director, Control, Prevention and Eradication (CPE), Communicable Diseases (CDS).

Dr E. Ottesen, Lymphatic Filariasis Elimination, Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Evaluation (CPE), Communicable Diseases (CDS).

Dr H. Remme, Filariasis, Intervention Development and Evaluation (IDE), Research and Development (TDR/CRD), Communicable Diseases (CDS).

Dr N. Zagaria, Coordinator, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS).
OPENING REMARKS

The meeting was opened by Dr Maria Neira [Director, Control, Prevention and Eradication (CPE), Communicable Diseases (CDS)], who welcomed the participants.

She pointed out that much work had already been done by PAHO and OEPA to develop methods and criteria for the elimination of human onchocerciasis from the Americas and that the present meeting would involve input from workers with rich experience of Africa, particularly those from the CCP and from APOC. The present main objectives of onchocerciasis control campaigns in Africa are to eliminate onchocerciasis as a disease of public health importance, i.e. to eliminate river blindness and the severe itching skin lesions; and, by so doing, to halt the devastating socio-economic effects of the disease. In the course of these operations in Africa, carried out by WHO and others over the last 25 years, a wealth of knowledge has been acquired, much of which should be of great value in advancing the more ambitious campaign in the Americas, which aims to eliminate not only onchocerciasis morbidity but also all infection and transmission of *Onchocerca volvulus*.

Dr J. Méndez was elected to Chair the meeting; Dr B. Duke was appointed Rapporteur, and the proposed agenda was agreed and adopted.

Certain invited participants then made presentations, summaries of which are provided in ANNEX.
EXECUTIVE SUMMARY

Onchocerciasis is still endemic in 34 countries, 26 in WHO's African Region, six in the Region of the Americas, and two in the Eastern Mediterranean Region. The epidemiology of onchocerciasis is that of a vector-borne disease, of which human beings are the only vertebrate host, showing coincidence between the degree of human infection and the intensity of exposure to infected vectors. However, the epidemiology of onchocerciasis is not uniform throughout its distribution because different disease patterns are associated with different variants or strains of the parasite, with differences in the vector competence and feeding characteristics of local blackfly populations, with the abundance of the vector, and with differences in the human host responses to the parasite. These factors, together with those related to environment, geographical, social and demographic influences, increase the complexity of the epidemiology of the disease in the different areas of its distribution.

The framework presented in this document is the result of a broad consultative process led by WHO, which was initially triggered by the wish of the Latin American Onchocerciasis Elimination Programmes to describe the process, milestones and procedures needed to certify an eventual future elimination of onchocerciasis in its countries. In view of the relative few isolated foci in Latin America, this might be an ambitious but theoretically reachable goal on the American continent. These epidemiological settings might only be comparable to isolated foci in Yemen, and some few isolated foci in Africa. In contrast, the distribution of *O. volvulus* in the tropical belt of Africa, hosting about 99% of the worldwide-infected persons, does not show clearly defined boundaries. The epidemiological characteristics in Africa imply that the elaborated framework might not be technically and operationally feasible in most endemic areas of the African continent.

An account is given of previous efforts to control or eliminate onchocerciasis in various areas of Africa and of Latin America by the use of vector larvicidal control (which has proved successful in several areas), or by treatment with drugs unsuitable for large-scale use, or by nodulectomy (neither of which has been successful).

The advent of ivermectin (as Mectizan® provided free-of-charge under the Mectizan Donation Program of Merck & Co. Inc.), an effective microfilaricide currently microfilarial suppressant that is suitable for large-scale rural use, has greatly improved the chances of controlling, or even eliminating onchocerciasis in many areas. Given as a single oral dose, once or twice a year, ivermectin can lower *Onchocerca volvulus* microfilarial skin loads to levels below those required for effective transmission by *Simulium spp.* (blackflies).

In Africa, annual distribution of ivermectin is being used to supplement or replace the larvicidal vector control activities of the Onchocerciasis Control Programme in West Africa (OCP); and, distributed annually in community-directed country programmes, it is the mainstay of the African Programme for Onchocerciasis Control (APOC), which covers all the non-OCP African countries wherein onchocerciasis is endemic.

In Latin America, semi-annual mass treatment with ivermectin in all endemic communities is now the strategy adopted by all endemic countries. In 1991, Resolution XIV of the XXXVth. Directing Council of the Pan American Health called for the elimination of morbidity due to onchocerciasis by the year 2007. The Onchocerciasis Elimination Program for the Americas (OEPA) was established in 1992 as a multi-national, multi-agency coalition aiming to eliminate morbidity due to infection with *O. volvulus* in the Americas by the year 2007, and to eliminate onchocerciasis in those countries or foci where feasible (no time limit was specified for this second goal).

In order to eliminate onchocerciasis through mass-community treatments with the temporary-microfilarial-suppressive drug ivermectin, parasite transmission must be continuously suppressed for a period longer than the maximum life span of adult female worms plus that of their last-produced microfilariae. If treatment is discontinued or interrupted, transmission can be re-established, and morbidity again develop in the human population. Thus, the expected period required to terminate both infection and parasite transmission, might be 14 to 18 years of sustained and uninterrupted interventions. The described framework and time horizon
relates to a scenario with semi-annual ivermectin treatment, but other treatment schemes with longer treatment intervals could eventually also lead to an elimination if applied over longer treatment periods. On the other hand, the period of sustained interventions could eventually also be shorter than expected, if ivermectin would show a cumulative effect on the adult worms.

Studies in several endemic onchocerciasis foci in Africa and the Americas have shown that a sustained, high level of ivermectin coverage is absolutely crucial for successful control of transmission and morbidity. Therefore, an important criterion to trigger the initial evaluation of a country’s control programme is evidence that broad, effective ivermectin coverage has been achieved over a 2-4 year period.

An intensified control programme leading to an elimination of onchocerciasis and its certification can be divided into four phases.

The **first phase** consists in interventions (by mass treatments with ivermectin, each at a minimum of 85% coverage of the whole population that is eligible to take ivermectin) leading effectively to a total suppression of infectivity. This temporary interruption of transmission conditioned to the effect of ivermectin might be reached after 2-4 years (4-8 treatment rounds), depending on the local circumstances.

During the **second phase**, the microfilarial population and infectivity remain suppressed and will stay that way, provided that regular ivermectin distribution continues without interruption and with the same high degree of coverage in all endemic communities. There should be evidence, confirmed at regular intervals, that those areas at highest risk of continuing transmission have zero positive flies tested by the polymerase chain reaction (PCR); and zero incidence of onchocerciasis cases. This phase lasts for a period of 12-14 years, corresponding to the life span of the adult female parasite. By the end of this phase all the adult worms should have died of old age.

The **third phase** will begin 12-14 years after suppression of infectivity started corresponding to 14-18 years after starting sustained control interventions. At this point the adult worm population has died out from old age and the interruption of transmission is no longer conditioned to the ivermectin treatment. After satisfactory assessment by a WHO International Certification Team (WHO/ICT), a “pre-certification period” will begin and lasts for 3 years. During this phase no further ivermectin treatment is given, as all the adult worms and their microfilariae should by then be dead. Transmission should remain interrupted and all infections and new morbidity should have been eliminated. However, during this period, surveillance of the erstwhile endemic foci must be maintained.

At the end of the 3-year pre-certification period, and provided that no further evidence of active infection or transmission has been revealed in the country, WHO may grant a certificate of interruption of transmission and the country concerned enters the **fourth or post-endemic phase**. This final phase, during which post-endemic surveys and surveillance must still be maintained, will last until such time as the Regional Elimination of Onchocerciasis is declared.

The certification process described herein endeavours to provide a guide to document and describe the status of parasite transmission, infection, and new morbidity in foci under long-term, continuous ivermectin treatment. Based on the results, an International Certification Team will be able to verify when elimination has been achieved. Isolated foci existing in the same country can be evaluated and undergo the described technical monitoring exercises at different times if their control efforts are not implemented or progressing in a synchronised manner. Different foci may complete the various steps of the certification process in a staggered manner. Although a team with international participation can verify recognition of achievements, certification can only be granted to the country after elimination has been achieved in all foci of that country.
INTRODUCTION

Onchocerciasis has long been recognized as disease of public health importance. In 1974, the first regional onchocerciasis control programme (OCP) was launched in west Africa, based on a vector control strategy and sponsored by the FAO, UNDP, World Bank and WHO as the executing agency. With the development of a safe drug for use in public health programmes, two other large programmes were launched subsequently in the Americas (GEPA) and in Africa (APOC).

After more that 25 years of onchocerciasis control, the World Health Organization convened a meeting in September 2000 to provide, in the light of progress so far achieved by the above mentioned programmes, guidance for the verification and the certification of interruption of transmission. This document is the outcome of this meeting and is meant to guide in a consistent manner, the work undertaken by International Certification Teams and the country approach to certification.

1. HUMAN ONCHOCERCIASIS AS A DISEASE OF PUBLIC HEALTH IMPORTANCE

Human onchocerciasis is a vector-borne disease, endemic in parts of Africa, the Arabian Peninsula, and Latin America, and caused by a filarial nematode worm, *Onchocerca volvulus*. It produces eye lesions, which can lead on to blindness, and also itching and disfiguring lesions of the skin. Because the vectors (blackflies belonging to the genus *Simulium*) are insects which breed in fast-flowing rivers and streams and bite humans near these sites, the disease is often known as River Blindness. In Africa the blindness and the severity of the skin lesions can have severe socio-economic consequences and, in the past, River Blindness has led to the desertion of large areas of fertile land adjacent to *Simulium damnosum* s.l. breeding rivers, thus seriously impeding the economic development of the countries concerned. In Latin America the disease is sometimes referred to as Robles' Disease in honour of Dr Rodolfo Robles, the Guatemala physician who first recorded its existence in the New World.

Estimates of the prevalence of onchocerciasis made in the mid-1990s indicated that, worldwide, approximately 123 million persons were at risk of infection, and some 17.6 million were infected (WHO, 1995), the vast majority of them in Africa.

In Latin America, the at-risk population was estimated in the mid 1990s at 4.7 million, with 150,000-200,000 persons infected. More recently, the thorough epidemiological characterisations of northern Venezuela and the re-assessment of Guatemala have lowered the total population at risk in Latin America to approximately 660,000 persons living in 2773 villages, of which only 200 are considered to be hyperendemic with high risk of ocular disease (WHO, 1999b).

Adult *Onchocerca volvulus* worms (females 30-80 cm long; males 3-5 cm) are thin worms which live coiled up in fibrous nodules situated just under the skin or deep in the intermuscular and periarticular connective tissue. They live for some 9-14 years and the females produce very large numbers of microfilariae, 250-300 μm in length, which invade the skin and eye and cause the signs and symptoms of disease. The microfilariae live for 6-24 months in the human body. When they die they cause lesions in the skin or eye of the human host. Only those living microfilariae that are ingested by blood-feeding *Simulium* vectors will survive and develop in the fly over 6-12 days to become infective larvae or L3s. These, when they are inoculated into a new human host, usually at the next but one time that the fly feeds, will enter a new human host, develop into adult worms (without any multiplication) over a period of some 10-15 months, mate and start a new generation of the parasite. Thus, with this infection, prolonged and repeated exposure to the parasite is necessary before an intense infection can be established in the human host.

Definitions of some of the terms used in this document, together with information on the various methods used to stratify the endemicity levels of communities with onchocerciasis, are to be found in APPENDIX I.
2. THE CONTROL OF HUMAN ONCHOCERCIASIS

2.1. CONTROL IN AFRICA

The control of transmission of *O. volvulus*, and hence the local elimination of onchocerciasis as a disease, was first shown to be feasible, using DDT as a *Simulium* larvicide, in the Koderak River focus in Kenya, then known as the "Valley of the Blind". Painstaking and accurate surveying of all the breeding sites of the vector, *S. neavei* s.l. (a species whose larvae live attached to crabs), resulted in the extermination of the vector from that isolated focus (McMahon et al., 1958); and the interruption of transmission which followed led to the elimination of onchocerciasis from the only known focus in Kenya (Roberts et al. 1967).

Based largely on these findings, a Joint US-AID/OCCGE/WHO meeting on the feasibility of onchocerciasis control was organized by Dr N. Ansari (Chief, Parasitic Diseases, at WHO) and Médecin-Inspecteur-Général P. Richet (Director of the OCCGE in Bobo Dioulasso) and held in Tunis in 1968. The meeting came to the conclusion that control should be possible using *Simulium* larviciding by means of aerial applications over a sufficiently large area (which would involve a number of adjacent countries) covered by the Sudan-savannah strain of *O. volvulus*, provided operations continued for a period of time in excess of the combined life-span of the adult worms and their microfilariae. On the basis of these deliberations, the area of the Volta River Basin in West Africa was selected as being an area of Africa, in which it was at that time feasible to operate, where the socio-economic effects of the disease were severely impeding development, and where there was already considerable knowledge of the distribution of the disease and of the *Simulium* breeding sites. Preparations were thus set in motion for the establishment of the Onchocerciasis Control Programme in the Volta River Basin (OCP), which began its vector control operations in 1974.

Subsequently, unexpected problems arose with *Simulium sirbanum* and *S. damnosum* s.s. vectors from untreated breeding sites outside the OCP area, which were flying long distances (200-400 Km) on the prevailing wind to re-invoke the control area. To counteract this re-invasion phenomenon the OCP was obliged to start expanding in 1982 into its present Western and Southern Extensions, thus becoming the Onchocerciasis Control Programme in West Africa. Later, in 1987, the development of ivermectin (as Mectizan®) by Merck & Co. Inc. (as a microfiliaricide and a temporary microfilarial suppressant, given as a single dose annually, that is safe for widespread use in rural communities) led to the inclusion of this drug as a control measure in the OCP area.

Finally, the establishment by Merck & Co. Inc of the Mectizan Donation Program (which generously provides the drug free-of-charge to all those affected in endemic countries for as long as necessary), coupled with the increasing involvement of non-governmental development organizations (NGDO) in Mectizan Distribution Programmes, enabled all the other countries where onchocerciasis is endemic to benefit from the new drug. In Africa, this resulted in the establishment of the African Programme for Onchocerciasis Control (APOC), which is now responsible, along with national Ministries of Health and NGDO, for the community-directed distribution of ivermectin in all the onchocerciasis endemic countries of Africa.

2.2. CONTROL IN LATIN AMERICA

Before the advent of ivermectin, attempts to control onchocerciasis in Latin America had varied from country to country. In Guatemala and Mexico it had been largely dependent on nodulectomy, coupled sometimes with the administration of diethylcarbamazine citrate (DEC) and occasionally with localised attempts at *Simulium* larvicidal control. Since many of the nodules in these countries, where *S. ochraceum* (a species which bites high on the body) is the main vector, are found on the head, nodulectomy was probably beneficial in reducing the incidence of severe eye lesions and blindness, but it had little or no effect in reducing transmission. Moreover the reactions which followed DEC treatment made the use of this drug unpopular.
In northern Venezuela, widespread campaigns with suramin were introduced and continued for some years. They were doubtless of value to the individuals who were treated but they did little towards reducing transmission. In the southern Venezuelan endemic area in the Amazon Basin, which is contiguous with the foci in the Brazilian rain forest, the presence of the disease had only recently been revealed and virtually no effective control measures had been undertaken.

Again, the advent of ivermectin and the establishment of the Mectizan Donation Program sparked widespread interest in the control of onchocerciasis in the various foci in Latin America. Indeed, beyond mere control, support for a regionally-coordinated campaign to eliminate human onchocerciasis in the Western Hemisphere developed and grew during the nineteen nineties. The Onchocerciasis Elimination Program for the Americas (OEPA), established in 1992, now provides the administrative structure and the technical co-ordination of a multi-national, multi-agency coalition aiming to eliminate onchocerciasis in Latin America by coordinating the campaigns in each of the six affected countries—Brazil, Colombia, Ecuador, Guatemala, Mexico and Venezuela (Blanks, et. al 1998). OEPA, with its headquarters in Guatemala, is the technical and coordinating body of a multi-national, multi-agency coalition which acts under the 1991 Resolution XIV of the XXXVth. Directing Council of the Pan American Health Organization calling for the elimination of all onchocerciasis morbidity from the Americas by the year 2007.

3. CONTROL AND ELIMINATION STRATEGIES

3.1. AFRICA

In Africa the goals of the onchocerciasis control programmes are the elimination of eye disease, the reduction of skin disease, and the prevention of the severe socio-economic effects of onchocerciasis. In Africa, WHO used extensive and repeated aerial application of rapidly-biodegradable insecticides as the original basis of the Onchocerciasis Control Programme in the Volta River Basin and later, after the Western and Southern Extensions were taken on, of the Onchocerciasis Control Programme in West Africa (OCP). As a result of larviciding against *Simulium*, transmission was interrupted over large areas but the parasite population in humans was not immediately affected, except in so far as it became an ageing population that was not rejuvenated by newly transmitted parasites. Onchocercal punctate keratitis (a reversible lesion) became less frequent but the serious skin and eye lesions of those persons already infected still progressed, although at a somewhat lower rate because their original parasite loads were slowly dying out and were no longer being reinforced by new infections. In addition children born after the larviciding programme started remained free of infection.

When ivermectin became available, WHO adopted annual treatments with ivermectin both to supplement the insecticidal programme in the OCP and also to form almost the sole basis of the interventions of the APOC, which now covers the remaining onchocerciasis-afflicted countries of Africa. Under APOC, the ivermectin distribution is Community-Directed and the treatments are also given annually. There is no vector control under APOC except in a few small isolated foci of transmission where vector eradication appears feasible. On the other hand there is an immediate benefit to the human population as a result of the rapid lowering of their microfilarial loads by ivermectin. In addition, a degree of reduction of transmission is achieved, which depends solely on the ivermectin-induced reduction in the human microfilarial reservoir. The duration of control based on ivermectin alone may thus have to be longer than that following *Simulium* larvicidal control. However, follow-up studies in the OCP have demonstrated that repeated ivermectin treatment does significantly affect the embryonic productivity of *O. volvulus* (Alley et al., 1998; Plaisier et al., 1995) and that this could result in a shortening of the control period (Plaisier et al., 1997). Hence the OCP has ceased larviciding after 14 years in areas with only vector control, but after 12 years in areas where there has been a combination of vector control and ivermectin treatment (Guillet et al., 1995). The incidence of new infections in the central OCP area has been zero or near zero for the past 11 years, despite the presence of potential *Simulium* vectors.
Data from the OCP in West Africa provide information on the suppression of infectivity, which is defined as "the absence of infective stage larvae in the vector", this absence having been determined by the polymerase chain reaction (PCR). The complete absence of L3s from a large enough sample of vector *Simulium*, collected during the hours when most parous flies are biting and at times of the year when transmission is normally highest, implies that there is no transmission at that time. However, a few L3s are not enough to reactivate transmission and the experience gained in the OCP suggests that 1 L3 per 1'000 parous flies could be defined as a safe level at or below which transmission does not occur (Remme et al., 1995). This concept has been tested and proven in the central OCP area where, in 1989, vector control was stopped after 14 years. Subsequent entomological investigations found scanty L3s at all collecting sites but never much above the above-mentioned threshold; and, to date, after 10 years without any intervention, there is still no epidemiological evidence of renewed transmission. On the basis of these findings it can be assumed that interruption of transmission is achieved when not more than 1 L3 is found per 1'000 parous flies; and that, after a 5-year cumulative incidence of less than one new case of *O. volvulus* per 1'000 persons has been achieved, the parasite reservoir will have been brought below the transmission break-point.

In some areas of Africa, notably in central parts of the Cameroonian Republic, where some very heavy co-existent microfilarial infections with *Loa loa* are encountered, mass treatment campaigns with ivermectin to control onchocerciasis have given rise to a small number of cases of *Loa*-encephalopathy, some of which have proved fatal. This has led to the need for increased caution in distributing ivermectin for mass treatment in areas where *loasis is co-endemic with onchocerciasis*. On the other hand, plans to use mass ivermectin treatment, given along with albendazole, in those African countries taking part in the new Programme for the Elimination of Lymphatic Filariasis (PELF) mean that ivermectin is likely to be distributed to an increasing number of LF-afflicted communities, which have coincident low-prevalence onchocerciasis but which are not at present reached by the activities of OCP or APOC.

In summary, it is fair to say that a high degree of control, rather than elimination, is the current target for onchocerciasis in Africa, where the problem is greater than that in Latin America by at least one, and possibly two, orders of magnitude. However, the present situation may change, when more experience is gained of the long-term potential of ivermectin and/or if a new and widely applicable macrofilaricidae for *O. volvulus* should appear. Experience obtained by the Onchocerciasis Elimination Program for the Americas (OEPA) will, at that time, doubtless be of great help to the African programmes.

### 3.2. LATIN AMERICA

OEPA’s partners include representatives from the six endemic countries in the region, WHO/PAHO, NGDO, the Centers for Disease Control and Prevention in Atlanta, USA, academic institutions, funding agencies, and other interested parties. Since its inception, OEPA has provided increasing levels of management, as well as technical and financial assistance, to stimulate existing national onchocerciasis elimination programmes and to promote new ones. These efforts have been based on a strategy of preventing disease and interrupting transmission through sustained 6-monthly treatments with ivermectin (Mectizan®, donated by Merck and Co. Inc.) given to all persons who are eligible to take the drug in all known endemic communities. An annual review of regional control programmes (the Inter-American Conference on Onchocerciasis [IACO]) has been held in each of the past nine years to provide a forum for the participating countries to discuss progress being made toward accomplishing national and regional goals of onchocerciasis elimination.

In 1997, the IACO in Cali, Colombia, officially endorsed efforts to certify the elimination of transmission of onchocerciasis on a country-by-country basis, using criteria agreed upon at that meeting. It was resolved that certification of elimination must be done on an objective basis, according to internationally accepted criteria. A central criterion is the determination of whether transmission of *O. volvulus* has indeed been eliminated and/or reduced to the point of being biologically inconsequential, i.e. below the reproductive potential ($R_0$) of the parasite. Other criteria must take into account the level of documented treatments, the change in the incidence of new infections in untreated children, and the risk of importation of the parasite
from other endemic foci. It was agreed that efforts towards elimination of onchocerciasis for individual countries would be continued until certification of elimination of the disease in the entire region has been achieved.

The most important requirement for attaining elimination is sustained, high-level coverage with ivermectin, and the 1998 IACO, held in Caracas, Venezuela, focused on strategies for sustaining high treatment coverage throughout the region (WHO, 1999b). The term "coverage", as used here, has two dimensions:

(1) **Extent of Coverage**, meaning endemic communities receiving ivermectin. The requirement being that all endemic (100%) communities be identified and receive regular mass distribution of ivermectin; and

(2) **Depth of Coverage**, meaning percentage of the eligible population treated. The requirement being that 85% of the eligible population in each community be treated at each treatment round.

Indeed, any country wishing to certify elimination of onchocerciasis must demonstrate that it has met these two prerequisites before the certification process can begin.

To carry out the process of certifying elimination, WHO in collaboration with its regional Office will designate a panel of specialists, whose members can be assigned to International Certification Teams (ICT). The ICT will operate under the auspices of WHO and will inform both WHO, its Regional Office and the respective regional Onchocerciasis Programme (OEP in Latin America) regarding those countries that fulfil the requirements for certification as well as the criteria, procedures, and progress made towards verification of the absence of disease and parasite transmission in endemic areas.

In Latin America, OEP will facilitate national preparations for certification by carrying out regular visits by staff or by consultants to the country or sub-region concerned. A register will be established of countries requesting certification and also of those countries where official certification of elimination is pending. Finally, WHO/PAHO in conjunction with OEP will establish an official register of countries where onchocerciasis has been eliminated, based on evaluations made by the ICT and their review. Countries on this register will be classified as Post-endemic - Past history of onchocerciasis, but no current evidence of transmission or new clinical disease.

One of the aims of the present document is to describe the criteria and procedures for verifying the elimination of new and reversible onchocerciasis morbidity together with the transmission of, and infection with, *O. volvulus* in Latin America. In addition OEP has developed programmatic guidelines for monitoring the impact of ivermectin distribution through in-depth epidemiological assessments that include the entomological evaluation of parasite transmission.

In Latin America, the elimination strategy is based on regular, 6-monthly mass distribution of ivermectin to all persons who are eligible to take the drug in all endemic communities. The aim is to make use of this drug to suppress greatly or, better still, to interrupt transmission of the parasite for longer than the maximum life span of the adult female worm. If this can be achieved, the adult worm population will gradually die out from old age and will not be replenished by new infections, thus leading to the elimination of the parasite from a defined geographical area.

The ivermectin should be given out to all persons at risk of infection and who are eligible to take ivermectin, regardless of whether or not they have positive skin biopsies, nodules or other evidence of infection. In fact, biopsies, nodulectomies and physical examinations should not be done during mass treatment because this has been shown to reduce participation by the communities.
3.2.1. Rationale for the Strategy in Latin America

Ivermectin, given as a single oral dose, lowers microfilarial skin loads to levels below those required for effective transmission by the vectors (Cupp et al., 1986). The rationale for 6-monthly treatments came from observations that two doses of ivermectin at 7-month intervals resulted in almost complete suppression of patient infectivity to vector blackflies (Simulium ochraceum s.l.), which lasted for 6 months after the second dose (Cupp et al., 1989). Later, community-based trials in five hyperendemic villages in Guatemala showed that parasite transmission could be completely blocked after four 6-monthly treatments when coverage averaged 92.7% of the eligible population, and was substantially reduced when coverage ranged from 71.0 - 81.9% (Cupp et al., 1992; Collins et al., 1992).

The vector in Guatemala, Simulium ochraceum, appears to have in its saliva a substance, which attracts the microfilariae of the local strain of O. volvulus towards the mouthparts of the feeding fly (De León & Duke, 1966). This characteristic, which is probably also found in some other Latin American vectors, may render them useful for xenodiagnostic purposes since they are capable of concentrating microfilariae when fed on carriers with very low microfilarial concentrations in their skins.

However, despite its high microfilarial intake, S. ochraceum is, for another reason, relatively inefficient at transmitting parasites. This is because it has a cibarial armature in its "pharynx" that shreds microfilariae as they are being ingested by the fly (Omar and Garms, 1978). In consequence, this species must feed on people with a relatively high microfilaremia in order to develop sufficient infective third stage larvae for transmission purposes (Collins, 1979). Other Latin American vectors, which possess a cibarial armature, are S. quadrivittatum, S. oyackpoense and S. incuratum. Several other vectors in Latin America (S. metallicum, S. exiguum and S. guianensis) lack a cibarial armature (as indeed do all the African vectors). Accordingly they are thus probably more efficient vectors, except in so far as the attraction of microfilariae towards their saliva may lead them to ingest heavy loads of microfilariae, which may turn out to be lethal to the fly.

The effect of 6-monthly ivermectin treatment on transmission in other areas of Latin America was uncertain until the Ecuador programme reported at IACO 1995 that, after five years of 6-monthly treatments, transmission had been completely blocked in spite of the fact that the vector, S. exiguum s.l., lacks a cibarial armature and ranks high in vector efficiency (Collins, et al. 1995). Ivermectin coverage rates were high and averaged 90% of the eligible population for each treatment round. This result was even more encouraging because transmission may have been blocked after the first round of treatment, as evidenced by the fact that no children born after ivermectin distribution had commenced were infected when examined five years later. In comparison, children of 1-5 years old born before treatment started had a 64.3% positive biopsy rate. Thus, it became clear that elimination of parasite transmission was a realistic goal even in the face of a highly efficient vector, and that sustained, high-level coverage with ivermectin is the key to success (Guderian et al 1997). These results are the more encouraging in that they were obtained in an operational programme with direct community participation.

3.2.2. Goals of the Onchocerciasis Elimination Program for the Americas

The programme has two primary goals:

First, to eliminate new morbidity due to infection with Onchocerca volvulus by the year 2007. This is also stated as elimination of onchocerciasis as a public health problem by the year 2007.

Second, to eliminate parasite transmission in those countries or foci where feasible. No time limit was specified, but elimination implies that the parasite ceases to exist in the area concerned. Unless suppression of parasite infectivity is maintained (currently by 6-monthly ivermectin treatments) for longer than the maximum life-span of the adult female worms (thus ensuring interruption of transmission), microfilaremia will recur, transmission will become re-
established, and morbidity will again develop in the human population. Thus, the minimum
time required to terminate new morbidity, infection and parasite transmission is 14-18 years,
based on the observed longevity of adult worms in other control programmes (Duke, 1993).
This variable time-schedule gives some flexibility should ivermectin prove effective against
adult worms, or should a new and safe macrofilaricide be found. Also the periodic in-depth
evaluations after 6, 10 and 14 years of 6-monthly treatments may help to determine the exact
length of the necessary time frame.

The level of 1 L3 of *O. volvulus* per 1’000 parous vector *Simulium*, which has been adopted
by the OCP as a safe level at or below which transmission does not occur, is unlikely to be a
useful index for Latin America, for two reasons. The first is that by using PCR there will not be
data available on the parous ratios of biting populations. The second is that the OCP index is
above the transmission threshold for *Simulium* spp with very high biting densities. For
example at the Finca El Vesuvio in Guatemala (Porter et al., 1988), the biting density was
550’599 flies per year, with 49.2% parous. At the rate of 1 L3 per 1’000 flies this would give
an estimated Annual Transmission Potential (ATP) of 271 L3s per person per year but, as the
mean number of L3 per infective fly was 2.0, this would equate to an ATP of 542. However,
the biting density obtained in this experiment was really a landing rate because it was
necessary to collect the flies before they had had time to bite. Assuming that the biting rate
would be one quarter of the landing rate, this results in an estimated ATP of 68-136, which
could very well be above the transmission threshold for *S. ochraceum*. In Latin America it is
considered that it is more useful to take the measure of the safe level of transmission (at or
below which there is “suppression of infectivity”) as being "a minimum reduction of 99% of the
Base-line ATP".

4. CRITERIA FOR CERTIFICATION OF INTERRUPTION OF
TRANSMISSION / ELIMINATION

Standard criteria for certification of elimination are needed for the following reasons.

A. To give national onchocerciasis elimination programmes the step-by-step accomplishments required eliminating reversible morbidity, parasite transmission and infection over a specified period of time.

B. To give national elimination programmes and external agencies a consistent and established mechanism for monitoring and evaluating programme achievement.

C. To insure international credibility for the expected future claim that onchocerciasis has been eliminated from a country or other area.

D. To insure that national programmes have ascertained and classified all endemic communities in their countries by the application of guidelines developed by the Task Force on Epidemiological Characterisation of Onchocerciasis.

Elimination should be considered as achieved in a country when adequate surveillance in all endemic regions in that country has shown the following.

4.1. Elimination of Morbidity

The absence of reversible lesions in the anterior segment of the eye (punctate keratitis, microfilariae in the anterior chamber), which are here referred to as "new morbidity". A 5-year cumulative incidence rate of less than 1 new case per 1000 is acceptable (provided this size of the population is available)

It must be remembered that permanent eye lesions or onchocercal blindness, as well as some severe skin or lymphatic lesions, are irreversible and will persist after the person so affected ceases to be a source of transmissible microfilariae, until he or she dies. Such "old morbidity" cannot be eliminated except by death.
4.2. Interruption of Transmission

4.2.1. The absence, or near absence, of infective-stage larvae of *O. volvulus* in the vector population as determined by PCR using *O. volvulus*-specific DNA probes and/or any other valid method. A minimum sample size of 10,000 flies is required for each endemic community tested. The *Simulium* flies must be collected during the hours of the day when parous flies are most abundant (which implies a knowledge of the diurnal biting cycle of the parous flies of each species concerned), and during the peak transmission season of the year, in order to increase the chances of collecting infected specimens. A 99% reduction in baseline transmission rates is the target for those areas where pre-treatment baseline data are available.

4.2.2. The absence of detectable infection (as evidenced by microfilariiae, nodules, immunological or other proven tests) in untreated children reaching the age of 5 (i.e. those who are about to take their first dose of ivermectin). The *O. volvulus* antibody test recently developed by Weil et al. (2000), which can be performed on finger-stick blood samples, may be a valuable and minimally-invasive investigation to achieve this end. A 5-year cumulative incidence rate of less than 1 new case per 1000 susceptible children is acceptable (provided a population of this size is available).

4.2.3. The absence of detectable infection (as evidenced by microfilariiae, nodules, immunological or other proven tests) in untreated, new residents who have migrated into an endemic area where transmission has been interrupted. A 5-year cumulative incidence rate of less than 1 new case per 1000 susceptible individuals is acceptable (provided a population of this size is available).

5. QUALIFYING REQUIREMENTS FOR CERTIFICATION

Countries wishing to be certified as free of onchocerciasis transmission must meet certain conditions in order to initiate the certification process. Each country programme must demonstrate that the following conditions have been met. Any country that feels it has completed these requirements is encouraged to apply, because a pre-certification audit will also be an important step in the programme evaluation.

5.1. When requesting certification, a country submits a detailed report to WHO and to the respective WHO Regional Office describing the history, structure and operation of its programme, as well as data on treatment coverage, surveillance and monitoring, including results of the in-depth epidemiological surveys, i.e., ophthalmologic, parasitological and entomological evaluations. The country programme's annual report should be expanded to include surveillance, coverage and evaluation data from previous years, so that it can form the basis for the Country Report. The Ministry of Health should appoint a task force to accomplish the internal programme review necessary for preparing the Country Report.

5.2. In the certification request, the country should show that all endemic foci have been discovered and investigated, and that each community has been stratified by endemicity as being hyperendemic, mesoendemic, hypoendemic, or non-endemic. While historical records can be used as an initial step to locate foci, recent information based on active monitoring and surveillance can only be used for final analysis.

5.3. The time taken to achieve suppression of infectivity by means of 6-monthly ivermectin treatments should be a minimum of 2 years (i.e., 4 treatment rounds) up to a maximum of 4 years (8 treatment rounds) – each round with 85% coverage of the total population that is eligible to take ivermectin. The country should then show that all endemic communities have continued to be treated with ivermectin (at intervals and with 85% coverage of the eligible population) for at least 12 consecutive years after first achieving suppression of infectivity. In-depth epidemiological evaluation should determine the time at which suppression of infectivity was first achieved, thus marking the start of the 12-year period during which treatment needs to be sustained.
5.4. In-depth epidemiological surveys of sentinel communities after six years of treatment shows no infection (skin microfilariae, nodules) in untreated 5-year old children who are about to take their first dose of ivermectin. Antibody testing using specific *O. volvulus* antigens and finger-stick blood samples (Weil et al., 2000) may be used if skin snipping of young children is resisted by mothers and/or children. There should be a 5-year cumulative incidence of < 1 new case per 1000 persons.

5.5. Entomological assessments in sentinel communities after 12 years of thorough suppression or complete interruption of transmission indicate that infective stage larvae (L3s) are absent from the vector population, thus making the beginning of pre-certification period. As an intermediate step, and where resources are available, each country should carry out entomological evaluations of sentinel communities at 2-4 year intervals after initiating treatment, in order to ascertain whether adequate suppression or interruption of transmission is being sustained.

6. CERTIFICATION PROCEDURES

The Ministry of Health in the endemic country initiates the certification process by sending a letter to WHO, to the WHO Regional Office and to the Regional Onchocerciasis Programme, saying that it is preparing a country report and plans to apply for certification. WHO, after consultation with its Regional Office and with the health authorities of the country concerned, will appoint an International Certification Team (ICT). The ICT must be able to communicate and report in the official language of the country concerned, although this does not imply that all members of the ICT must be fluent in the relevant national language. The team will review the country report in detail, including data supporting the extent and depth of coverage obtained at each treatment cycle and the results of in-depth surveys in sentinel communities. Prior to the ICT nomination, visits by selected consultants can be arranged by WHO or the Regional Onchocerciasis Programme to help in the preparation of the country report and to recommend additional data analysis or surveys before the ICT begins its audit.

6.1. Operation of the International Certification Team

6.1.1. ICT Evaluation

The ICT will visit the applicant country to become acquainted with the operation and personnel of the control programme. The visit will take place before certification surveys are carried out (see 7.1.2 below). The principal aim of the first ICT visit will be to evaluate the reliability of the country report by interviewing health personnel and others, and by examining records at both central and peripheral levels. Good evidence of high treatment coverage is essential and certification should only be triggered if it is certain that the required coverage levels (at least 85% of the population eligible to take ivermectin in all endemic communities) have been reached during the indicated number of treatment rounds. At the end of this visit, the ICT will ascertain the likelihood that transmission of *O. volvulus* has been interrupted and that certification surveys are justified.

After arrival, national control programme personnel and other health authorities will brief the ICT on the country report. Of particular importance are (1) the accuracy and completeness with which the programme has investigated and stratified all endemic communities, and (2) the extent and level of coverage obtained throughout the various treatment cycles. While negative results from the in-depth epidemiological surveys of sentinel communities (paragraphs 5.4 and 5.5 above) are useful indicators of possible elimination throughout the country or focus, sustained, high-level coverage of all endemic communities (paragraphs 5.2, 5.3, above) is crucial. Indeed, if for some reason (economic, civil unrest, natural disasters) the in-depth evaluations of sentinel communities have not been completed, and yet high coverage has been maintained, the certification process could still go forward.

The ICT should be able to visit any epidemiologically important areas identified in the country report. These could be (i) areas identified as potentially having been missed in the original assessment, (ii) areas contiguous with neighbouring countries affected by onchocerciasis,
(iii) previous highly endemic areas, or (iv) areas where sporadic cases have occurred, especially if these occur in regions of the country with a weaker health infrastructure. Sentinel and non-sentinel communities should be visited to observe how census records and lists of eligible people are obtained and kept in the field and passed on to the central offices; and to observe and evaluate the method of drug distribution. (It is important that a house-to-house census of each community should have been be taken by the team personnel just before treatment. Previous “official” census figures, which are usually out-of date and of uncertain value should not be relied upon.) Regardless of the criteria for selection, team members will decide which areas, villages and health units they wish to visit. At the end of its tour, the ICT, in consultation with the host country, will decide whether or not field surveys are justified to certify interruption of transmission/elimination.

6.1.2. Field Evaluation: Survey and Sampling Procedures

Field surveys to certify that onchocerciasis has been eliminated will take place after the ICT visits the host country and has decided that the field survey certification process should go ahead. At least one member of the ICT (or its representative) will actively participate in the field survey work and data analysis. The indicators and methods of assessing morbidity and transmission for the pre-certification and certification processes are the same as those used for on-going programme monitoring during the treatment phase of the elimination programme. The difference will be that certification surveys will be carried out in communities other than sentinel communities. The ICT, in collaboration with the national programme director and with the assistance of a statistician, will choose the number and locations of the communities to be surveyed. For example, they may be chosen at random, or by selection of communities with higher risk of infection and/or eye disease, or those that have demographic, ethnographic, or entomological characteristics that might allow infection and transmission to persist. Examples of the latter are: - communities where low-level transmission may be maintained by a secondary vector; hypoendemic communities that may have received annual treatments with coverage below 85%; and communities where part of the population is transient, as on the frontier between two countries. In any case, the survey population and communities must be sufficiently large and geographically dispersed to allow statistically valid conclusions to be made.

6.1.3. Timing of Certification

The timing of certification activities is driven by: (1) estimates of the reproductive life-span of adult female *O. volvulus*, which range from an average of 12 years to a maximum of 15 years (Duke, 1993); (2) the objectives of sustained suppression of infectivity (conditional upon continued interruption of transmission by regular ivermectin treatments) and elimination of infection and superinfection until the parasite population has died out and permanent interruption of transmission is achieved; and (3) the established cycle of in-depth surveys in sentinel communities. In-depth surveys should be carried out two years after the initiation of ivermectin treatments to determine the point when suppression of infectivity is being achieved. From this point on, the count down could start maintaining the indicated minimum coverage rates for at least 12 years. Subsequent in-depth surveys may be carried out every four years. After such surveys show that the conditional suppression of infectivity has been maintained over the whole period of 12 years, community treatment could be stopped. It is assumed that, at this stage, transmission will have been interrupted permanently because the adult worms will have died out. With the ceasing of the interventions, a 3-year pre-certification period would start. At the end of this pre-certification period, it must be shown that, although intervention has ceased, no new incident onchocerciasis cases have been registered and no infected vectors identified. Certification of elimination could not take place sooner than the conclusion of the 17th year of treatment.
Flow chart 1 shows the time frame and steps leading to the cessation of control operations, the pre-certification period and final certification.

FLOW CHART 1

FLOW CHART OF ACTIVITIES LEADING TO CERTIFICATION OF INTERRUPTION OF TRANSMISSION / ELIMINATION OF ONCHOCERCIASIS

PRE-TREATMENT PHASE

1. Identify and stratify all endemic communities
2. Identify sentinel communities and carry out in-depth surveys therein for base-line data.

TREATMENT PHASE

1. Year 1. Initiate (yearly or 6-monthly) ivermectin treatment of all endemic communities (at 85% coverage of eligible population).
2. Year 2–14 or 16. Establish and maintain yearly or 6-monthly ivermectin treatment (at 85% coverage of eligible population).
4. Year 3–4. Check vector population for suppression or interruption of transmission.
5. Year 5. Check population for disappearance of reversible morbidity. Check that 5-year-old children are not infected.
6. Year 6-14 or 16. Maintain Steps 2-5 above.

PRE-CERTIFICATION PHASE

1. Year 14–16. Ascertain that transmission is interrupted.

POST-ENDEMIC PHASE


Figure 1 (on next page) shows the time-scale for the theoretical fall-off of the Annual Transmission Potential or ATP to zero (or near zero), together with the theoretical fall-off of the dying and unreplenished adult worm population, both in relation to the timing of the various interventions and certifications.

The fall-off of the ATP is shown here as taking place over a period of four years of 6-monthly ivermectin treatment (i.e. eight treatment rounds). In fact the 'zero' target for the ATP may well be achieved after two years of 6-monthly treatments (i.e. four treatment rounds), in which case the date for pre-certification may be advanced from year 17 to year 15.
FIGURE 1.

INTERVENTION – Ivermectin every 6 months (85% coverage of eligible population)

Pre-certification period (3 years)

Post-endemic period

(Unreplenished adult worm population dying of old age.)

(Surveillance continues until regional elimination is certified)

Base line start of 6-monthly ivermectin interventions (conditional on continued ivermectin intervention)

Annual Transmission Potential (ATP)

PRE-CERTIFICATION (CT/WHO)

CERTIFICATION OF ELIMINATION (CT/WHO)

TIME (in years)

Continued suppression of infectivity*. Unreplenished adult worm population dying out from old age (12 years)

* To the point where the Basic Reproduction Ratio for macrofilariae (R) is <1 and approaching or reaching 0.
6.1.4. Conclusions of the ICT

At the end of the verification surveys, the ICT will be asked to reach one of two possible conclusions: either (1) they are satisfied that elimination has been achieved and recommend that treatment be stopped, or (2) they are not satisfied to this effect. ICT reports must spell out the reasons for their conclusion. If the ICT decides it is not satisfied, then it must indicate what additional actions are required. These might be additional data analyses, additional surveys, more complete coverage or extended treatments.

6.2. Post-endemic Surveillance for Parasite Transmission

If elimination is certified, the applicant country will establish a surveillance system to detect possible renewal of parasite transmission, both in previously endemic areas and in areas where imported cases might be expected to occur. Entomological evaluation, using PCR to detect parasite larvae in vector populations, is recommended because of the long prepatent period in human infection. Both heads and bodies of flies should be tested because a positive test indicates contact with a microfilarial carrier. If positive flies are detected, epidemiological surveys should be carried out to identify and treat both infected people and the at-risk population. This post-endemic surveillance should be carried out until elimination of onchocerciasis is declared for the Region.

6.3. Selection of ICT Members

Persons selected as team members should be able to be critical in their assessments and their views as experts should be respected both nationally and internationally. Potential conflicts of interest, such as nomination of a national from a country under review as a member of the ICT, should be avoided. Members should be chosen from different areas of the world so that the nature and extent of the efforts made to document the interruption of transmission might become widely known. Scientists working on onchocerciasis and countries with elimination programmes should both be represented on ICTs so that technical expertise can be exchanged and applied to the certification process.

7. RESEARCH AND TRAINING NEEDS

Training and research is urgently needed on a number of subjects, as described below.

7.1. Each country should develop a Mectizan® distribution model that is most appropriate to its specific social and cultural circumstances and the organization of its health care services. Emphasis should be given to those elements which foster high coverage over the long term (15 years), for example:

- community participation in setting priorities for health;
- the effect of ivermectin on Ascaris;
- updating census records;
- community awareness of the disease;
- how to construct a community map of houses and families;
- central point vs house-to-house distribution of drugs;
- a method of "mop-up" to locate and treat individuals missed during regularly scheduled treatment rounds;
- recording and notification of new people migrating into the community; and
- infected people migrating to non-endemic areas (community and case surveillance).
The participation of local ivermectin distributors is essential for the development of strategies for high coverage. Ecuador has developed effective and sustainable community-based ivermectin distribution. This model should be studied, described, and interaction and exchange encouraged amongst these village-based health workers and those from other endemic countries. In general, activities involving the exchange of experiences at all levels of the distribution chain should be fostered.

7.2. If elimination of parasite transmission is the ultimate goal, measures of the impact of sustained ivermectin distribution on the adult worm population are needed. One of these could be the basic reproductive ratio (Ro), a parameter used in population biology and suggested specifically for *O. volvulus* in Latin America (Cupp, 1992). The analytical models used to estimate Ro require field data specific to each endemic area. At present, models have been developed only for West Africa and for the Mexico/Guatemala region where *S. ochraceum* is the vector (Basáñez and Boussinesq, 1999). Corresponding data - vector competence, annual biting rate, vector infection rate, community prevalence and microfilarial load, etc. - are needed for other endemic areas in Latin America. OEPA should support studies to collect these data, both pre-treatment baseline (where drug distribution has not yet started, especially northern Venezuela) and during the in-depth epidemiological assessments. It is also recommended that OEPA establish an institutional link with the Wellcome Trust Center for the Epidemiology of Infectious Diseases (Dr María-Gloria Basáñez) and with the Department of Public Health, Faculty of Medicine and Health, Erasmus University, Rotterdam, The Netherlands (Dr G. van Oortmarssen) to develop and field test various indicators and models of the impact of ivermectin on parasite populations. This would include both analytical and simulation modelling of the parasite transmission cycle under ivermectin pressure, as well as estimates of "acceptable" levels of infection in the human and vector populations.

7.3. Entomological evaluation using PCR and the "Poolscreen" algorithm calls for processing 10,000 flies (200 pools of 50 flies) from each endemic community without regard to the parous rate of flies in the population from which the sample is drawn (Katholi et al., 1995). Most vector species have distinct patterns of daily biting activity that differs for parous and for newly emerged flies. For *Simulium ochraceum*, for example, newly emerged flies seek the first blood meal during the morning hours, while parous flies are much more abundant in the afternoon. To increase the probability of collecting parous flies (those which have already taken a blood-meal and therefore could possibly be infected), the patterns of daily biting activity for parous and nulliparous flies need to be defined for other vector species. Having this information will increase the chances of detecting transmission as well as increase the validity of negative PCR determinations. In addition, as community prevalence and mf load decrease under repetitive treatment, infection rates in vectors will also decrease so that more flies will have to be processed to obtain a statistically reliable result (Basáñez et al., 1998). Pool size at present is limited to 50 flies. Laboratory techniques that allow increased pool size (100 flies is the standard for African species) are urgently needed. It is recommended that OEPA establish an institutional link between the University of Alabama-Birmingham and Dr T. Unnasch as a reference and quality control laboratory for PCR technology in the endemic countries.

7.4. Studies indicate that repetitive treatment with ivermectin reduces fecundity and may increase mortality of adult worms. If confirmed, the length of treatment required for elimination (15 years) could be shortened. This has been under investigation by a team in the Cameroon Republic, West Africa financed by the River Blindness Foundation. OEPA staff and the PCC should stay in close contact with the members of this team through its Director (Dr B. O. L. Duke), as their results could have important consequences to the Latin American elimination programme. It is also desirable that the adult worms in nodules from patients who have received repetitive 6-monthly treatments with ivermectin, should be studied histologically to detect any changes in their vitality or embryogenic potential.

7.5. Since ivermectin is given only to eligible persons, the non-eligible portion of the population (children under five years of age, pregnant women, mothers in the first week of lactation, and very sick persons) which is infected continues to serve as a reservoir of microfilariae for the community. However, this reservoir is relatively small (perhaps 12%) and
much of it is only temporary until the next round of treatment. Research should continue on formulations and treatment schedules which could reduce this reservoir.

7.6. Despite the long generation turn-over time of *O. volvulus* (perhaps 10-12 months), resistance to ivermectin may develop as a result of prolonged treatment. National Programmes in Africa and the Americas should be able to early detect recrudescence of mf in treated populations, as well as encourage the efforts of WHO and others to find an effective macrofilaricidal drug that is safe for large-scale use.

7.7. New tests, less invasive and easier to apply, are urgently needed for rapid detection of infection and transmission in sentinel populations. One test that is likely to be very useful for monitoring infection rates in children is the immunochromatographic card test (ICT) recently developed by Dr Gary Weil and his associates at the Washington University School of Medicine, St Louis, MO, USA. (Weil et al., 2000) The system uses whole blood obtained by finger puncture and allows a reaction with reagents impregnated at the top of the strip. A test can be read as positive or negative within 10 minutes. DEC skin tests and xenodiagnostic tests might also be considered in children.
REFERENCES


APPENDIX I

DEFINITIONS RELEVANT TO ONCHOCERCIASIS ELIMINATION

An onchocerciasis case is defined as an individual with evidence of current infection with Onchocerca volvulus.

Incidence is the rate at which new cases arise in a population within a defined interval of time.

Prevalence is the proportion of the host population infected at a particular point in time.

Morbidity is defined as the presence of disease manifestations caused by onchocerciasis.

Basic reproductive ratio ($R_0$) is a measure of the reproductive success of the parasite population. It encapsulates all the process rates that determine the flow of the parasite through its life cycle, and defines a theoretical threshold between extinction ($R_0$ continuously less than 1), and persistence of infection ($R_0$ continuously equal to or greater than 1) (Basañez and Boussinesq, 1999).

Transmission threshold occurs for a parasite when the basic reproductive rate is equal to 1.0. Below this threshold level the parasite is unable to maintain itself in the host population.

Suppression of infectivity (or conditional interruption of transmission) means the absence of infective larvae (L3s) in the Simulium vector population as determined by polymerase chain reaction (PCR) or any other valid method, coupled with a 5-year cumulative incidence of <1 new case per 1000 persons. Suppression of infectivity can be achieved through drug (ivermectin) pressure despite the fact that there can still be a population of adult worms capable of reinitiating transmission if the drug pressure is removed.

Interruption of transmission means the permanent interruption of transmission in a clearly-defined area after all the adult worms in the human population in that area have either died out from old age or been exterminated by some other intervention. This should occur within 15 years of the establishment of sustained interruption of infectivity.

Transmission breakpoint is a critical average worm burden below which the mating frequency of the parasites is too low to maintain the parasite population.

Sentinel Communities are pre-selected hyperendemic communities where in-depth epidemiological evaluations take place at regular intervals: first before treatment starts, then again after two years, and finally at 4-year intervals thereafter. The evaluations include parasitological (mf and nodules), ophthalmological, and entomological indicators. [It should be noted that the use of sentinel communities in this way has two disadvantages. First, the community populations may become tired of these repeated examinations and refuse to cooperate. Second, it will soon become known by those working in the programme which are the designated sentinel communities and they may reserve their best efforts for these communities at the expense of others. A possible way round this difficulty is to have a larger number of potential sentinel communities and just before each round of examinations to pick at random a smaller number of them that will be examined.] The International Certification Team is encouraged to use other villages for monitoring, pre-certification or certification activities.

Elimination (literally “casting out over the threshold”) of the parasite population from a defined geographical area means the sustained absence of transmission until the adult parasite population within that area has died out naturally or has been exterminated by some other intervention. This should occur within 15 years after interruption of transmission. When elimination of the parasite is certified, the endemic area moves into the ‘post-endemic’ phase.
Eradication (literally "pulling out by the roots") is a term that, strictly speaking, should only be applied when the parasite has been eliminated from the planet Earth.

Pre-certification period is the period following interruption of transmission, during which surveillance is carried out to verify that interruption of transmission has been sustained after ceasing all control interventions. This period lasts for 3 years. No intervention is carried out during this period.

Certification: a country will be eligible for certification as being in the post-endemic phase after successfully completing a 3-year pre-certification period in all its foci.

WHO Regional elimination of onchocerciasis will be considered to have been achieved when all countries in that Region have been certified as having eliminated onchocerciasis.

Countries are classified as:

Endemic: When onchocerciasis morbidity, transmission and infection are present.

Post-endemic: When a country with a past history of endemic onchocerciasis is officially certified as having successfully completed a 3-year pre-certification period of interrupted transmission in all its previously endemic onchocerciasis foci.

1. Endemicity

Endemicity is the permanent presence of a disease or pathogenic agent in a given region. Its level is determined according to the prevalence of the disease or pathogenic agent, i.e. the percentage of diseased persons or carriers in a given population.

An endemic onchocerciasis focus is an area within a country where a local cycle of Onchocerca volvulus transmission is maintained and is giving rise to autochthonous infections. In terms of population biology of the parasite, this is an area where the basic reproductive ratio (Ro) is 1.0 or greater. Endemicity is stable where the incidence of the infection shows little or no trend to increase or decrease over time.

REA is an abbreviation for "rapid epidemiological assessment" based on the prevalence of nodules in a sample of 30 adult males who have lived in the community for at least 5 years and who are engaged in rural activities. It is about half the prevalence of microfilariae in skin snips.

REMO is an abbreviation for "rapid epidemiological mapping" of onchocerciasis in a country or other large area. It is based on REA in communities carefully selected (by an epidemiologist and an entomologist, both with experience of onchocerciasis, and a geographer) as likely to reveal the maximum of information about the distribution of onchocerciasis in the area or country concerned.

2. Stratification of endemicity

Stratification of endemicity has not been standardised in all onchocerciasis control programmes.

2.1. OCP. For OCP, the objective was to treat all endemic areas where there was a risk of blindness. Therefore the levels of endemicity were fixed as follows (source: OCP 1994):

- Hypoendemic - less than 40% of mf carriers;
- Mesoendemic - 41-59% of mf carriers;
- Hyperendemic - 60% or more of mf carriers

2.2. APOC. APOC is also concerned by the public health importance of onchocerciasis (i.e. eye and skin lesions, as these lesions are directly related to the level of endemicity). In West African savannah, communities with a microfilarial prevalence of 55% account for 80% of the blindness due to onchocerciasis. If communities with a microfilarial prevalence of
40-50% are included, then the two groups will account for nearly all the blindness due to onchocerciasis. Therefore the treatment strategy is as follows: large-scale ivermectin treatment is a "must" where the microfilarial prevalence is greater than 60% and highly desirable where it is 40-59%. No attempt was made to define the threshold below which mass treatment with ivermectin was not indicated, as such a lower limit depends primarily on the locally available resources.

Because it was found that a good 2:1 relationship exists between classification of onchocerciasis levels of endemicity based on skin-snip data and those based on nodule palpation, a rapid epidemiological assessment method (REA), based on the proportion of nodule carriers in a sample of 30-50 adult males, who have been resident in the community for at least five years and who are engaged in rural activities was developed and tested (Taylor et al., 1992). This method is now widely used as being more practical and faster than skin snip surveys for making the decision on whether to undertake mass treatment or not (see equivalence table attached).

<table>
<thead>
<tr>
<th>Assessment method</th>
<th>Large scale treatment</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Treatment is a &quot;must&quot;</td>
</tr>
<tr>
<td>Parasitological assessment</td>
<td></td>
</tr>
<tr>
<td>Prevalence of mf in skin snips</td>
<td></td>
</tr>
<tr>
<td>- Males and females of all age</td>
<td>60% and over</td>
</tr>
<tr>
<td>- Males over 20 years</td>
<td>90% and over</td>
</tr>
<tr>
<td>Rapid assessment methods</td>
<td></td>
</tr>
<tr>
<td>Prevalence of nodules in males over 20 years</td>
<td>40% and over</td>
</tr>
<tr>
<td>Prevalence of leopard skin in males over 20 years</td>
<td>20% and over</td>
</tr>
</tbody>
</table>

2.3. Latin America. In Latin America, the levels of endemicity are defined as follows:

*Hypoendemic* is a term used to mean an area with little transmission. It corresponds to communities where the microfilarial biopsy positive rate is 20% or less in 30 adult males who have lived in the community for at least 5 years.

*Mesoendemic* means an area of moderate parasite transmission where the microfilarial biopsy positive rate is greater than 20% and less than 60 %.

*Hyperendemic* means an area of high parasite transmission where the microfilarial biopsy positive rate is 60% or more. In Latin America, most eye disease is found in hyperendemic communities (Brandling-Bennett et al., 1981).
APPENDIX II

GUIDELINES FOR THE PREPARATION OF A COUNTRY REPORT

To initiate the certification process, each country will submit a comprehensive written report to WHO. The length and detail of this report will vary widely from a brief document for those countries that have few foci, to highly detailed documents with supporting data needed from those countries applying with many foci and a large population at risk. The report will be examined by the ICT for records to substantiate the extent and depth of coverage obtained over the life of the elimination programme. Extent of coverage means that all endemic communities have been discovered and treated; depth of coverage means that at least 85% of the population eligible to take ivermectin and living in these communities were treated at each round of treatment. In addition, methods and results of in-depth epidemiological and entomological surveys should be given. Countries are encouraged to set up a National Review Committee to compile and review the report as an internal programme review before starting the certification process. The format of the report is optional but should contain the following common elements.

1. Historical account and background information on onchocerciasis in the country concerned

- How the disease was discovered and/or imported into the country or focus concerned.
- Demographic information, including population distribution by geographical region of the country and indicating the populations in onchocerciasis endemic areas.
- Ethnographic information on the populations affected by onchocerciasis.
- Economic activities of the affected regions - agriculture, mining, forestry, etc.
- Migration patterns within the country and between adjacent countries, especially those where onchocerciasis is also endemic.
- Information on primary and secondary vectors of *O. volvulus* (including their parous biting cycles) and with their distribution shown on maps.
- Bibliography of published literature on onchocerciasis in the affected country.
- Health care infrastructure of the endemic areas.

2. Methodology and findings of original assessments of the extent of onchocerciasis

- Methods used and data obtained from any epidemiological, ophthalmological, and entomological surveys.
- Maps delineating the endemic regions and areas investigated for onchocerciasis. These maps should be topographical and locate communities by name.
- Lists of communities surveyed for onchocerciasis, giving the rationale for including them as well as reasons for not surveying adjacent communities.
- Lists of any communities where onchocerciasis is suspected but not at present confirmed.
- Pre-treatment results of REA, used to stratify endemic communities and to select sentinel communities.
- Results of in-depth pre-treatment epidemiological surveys carried out in sentinel communities.
3. Detailed overview of the national elimination programme

Detailed description of intervention efforts to date, including the following:

- Participating organizations (Ministry of Health, NGDO, etc.) and their responsibilities, sources of financing.
- Organizational chart delineating areas of responsibilities and personnel.
- Programme management, whether horizontal or vertical, methods of distribution (mass target, house-to-house vs central point).
- Methods used to assure maximum coverage, such as health-educational programmes, community participation, etc.

4. Data verifying the extent and depth of ivermectin coverage by treatment round

- Total number of communities and individuals in each community eligible for treatment.
- Total number of communities and eligible individuals treated by treatment round.
- Updated census for each treatment round.
- Steps taken to assure validity of census, maps, and treatment lists.
- Measures taken to control ivermectin tablets used vs those programmed for use.

5. Evaluations of treatment effects

- Data and results of in-depth epidemiological, entomological and ophthalmological evaluations in sentinel communities.
- Description and operation of post-endemic surveillance systems and results, if any.
APPENDIX III

SUMMARY OF GUIDELINES FOR IN-DEPTH EPIDEMIOLOGICAL EVALUATIONS

1. Inventory of communities

A. Identification of all permanent communities located within or in close proximity to the known endemic foci.

B. This identification and an inventory of communities is entered in a database using geographic information system (G.I.S.) technology to map communities.

C. Basic epidemiological information on onchocerciasis gathered from current field surveys and from historical registers must be included.

D. Communities are characterised by:

1. Name;
2. Political/administrative classification (e.g. municipality, district, state, etc);
3. Total population from census (with date of last census) preferably from a recent house-to-house census conducted by the programme staff;
4. Economic base (e.g. coffee production);
5. Geographic location (altitude, map co-ordinates, etc);
6. Source of information on community and its reliability;
7. A permanent identification number.

2. Initial classification and stratification of the community

Risk factors, historical record or other information suggests classification as an endemic community and its level of endemicity, such as:

1. Hyperendemic, mesoendemic, hypoendemic;
2. Suspected endemic for onchocerciasis;
3. Non-endemic.

3. Rapid Epidemiological Assessment (REA)

Procedure:

1. Evaluation carried out rapidly, no more than 1 day per community;
2. Test group is 30 adult males with a minimum of 5 years residence in the zone and employed in rural tasks;
3. Should be carried out in all suspected and known endemic communities (the latter to detect any change in endemic status);
4. Obtain and process skin biopsies and process them according to standard criteria (incubation time, media, mf counts, etc);
5. Palpation of test subjects to nodules.
4. Treatment of community with ivermectin according to programme standards

A. All eligible persons should be treated.

B. Treatment register should be developed with updated house-to-house census.

C. Data on treatment (total population from updated census, total number treated, number eligible, refusals, etc.) should be reported to central office for data entry.

5. Evaluation of treatment effect in sentinel communities selected according to the prescribed guidelines

A. Done in sentinel communities selected according to the prescribed guidelines.

B. In-depth epidemiological surveys carried out:
   1. Frequency of two years after first treatment and every four years thereafter;
   2. Include parasitological, entomological and ophthalmological surveys, according to guideline specifications.
APPENDIX IV

GUIDELINES FOR THE ENTOMOLOGICAL EVALUATION OF THE IMPACT OF COMMUNITY-WIDE IVERMECTIN DISTRIBUTION ON ONCHOCERCIASIS TRANSMISSION

1. General remarks

The effects of ivermectin distribution on parasite transmission can be evaluated by monitoring infection rates of vector blackflies with larvae of *Onchocerca volvulus*. This method has several advantages over parasitological evaluation of the human population, especially when children are involved, for the following reasons:

- Infection rates in blackflies are rapid and sensitive indicators of the change in community microfiliarial load that results from ivermectin distribution.
- Changes in vector infection rates correlate well with the percentage coverage of the human population with ivermectin.
- Absence of infective stage larvae in the vector population during the transmission season is the first indicator of having achieved interruption of parasite transmission. By contrast, the prepatent period for the appearance of nodules or skin microfilariae is about 10-24 months.
- Monitoring very low vector infection rates with polymerase chain reaction and DNA technology is easier and less expensive than monitoring very low levels of infection in children.
- Use of a *O. volvulus*-specific DNA probes guarantees absolute specificity and allows for processing large numbers of flies, thus increasing reliability of the results.
- Vector collection teams working in the community can deliver health messages about ivermectin, thereby increasing coverage.
- It is completely non-invasive and well accepted by the community.

For pre-treatment baseline data, vector infection rates are ideally measured over a complete year, or at least a complete transmission season. This provides baseline data for comparison with post-treatment evaluations. At present, such information is available only for *Simulium damnosum* complex in Africa, for *Simulium ochraceum* areas in Mexico and Guatemala, and to a lesser extent for *Simulium exiguum* in Ecuador (hyperendemic areas only). As of 1999, however, studies are under way in northern and southern Venezuela to obtain pre-treatment data on other vector species (M.-G. Basáñez, personal communication).

The methodology outlined here for the collection of vectors is based on studies of biting behaviour by Porter, CH, and RC Collins, 1988 (Am J Trop Hyg 38:142-152), and was used to evaluate community-based ivermectin trials in Guatemala (Cupp et al., 1992. Am J Trop Med Hyg 47: 178-180). Therefore, the described schedules for blackfly collection are for *S. ochraceum*. For other vectors, some modifications will have to be made because of differences in transmission season and vector biting behaviour.

The collection methodology can also be used to investigate areas that might be susceptible to introduction of the parasite. The systematic collections will determine if a competent vector is present, and if the biting density is sufficiently high to support a transmission cycle.

*PCR technology vs dissection of flies*. To monitor the effects of ivermectin in the WHO-sponsored community trials in Guatemala, the annual transmission potential (ATP) and infective biting density (IBD) were determined by individual dissection of over 110,000 flies
over a 30-month period. This effort is clearly beyond the capacity of an operational programme. Moreover, under repetitive treatment, the community microfilarial load is reduced further and infection rates in flies drop accordingly, so that even more flies would have to be examined to produce statistically reliable data. For this reason, the use of PCR technology is recommended rather than dissections, although dissections are still valid and can be done. Fly collections are grouped in pools of 50 flies each, and tested for *O. volvulus* larvae. A minimum of 10,000 flies is required per community. The data are analysed by a statistical software program ("Poolscreen") made available by Drs Charles Katoli and Tom Unnasch at the University of Alabama at Birmingham, USA (Katholi et al., 1995. J Inf Dis 172:1414-1417).

2. Methodology

2.1. Selection of communities for evaluation. Preferably these should be sentinel communities (or communities selected by the International Certification Teams in the case of certification surveys) where pre-treatment baseline data are available. Also, the coverage (percentage of the eligible population treated with ivermectin) during the past rounds of treatment should be available so that it can be related to vector infection rates. The number and location of communities is at the decision of the programme manager or the ICT and will depend on the resources available and the purpose of the study, *i.e.* whether it is routine monitoring or for certification purpose. For example, for routine monitoring in an area the size of the central zone of Guatemala, six communities would be a minimum number for routine monitoring.

2.2. Collector teams. A team consists of one collector and one attractant. The attractant must be an adult male resident of the endemic community, who has been treated with ivermectin at least one week before the collections are made. The collector will aspirate all flies landing on the exposed skin of the attractant before the flies commence biting. All flies are aspirated into a separate container for each collection period and labelled as to community, date, collection site, time of collection, and collector team.

2.3. Collection sites. Two sites for each community, one near the housing area, the other where people frequently spend their working time outdoors (coffee plantations, farms, gardens, riverbanks, etc.). The rule is to collect flies in those areas where people spend most of their time outdoors and are bitten most frequently.

2.4. Pre-treatment data. A full year is preferable, but 4 months taken during the transmission season is acceptable. Two months would be the minimum. For example, two or four months of pre-treatment data can be compared with two or four months of post-treatment data taken during the same months.

2.5. Monthly collection schedule. Four days of collection should be carried out during each of the four months of the peak transmission season. In the case of *S. ochraceum*, this is January-April. Some flexibility is allowed in the monthly schedule for working in remote areas, for example, 6 or 8 days of continuous collection could be done during two months of the transmission season. The rule is that at least 10,000 flies per community must be collected and that the collections should be spread out over several days and months. If fly density is low, more days of collection are required.

2.6. Daily collection schedule. Each species has distinct diel patterns of biting activity. The rule is that collections should be made when parous flies are most abundant in order to increase the probability of collecting infected flies. Parous flies are flies that have taken a blood-meal previously and therefore could be infected; nulliparous flies are newly emerged flies taking their first blood-meal and therefore cannot be infected. For *S. ochraceum*, collections are made between 12:00 and 17:00 hours because the biting population has a higher proportion of parous flies biting at that time. If the diel pattern of biting activity is unknown, then it should be determined by doing hourly catches during each of the daylight hours and dissecting the flies to determine the parous rate during each hour. If this cannot be done, then collections should be made over the complete daylight hours, between 07:00 and 18:00 hours with an hour's break at mid-day.
2.7. Hourly collection schedule. Each hour of collection for each team is divided into 50 minutes of collecting followed by 10 minutes of rest, during which time the collection can be labelled and stored. Each 50-minute collection unit must be maintained separately and labelled with the date, community, collection site, time of collection (e.g. 08:00-08:50, etc.), and collector team. Each 50-minute collection must be preserved in 100% isopropanol for PCR testing. This is most conveniently done in the evening after the daily catch is made.

2.8. Determination of the Biting Rate. Data analysis requires a biting rate as well as an infection rate. The biting rate is calculated as the geometric mean number of flies per 50-minute collection period, with 95% confidence intervals. These data can be used to estimate the biting rate per hour, per day, or per transmission season. The infection rate when applied to the biting rate yields the number of infective stage larvae potentially transmitted per unit time, and is a measure of the transmission potential. The biting rate and the infection rate are also required in order to estimate the basic reproductive ratio (Ro) for that community. Therefore, when the flies are processed for PCR testing, the number of flies collected during each 50-minute period must be counted and recorded.

2.9. Processing of flies for PCR. In the laboratory, flies from each 50-minute collection unit are examined under a stereomicroscope, identified as to species, and any flies containing ingested blood are discarded. Flies are then counted into "pools" of 50 each by species. The heads are separated from the bodies and tested separately, because most infective stage larvae are found in the head. If resources are available, testing the bodies as well is recommended. For example, if elimination has been certified for a focus and the purpose of testing flies is surveillance for renewed transmission, then it is important to test the bodies because a positive indicates previous contact with a microfilaria-positive person.

2.10. Data reporting and analysis. Three statistics can be reported. The minimum requirements are the infection rate, which is the proportion of flies infective based on heads alone (Proporción de Infectividad, PI) and the biting rate (Tasa de Picadura, TP). The proportion of flies infected based on the flies’ bodies (Proporción de Infección Parasitaria, PIB) can be calculated if the flies’ bodies are processed. PIB is calculated from fly bodies only because if pools of heads and bodies both test positives, it impossible to know whether the positives were caused by the same fly or different flies. Having infective stage larvae in the head with first and second stage larvae in the bodies simultaneously (asynchronous parasite development) is more frequent in vectors without cibarial armature, for example in S. metallicum, S. exiguum (Collins, RC. 1979. Am J Trop Med Hyg 28: 491-495; Vieira, JC. 1995. Master of Science Thesis, Univ AZ, Tucson). The "Poolscreen" programme calculates an infection rate plus or minus 95% confidence intervals. TP is the total number of flies collected divided by the total number of 50-minute collection units. However, the number of flies collected during each collection unit should also be reported separately in order to calculate the geometric mean biting rate with confidence intervals.

2.11. Transmission potential. Infectivity rate (PI) and biting rate (TP) are used to calculate a minimum transmission potential. The following example is taken from data presented by Juan Carlos Vieira from an entomological evaluation using PCR on flies collected from a hypoendemic, treated village in Ecuador.

- Geometric mean biting rate (TP) per 50-minute collection unit during June and July = 11.03 flies per period (95% c.i. = 8.38 – 13.68). 50 minutes = 0.833 of one hour; 11.03/0.833 = 13.24 flies per hour (95% c.i. = 10.06 – 16.42).

- Total biting density estimated for two months is 13.24 x 10 hr x 61 days = 8077 flies

- Infectivity rate (PI) from 1 positive pool of heads in 215 pools of 50 flies each calculated by the Poolscreen program is 0.000083 (95% confidence interval of 0.000002 to 0.000052).
- Transmission potential during June and July is infectivity rate x biting density = 8077 flies x 0.000093 = 0.75 infective stage larvae per person (95% c.i. = 0.01 – 5.21). This is minimum transmission potential because we assume only one larvae per infected fly.

- Transmission potential for the entire year (ATP) can be estimated from year-round collections of *S. exiguum*, which showed that population density of this species, is highly seasonal and 32% of the annual total was collected during the peak 2-month biting period. 8077/0.32 = 25.241 annual biting intensity.

- Total annual biting density = 8077 flies during June and July divided by 0.55 = 14,685 flies per person per year. Infectivity rate 0.000093 x 14,685 flies = 1.37 infective stage larvae per person per year (95% c.i. = 0.04 to 7.64).

- Rate of infection with immature larvae (PIP) can be calculated from PCR results on fly bodies, which in this case was zero pools positive.

2.12. Interpretation of results The indicators on the Transmission Potential are interpreted for suppression of infectivity / interruption of transmission. Interpretation of Transmission Potential calculated from data presented by Juan Carlos Vieira from an entomological evaluation using PCR on flies collected from a hypoendemic, treated village in Ecuador.

- The estimated minimum average annual exposure in this community was 1.37 infective stage larvae per person per year, with a possible maximum of 7.64 L3s per year. This is probably below the level required for maintenance of autochthonous infection.

- At least one person still positive for microfilariae may be living in the community.

- The fact that the fly bodies were negative, with only one positive pool for heads, suggests that few people are infected and the infections are light (community microfilarial load is probably quite low).
SUMMARIES OF PRESENTATIONS
MADE BY PARTICIPANTS AT THE MEETING ON
CRITERIA FOR CERTIFICATION OF INTERRUPTION OF TRANSMISSION / ELIMINATION OF HUMAN ONCHOCERCIASIS

(WHO, GENEVA, 28-29 SEPTEMBER 2000)

The following are summaries of the presentations, requested of certain participants, by WHO, which were made at the outset of the meeting in order to provide a background for the subsequent discussions. The summaries have been prepared by the authors of the presentations. The actual presentations were illustrated by numerous slides, which have not been reproduced in this annex.

The summaries of the presentations are given below, in the order in which they were made.

1. Goals of the Onchocerciasis Elimination Program for the Americas, certification criteria and how the certifications process could operate

Dr M. Sauerbrey and Dr R. Collins

The goals of the Onchocerciasis Elimination Program for the Americas are two-fold: (1) to prevent new cases of onchocerciasis morbidity; and (2) to block and eventually eliminate parasite transmission in those countries or foci where feasible. If parasite transmission can be effectively blocked throughout an endemic area and sustained for the maximum life span of the adult female worms, then those parasite populations will be eliminated and become extinct. The strategy is based on mass distribution of ivermectin to all endemic communities twice each year for a minimum of 15 years (the estimated maximum life span of adult *Onchocerca volvulus*).

The scientific basis for the programme comes from both controlled scientific studies and preliminary evaluations of the operational programme of Ecuador. Ivermectin given as a single oral dose lowers the concentrations of microfilariae in the skin to levels below those required for vector infection (Cupp et al., 1986). Furthermore, two doses of ivermectin at 6-7 months intervals resulted in complete suppression of patient infectivity to *Simulium ochraceum* s.l., which lasted for 6 months after the first dose (Cupp et al., 1989). Field trials sponsored by WHO/TDR in Guatemala showed that parasite transmission by *Simulium ochraceum* s.l. could be completely blocked after four semi-annual treatments when coverage was >92% of the eligible population (Cupp et al., 1992, Collins et al., 1992). Later, the Ecuador programme reported the complete absence of new infections in children fewer than five years of age in hyperendemic communities that had received semi-annual treatments for five years (Guderian et al., 1997). Coverage was uniformly high (90%). These preliminary results from Ecuador were particularly important because the vector *S. exiguum* ranks high in vector capacity compared to *S. ochraceum* s.l. (Collins et al., 1995) and because the high coverage was sustained by an operational programme, rather than a controlled scientific study as was the case in the TDR trials.

In addition to these results, the characteristics of parasite transmission, vector behaviour, and epidemiology of onchocerciasis in the Americas give hope that elimination of both morbidity and parasite transmission can be achieved. Endemic areas and affected populations in the Americas are relatively small and discrete centering on local vector breeding sites. They are also generally well known, well studied, and easily accessible compared to many places in Africa (the Amazon basin foci of southern Venezuela and Brazil are exceptions). The endemic countries have organized Ministries of Health and health delivery services, and three have historically had onchocerciasis control programmes (Mexico, Guatemala, Venezuela). New World vectors do not migrate long distances, as do some African species, so that reintroduction of the parasite into an area where elimination has been achieved is less likely.
Transmission is generally less intense and disease less severe. For example, the maximum ATP reported for *S. ochraceum* s.l. is about 2200 and in most hyper- and mesoendemic communities' ATP ranges from about 200 to 500.

The suggested criteria for judging whether or not elimination has been achieved are when adequate surveillance shows: for morbidity, the absence of reversible anterior segment lesions in the eye and the absence of skin microfilariae and nodules in untreated children born after ivermectin distribution has commenced; for transmission, the sustained absence of infective stage larvae in the vector population. The certification process is divided into two phases.

The first phase (called Pre-certification) can occur after a minimum number of treatments (4-6) and will establish whether or not transmission has been blocked in sentinel villages and that morbidity is decreasing compared to baseline. Pre-certification surveys are repeated at fixed intervals (after 2-3 years of treatments and every 4-5 years thereafter) to ascertain the status of transmission. The second phase (Certification) occurs 15 years after interruption of transmission and will involve the evaluation of sentinel and non-sentinel communities by an international certification team. If an entire endemic focus is certified, treatment can be stopped and post-endemic surveillance will be established to detect re-introduction of the parasite and re-establishment of parasite transmission. While 15 years has been set as the minimum, we must be alert to possible cumulative effects of repetitive treatments on adult worm populations that might reduce this period.

Much remains to be learned about parasite transmission under the pressure of repetitive ivermectin treatment. Theoretical studies by Wada (1982) on *S. ochraceum* s.l. in Guatemala suggest that the critical biting rate for parasite maintenance was 7665 flies per person per year. This correlated well with field observations that an ABR of 8800 with an ATP of 18.5 were required to establish and maintain autochthonous transmission (Porter et al., 1988). Such data indicate the existence of thresholds of parasite transmission below which the parasite population will not become established (or eventually become extinct). Establishing these threshold values for each vector and endemic focus is crucial and can possibly be done using results of the pre-certification surveys and population modelling.

The development of guidelines and criteria have been a valuable exercise in programme planning and on-going evaluation for the individual country programmes and for OEP. The principle challenge, however, is to establish and maintain high levels of ivermectin coverage in all endemic areas for the time required to terminate the adult parasite populations. Indeed, the most important criterion to trigger the pre-certification and eventually the certification processes is concrete evidence that the endemic countries have achieved sustained high level coverage of all their endemic populations.

References:

2. Effect of ivermectin treatment on transmission of *Onchocerca volvulus* in Ecuador

*Dr T. Mancero*

In South America, the communities affected with onchocerciasis are in Brazil, Colombia, Ecuador and Venezuela.

In Ecuador, the principal focus of onchocerciasis is in Esmeraldas province. This focus is located in the Santiago river basin, formed by the union of three rivers, Rio Cayapas, Onzole, Santiago and their tributaries.

Five other satellite foci are situated along several rivers in the same province (Tuluvi, Canande, Viche, Verde and Sucio). There is another focus in Pichincha province, which resulted from migration of infected individuals from the focus in Esmeraldas.

Epidemiological studies in 1980 and 1986 revealed overall prevalence rates of 38.9% and 68.6% respectively. A further study in an extensive area of the 119 endemic communities in the country suggested a 55.3% prevalence rate in 1990.

| DISTRIBUTION AND STRATIFICATION OF THE ONCHOCERCIASIS ENDEMIC COMMUNITIES IN ECUADOR |
|----------------------------------|---|---|---|---|
| Area                             | # | Hyper | Meso | Hypo |
| Total Rio Santiago               | 35| 8     | 4    | 23   |
| Total Rio Cayapas                | 47| 31    | 9    | 7    |
| Total Rio Onzole                 | 17| 3     | 1    | 13   |
| Total principal focus            | 99| 42    | 14   | 43   |

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<td>2</td>
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</tr>
<tr>
<td>Rio Canande</td>
<td>8</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rio Verde</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rio Viche</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rio Sucio</td>
<td>3</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sto. Domingo de los Colorados</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total satellite foci</td>
<td>20</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

| Total endemic area of Ecuador    | 119| 42| 23| 54 |

Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

**CONTROL STRATEGIES**

During the 1980’s, the only control strategy used to control the disease was nodulectomy. In 1990 a study was undertaken in seven hyperendemic communities along Rio Cayapas using amocarzine.

In 1990, the National Onchocerciasis Programme implemented ivermectin distribution as its control strategy in the endemic communities. At that time medication was only administered to positive patients.
Between 1991 and 1994, regardless of their parasitological condition, all persons in the hyperendemic areas, for whom ivermectin was not contraindicated, were treated twice yearly, whereas treatment was undertaken annually in the meso and hypoendemic communities. Between 1995 and 1997 treatment was administered just once yearly in all of the 119 endemic communities.

Trained local health workers from the endemic communities distribute and observe treatment compliance with ivermectin twice yearly in the hyperendemic and yearly in the meso and hypoendemic communities. During these visits information recorded is used for updating the census of each community.

Having undertaken epidemiological and economic analyses in 1998, the programme implemented a biannual treatment strategy in 31 hyperendemic communities along Rio Cayapas. In the remaining 88 endemic communities residents receive treatment annually.

<table>
<thead>
<tr>
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<td>RIO CAYAPAS</td>
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<td>NUEVO CAYAPAS</td>
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<td></td>
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<td></td>
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<tr>
<td><strong>SATELLITE FOCI</strong></td>
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<td></td>
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<td>RIO CANANDE</td>
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<td>RIO SUCIO</td>
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<td></td>
</tr>
<tr>
<td>RIO TULULVI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STO DOMINGO de los COLORADOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

<table>
<thead>
<tr>
<th>TREATMENTS ADMINISTERED</th>
<th>NUMBER OF PERSONS</th>
<th>PERCENTAGE</th>
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<td>14</td>
<td>1367</td>
<td>4.2</td>
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<tr>
<td>13</td>
<td>350</td>
<td>1.1</td>
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<tr>
<td>12</td>
<td>2497</td>
<td>7.6</td>
</tr>
<tr>
<td>11</td>
<td>3178</td>
<td>9.7</td>
</tr>
<tr>
<td>10</td>
<td>2022</td>
<td>6.2</td>
</tr>
<tr>
<td>9</td>
<td>15167</td>
<td>46.3</td>
</tr>
<tr>
<td>8</td>
<td>2087</td>
<td>6.4</td>
</tr>
<tr>
<td>7</td>
<td>3118</td>
<td>9.5</td>
</tr>
<tr>
<td>6</td>
<td>1456</td>
<td>4.4</td>
</tr>
<tr>
<td>5</td>
<td>269</td>
<td>0.8</td>
</tr>
<tr>
<td>4</td>
<td>1237</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>32750</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000
### IVERMECTIN DISTRIBUTION. PERCENTAGE ELIGIBLE POPULATION TREATED BY FOCUS AND YEAR
**ECUADOR 1990-1999**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SANTIAGO</strong></td>
<td>90.1</td>
<td>83.5</td>
<td>72.2</td>
<td>82</td>
<td>87.6</td>
<td>82.9</td>
<td>75.8</td>
<td>80</td>
<td>81.6</td>
<td>82.1</td>
<td>86.7</td>
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<tr>
<td><strong>CAYAPAS</strong></td>
<td>71.1</td>
<td>69.06</td>
<td>49.92</td>
<td>75.99</td>
<td>75.39</td>
<td>79.81</td>
<td>81.92</td>
<td>79.58</td>
<td>83.96</td>
<td>82.61</td>
<td>83.6</td>
</tr>
<tr>
<td><strong>ONZOLE</strong></td>
<td>76.6</td>
<td>66.96</td>
<td>82.05</td>
<td>80.41</td>
<td>88.15</td>
<td>77.72</td>
<td>80.33</td>
<td>85.91</td>
<td>75.49</td>
<td>80.32</td>
<td>79.44</td>
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<tr>
<td><strong>SATELLITE FOCI</strong></td>
<td>93.9</td>
<td>78.47</td>
<td>40.3</td>
<td>53.85</td>
<td>62.22</td>
<td>80.74</td>
<td>82.95</td>
<td>79.83</td>
<td>97.1</td>
<td>86.66</td>
<td>94.61</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>92</td>
<td>77.43</td>
<td>56.11</td>
<td>67.96</td>
<td>66.58</td>
<td>80.42</td>
<td>79.17</td>
<td>80.73</td>
<td>89.05</td>
<td>79.94</td>
<td>84.85</td>
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Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

### IVERMECTIN TREATMENT COVERAGE OF ELIGIBLES BY ROUND & POINT COMPLIANCE ANALYSIS.
**ECUADOR, 1991-1999**

![Graph showing Ivermectin treatment coverage by round and point compliance analysis for Ecuador, 1991-1999.](image-url)
### Compliance: Relation between Received and Offered Treatments by Focus and Year


<table>
<thead>
<tr>
<th>Principal Focus</th>
<th>1992</th>
<th>1996</th>
<th>2000</th>
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<tr>
<td>SANTIAGO</td>
<td>18.17</td>
<td>33.47</td>
<td>34.18</td>
</tr>
<tr>
<td>CAYAPAS</td>
<td>29.01</td>
<td>30.52</td>
<td>39.02</td>
</tr>
<tr>
<td>ONZOLE</td>
<td>12.09</td>
<td>32</td>
<td>34</td>
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<table>
<thead>
<tr>
<th>Satellite Foci</th>
<th></th>
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<tbody>
<tr>
<td>CANANDE</td>
<td>34.16</td>
<td>38.84</td>
<td>43.1</td>
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<tr>
<td>SANTO DOMINGO</td>
<td>10</td>
<td>21.1</td>
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<tr>
<td>SUCIO</td>
<td>27.09</td>
<td>29.25</td>
<td>36</td>
</tr>
<tr>
<td>TULULVI</td>
<td>25.18</td>
<td>39.8</td>
<td></td>
</tr>
<tr>
<td>VERDE</td>
<td>27.00</td>
<td>37</td>
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<tr>
<td>VICHE</td>
<td>28.07</td>
<td>28.89</td>
<td>40</td>
</tr>
</tbody>
</table>

**Total**        | 22.03| 26.52| 36.02|

*Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000*

### Skin Biopsies

**Point Prevalence in Sentinel Communities* by Location and Year**


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SANTIAGO</td>
<td>65.47%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>CAYAPA</td>
<td>99.60%</td>
<td>0.0%</td>
<td>4.70%</td>
</tr>
<tr>
<td>CAYAPA NUEVO</td>
<td>-</td>
<td>48.51%</td>
<td>7.90%</td>
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</tbody>
</table>

*Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

*N* > 200

### Prevalence of Nodules and Positive Biopsies

**Among Children Under 5 Years of Age**

**Ecuador 1986-1996-2000**

<table>
<thead>
<tr>
<th>Year</th>
<th>1986</th>
<th>1996</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sentinel Communities</td>
<td>Nuevo Cayapa</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>64.30%</td>
<td>0.0</td>
<td>1.53</td>
</tr>
<tr>
<td><strong>Nodules</strong></td>
<td>19.60%</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*N* = 255 233 65 41

*Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

*Etiology has not been verified.*
## ENTOMOLOGICAL STUDIES ON SIMULIUM IN ECUADOR 1991-2000

<table>
<thead>
<tr>
<th>Community</th>
<th>Vector (Specie)</th>
<th>TI* %</th>
<th>TIP** %</th>
<th>Year of evaluation</th>
<th>TI*</th>
<th>TIP***</th>
<th>Year of evaluation</th>
<th>Starting year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Río Cayapas</td>
<td>S. exiguum</td>
<td>2.03</td>
<td>3.87</td>
<td>1996</td>
<td>0.0</td>
<td>0.0</td>
<td>2000</td>
<td>1996</td>
</tr>
<tr>
<td>Río Cayapas</td>
<td>S. quadrivittatum</td>
<td>0.54</td>
<td>0.54</td>
<td>1996</td>
<td>0.0</td>
<td>0.0</td>
<td>2000</td>
<td>1996</td>
</tr>
<tr>
<td>Río Cayapas</td>
<td>S. exiguum</td>
<td>0.99</td>
<td>4.95</td>
<td>1996</td>
<td>0.0</td>
<td>0.0</td>
<td>2000</td>
<td>1996</td>
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<tr>
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<td>0.15</td>
<td>0.00</td>
<td>1996</td>
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<tr>
<td>Río Santiago</td>
<td>S. exiguum</td>
<td>0.08</td>
<td>-</td>
<td>1996</td>
<td>0.0</td>
<td>0.0</td>
<td>2000</td>
<td>1991</td>
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<td>Río Santiago</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>0.0</td>
<td>0.0</td>
<td>2000</td>
<td>1991</td>
</tr>
<tr>
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<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
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<td>0.4</td>
<td>-</td>
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<td>1991</td>
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<tr>
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<td>S. quadrivittatum</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
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</tbody>
</table>

Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

*TI: Infectivity rate (% flies with third stage larvae)
**TIP: Rate of infection with immature larvae
***Parity study in 10,000 flies approximately

## SENTINEL COMMUNITIES

<table>
<thead>
<tr>
<th>Community</th>
<th>Prevalence before treatment</th>
<th>Level of endemicity</th>
<th>CMFL*</th>
<th>Starting year of treatment</th>
<th>Number of Rounds Received</th>
<th>Population 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Corriente Grande</td>
<td>96.3</td>
<td>Hyperendemic</td>
<td>34.8</td>
<td>1991</td>
<td>14</td>
<td>199</td>
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<tr>
<td>2. El Tigre</td>
<td>94.2</td>
<td>Hyperendemic</td>
<td>59.3</td>
<td>1996</td>
<td>16</td>
<td>120</td>
</tr>
<tr>
<td>3. San Miguel</td>
<td>96.3</td>
<td>Hyperendemic</td>
<td>57.4</td>
<td>1996</td>
<td>6</td>
<td>224</td>
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<tr>
<td>4. Playa de Oro</td>
<td>66.6</td>
<td>Hyperendemic</td>
<td>23.6</td>
<td>1991</td>
<td>12</td>
<td>237</td>
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<tr>
<td>5. Guayabal</td>
<td>63.6</td>
<td>Hyperendemic</td>
<td>29.4</td>
<td>1991</td>
<td>12</td>
<td>145</td>
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<td>6. Angostura</td>
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<td>Hyperendemic</td>
<td>34.7</td>
<td>1991</td>
<td>10</td>
<td>74</td>
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Source: Programa de Oncocercosis, Ministerio de Salud, Ecuador 2000

*Community microfilarial load
References:


3. Effect of ivermectin treatment and of combined ivermectin and vector control on transmission in the OCP area

Dr B. A. Boatin

The Onchocerciasis Control Programme in West Africa was launched in 1974. The sole strategy when the Programme started was larviciding to interrupt transmission given that at that time there was no available drug which could be used on large-scale against the disease. Computer simulations based on the available information and using the ONCHOSIM model suggested that 14 years of effective vector-control was sufficient to permanently interrupt transmission. The Programme was therefore guided in operations by the model predictions for decision making about when to cease larviciding. With the registration of ivermectin in 1987 for human use and its suitability for large-scale treatment (Awadzi et al. 1985, De Sole et al. 1989, Prod'hon et al. 1991, Whitworth et al. 1991, Collins et al. 1992) prospects for the control of onchocerciasis through chemotherapy were opened up. The Programme, now having two approaches for control, proceeded to ascertain what impact ivermectin would have on transmission (a) on its own and (b) when combined with vector control.

Since its utilization in 1990 on a large scale in the OCP area, ivermectin treatment on its own or combined with vector control has proved to be effective in reducing transmission of infection. This was established through several studies, which included both fly-feeding experiments and community trials that have been carried out in the OCP.

Effect of combined ivermectin treatment and vector control on transmission

Routine pre-control entomological evaluation data from an area with the combined strategies (larviciding plus ivermectin distribution) located in the humid savannah zone of Guinea, in the Upper Niger basin, showed that the transmission levels were around 14.5 infective females and 18.8 infective larvae per 1000 parous females (averages over a two-year period). Following a combined larviciding and ivermectin distribution there was an immediate impact on transmission, which fell by about 90% after only two years of intervention. On the other hand in the Côte d'Ivoire where pre-control transmission levels were around 13.8 infective females and 31.2 infective larvae per 1000 parous females (averages over a five-year period), it took six years following vector control alone 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).

The results of fly-feeding experiments carried out in 1987 (before the first ivermectin treatment) and at the end of 1995 (after nine rounds of ivermectin treatments combined with seven years of full vector control) in Asubende were compared. The fitting curve of results obtained in 1995 showed that the lowering of the microfilarial load after ivermectin treatment resulted in a decrease of the transmission potential of the blackflies. On the other hand, the effect of the drug seems to be marginal on the proportion of microfilariae ingested as well as on their potential development. It was concluded that the ivermectin-induced reduction of microfilariae in the skin resulted in a reduction of the intensity of transmission.

Recent results obtained routinely in the focus of Asubende after nine rounds of ivermectin treatment combined with eight years of full vector control showed these trends: - prevalence decreased from 85.9% to 24.7% and CMFL from 65.7 mf/s to 0.84 mf/s in 1987 and 1997 respectively. Only one child in 126 examined (0.8%), who were less than 5 years old and who had never received ivermectin, was found to be positive compared to 28.4% had there been no control.
Effect of ivermectin treatment alone on transmission

Community trials, which were initiated soon after ivermectin was registered for human use, attempted to establish the effect of mass treatment with ivermectin on transmission following: (a) single annual dosage, (b) repeated treatment at different frequency per year, and (c) prolonged treatment in the longer term. The community trial with ivermectin in the Pru basin in Ghana (Remme et al., 1989) was one of the earliest and largest of a series that was undertaken in the OCP area in 1987. This took place in an isolated focus of hyperendemic savannah onchocerciasis in Asubende in Ghana. The thrust of the trial among others, was an attempt to assess the effect of mass treatment with ivermectin on the transmission of Onchocerca volvulus.

Well over 14900 people were treated with a single dose of ivermectin at 150μg/kg. This was repeated one year later. The study showed that the total reservoir of skin microfilariae, as measured by the mean number of microfilariae available for transmission, had been reduced by an estimated 68%-78% two months after treatment. This was also consistent with the entomological results, which showed a reduction in transmission of 65-85% in the first three months after treatment, based on the L3 heads. The study showed for the first time that mass chemotherapy could significantly reduce onchocerciasis transmission, however the level of transmission that remained was unacceptably high. This was confirmed by preliminary model predictions showing that annual ivermectin treatment was not expected to eradicate the parasite from an endemic area within a period of 25 years (Habbema et al., 1992). Furthermore, the first results from the period after the second treatment round showed no evidence of an additional reduction in transmission.

Follow-up studies were also carried out in several river basins under only ivermectin distribution in the western extension of the Programme, where transmission is by S. damnosum s.l. The basins concerned were those of the Rio Geba (hyperendemic) and the Rio Corubal (mesoendemic) in Guinea-Bissau, and the Gambia Basin in Senegal (hyperendemic focus). In all these studies ivermectin was given at the recommended dose of 150 μg/kg body weight to all individuals who were eligible for treatment. Children aged 5 years old and below were not treated. The study period lasted through 4-5 years or more and the frequency of treatment per year was different for the river basins. Epidemiological evaluations were conducted just before the ivermectin treatment in the indicator villages and in any event one year after the last treatment.

The available results show a marked decrease in the overall prevalence of infection in all the basins concerned, almost 100% in the Rio Geba basin. What is remarkable is that no infections were detected in any of the children of 0-5 years old living in the areas. In addition, entomological assessment showed an 88% reduction in infective flies. The Rio Geba basin in Guinea-Bissau is hyperendemic for onchocerciasis. The remarkable results, which showed near 100% reduction in the prevalence of infection in the total examined population of 1807 and complete absence of incidence of infection in the 15% of children of less than 5 year olds who never received ivermectin, would suggest virtual interruption of transmission in humans in the basin. While it is clear that there is a profound reduction in transmission with ivermectin treatment, further follow up studies will be needed to confirm these findings. The findings in the Rio Corubal, where ivermectin was given three times a year for 3 years following 2 years of annual treatment, were equally remarkable. The area was hyperendemic to mesoendemic at the start of treatment. The evidence suggests a trend towards a virtual interruption of transmission in this area, where there was 89% reduction in infective flies.

In the Gambia basin in the Mako focus in Senegal, nine selected villages (total population of 1598) with longitudinal epidemiological follow-up have shown that the prevalence rates dropped from a maximum of 82% to 2.9% after 19 ivermectin treatment rounds starting from 1988 (from 1990 to 1995 and 1999, twice a year treatment was carried out). Incidence rates fell from 9.8% before the large-scale ivermectin treatment in the focus to 0.2% after 12 consecutive years of treatments, suggesting that interruption of transmission may have been achieved. In this same focus, the Community Microfilarial Load (CMFL) of one village has dropped from 48.1 microfilariae per snip (mf/s) before ivermectin treatment to the recent load of 0.01 mf/s observed in 1999, before the nineteenth treatment round.
Conclusions

This paper has attempted to review the evidence for the impact of ivermectin treatment on transmission in various studies in the OCP - ivermectin treatment being given over periods of short and long duration, at different frequencies per year and at different endemicity levels of onchocerciasis.

The available evidence so far firmly confirms the significant impact of ivermectin treatment on transmission of onchocerciasis infection. In some isolated situations, as in the mesoendemic and hypoendemic situations, repeat treatments over several years appears to interrupt transmission, although a longer period of follow-up is required before firm conclusions can be made.

The likelihood as to whether ivermectin treatment will interrupt transmission may lie in its long-term use, with optimum population coverage and total community or village coverage. Treatment given more than once a year appears to have a quicker and cumulative reduction in transmission but, for a maximum impact, the timing of the treatment will need to be targeted to the period of intense blackfly activity. It is recognised that treatment given more frequently than once a year might create operational problems, but this is feasible in isolated areas where suppression of transmission is the main goal, as at the beginning of a recrudescence of infection.

Although long-term treatment in some isolated foci appears to interrupt transmission, more prolonged treatment is required to prove whether transmission can be stopped. Advantage could be taken of the significant impact of ivermectin on transmission by giving treatment while, or just before, transmission by blackflies is most intense.

References:


4. Effect of vector control on transmission in OCP central area.

Dr L. Yaméogo

The Onchocerciasis Control Programme in West Africa (OCP) started its activities in 1975 in the most blinding onchocerciasis area, a large savannah area (654 000 km²). Before the launching of the Programme in 1974, this area was hyper-endemic showing prevalence rates of about 70% and, in some villages, blindness rates up to 9%\(^1\). Moreover, the frequency and level of evolution of ocular lesions and of onchocercal blindness were among the highest in the world. In Burkina Faso particularly, the entomological studies carried out before the inception of the Programme\(^1\) had clearly shown that the Annual Transmission Potentials (ATP) could reach 2 000 infective larvae/man/year.

The objective of the Programme was to eliminate onchocerciasis as a disease of public health importance as well as an obstacle to socio-economic development. To achieve this objective, 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 aerial spraying the rivers of the affected areas with rapidly biodegradable 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. 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\(^2\).

The size of the area under insecticide treatment was such that the regions located at its centre, colonised 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. It should be emphasized that all the rivers and tributaries of the area hosting larval stages of *S. damnosum* s.l. were treated on a weekly basis, each time the hydrological conditions were favourable to the development of blackfly larvae.

An entomological evaluation network was established to follow the efficiency of insecticide spraying. Catching points were selected in accessible sites where transmission could be noticeable, if possible nearby villages earmarked for epidemiological evaluation. Among the entomological indices monitored over these years, we shall essentially watch the Annual Biting Rates (ABR), the Annual Transmission Potential (ATP), as well as the infectivity rate. The ABR is the annual number of bites that theoretically a man located at a place heavily exposed to blackfly bites, twelve hours a day and for twelve months a year, would receive. 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 hyperendemicity\(^3\). 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 infective females (carrying infective larvae) per 1,000 females caught. This index will be mostly used to evaluate the residual transmission after the definitive cessation of insecticide spraying, because the collection of field data entails fewer operational constraints than 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 Loabe on the Nakambé and at Ziou Zabré on the Nazinon, 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 was also reduced from 309 and 880 to zero between 1982-1989. A similar trend was observed at Bagré on the Nazinon and at Bitou on the Nougao, a tributary of the Nakambé.
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.

<table>
<thead>
<tr>
<th></th>
<th>1975</th>
<th>1991</th>
<th>1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziou Zabré</td>
<td>33.05 (2,239)</td>
<td>0.25 (44,000)</td>
<td>0.05 (18,600)</td>
</tr>
<tr>
<td>Loaba</td>
<td>37.48 (1,574)</td>
<td>0.17 (6,000)</td>
<td>0.00 (8,500)</td>
</tr>
</tbody>
</table>

In certain zones situated 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 of the OCP area 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 frontière on the Leraba for example (from 26314 and 1263 in 1975 to 3418 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 neighbouring 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, from the results of prevalence and ophthalmological studies, it is quite obvious that transmission has been virtually interrupted in some areas through larviciding alone.

References:


5. Evaluation of ivermectin mass treatment for elimination of onchocerciasis using ONCHOSIM

G.J. van Oortmarssen

We used ONCHOSIM, the simulation model for onchocerciasis transmission and control, to evaluate the implications of different ivermectin-based treatment strategies. The main endpoint addressed is the long-term elimination of transmission. The ONCHOSIM model is quantified and validated on the basis of data from the Onchocerciasis Control Programme in West Africa (OCP). In particular, the effect of ivermectin on parasites and transmission is based on field data from annual ivermectin application at Asubende (Ghana) [1-3]. In the model, application of a standard dose of ivermectin of approximately 150 µg/kg body weight will immediately eliminate all microfilariae and, after temporarily losing their fecundity, the adult female worms gradually resume microfilarial production over an average period of 11 months, reaching a new production level that is on average 35% lower than before treatment. Each subsequent treatment will cause the same percentage of irreversible production loss. Coverage was modelled by assigning each individual a random, life-long "personal compliance factor"; resulting in a compliance pattern that was in good agreement with Asubende data.

The ONCHOSIM model was then used to simulate different ivermectin treatment policies in an (isolated) community. Policies are characterised by the following variables: treatment coverage (% treated in the community), total number of treatments applied, intervals between successive treatments. These policies were applied to different pre-control situations with respect to annual biting rate and individual variation in this rate. A very large number of simulations were performed and the results were statistically analysed to derive the policies that would give more than 99% probability of long-term elimination.

With annual treatment, the required number of treatments depends on the CMFL (geometric mean MF load in adults), and the coverage. With medium variation in biting rates and 65% coverage of the whole population, elimination is unlikely to be achieved within 25 years if the CMFL exceeds 30. A coverage of 80% in villages with CMFL<40 is predicted to have 99% probability of elimination if control is continued for 20 years. For 6-monthly treatments, the predictions depend on the assumptions made about the impact of such a regimen (we did not yet check the model with data on 6-monthly treatment). For optimistic assumptions about the impact on female worms, the required number of treatments is similar (or slightly lower) than with annual treatment which would imply halving the total duration of the programme. However, less optimistic assumptions show that this advantage needs not to be true. Another important parameter is the coverage pattern. If non-participation is mostly confined to certain groups, it will become more difficult to achieve elimination.

The results represent the situation in the savannah area of West Africa, in isolated villages of about 400 inhabitants (i.e. no migration). For other parts of Africa, or for America, the model would have to be adapted to different epidemiological, entomological and demographic conditions, requiring availability of local data on these aspects, especially from ivermectin studies.

References:

6. Modelling of onchocerciasis transmission in the Americas

Dr M.-G. Basañez

Onchocerciasis in the Americas occurs in smaller and more patchily distributed foci than in West Africa. In each of these foci there are one or more complexes of anthropophilic Simulium species playing a primary or secondary vectorial role: S. ochraceum s.l. in Mexico/Guatemala; S. exiguum s.l. in Colombia and Ecuador (with S. quadrivittatum also in Ecuador); S. metallicum s.l. (and S. exiguum s.l.) in northern Venezuela, and S. guianense s.l. (plus S. oyaepkense s.l. and S. incrustatum/limbatum) in the Amazonian focus between southern Venezuela and northern Brazil. These species complexes vary in vectorial competence and capacity determining, in part, the geographical and smaller scale spatial variation of observed epidemiological patterns in the region. In consequence, any modelling effort (development of new frameworks or application of existing ones) must take into account vector differences when incorporating vector-specific functional forms in the system equations and when estimating parameter values for model calibration.

As a way to simplify and incorporate vector characteristics into model equations, American vectors have been roughly classified into two main categories, those lacking a well-developed cibarial armature (S. exiguum, S. guianense, S. metallicum) and those possessing an 'armed' cibarium (S. ochraceum, S. quadrivittatum, S. oyaepkense, and S. incrustatum). The most important consequences of this feature are that the armature: 1) destroys an important, albeit variable, fraction of ingested microfilariae (mfs), reducing vector competence particularly at low intensities of skin mf infection, and 2) confers a certain degree of protection against parasite-induced vector mortality, allowing infected vectors to survive the extrinsic incubation period. The effects of the armature, therefore, represent a trade-off between parasite establishment and vector survival (Basañez et al. 1995, 1996). It also seems that the proportion of damaged mfs is dependent on the density of ingested parasites rather than being a constant, giving rise to an initial non-linearity in the relationship between the mean number of infective larvae (L₃) per fly and the mean mf intake known as 'initial facilitation' (Basañez et al. 1995; Collins et al. 1995). In those species with unarmed cibarium, this relationship is initially linear, although as mf intake increases the mean no. of L₃/fly levels-off and exhibits a pattern of 'saturation'. In the simulids with initial facilitation a pattern of subsequent limitation also ensues. Is this initial facilitation of armed blackflies that gives rise to transmission breakdown points when the equation for the parasite in the vector is coupled with equations for the parasite in humans. An additional reason for a transmission breakdown point is the functional form of the mating probability of adult worms, but in the case of a dioecious, polygamous, and highly aggregated parasites as Onchocerca volvulus, the mating probability rapidly rises up to 1 with increasing worm burden (Anderson & May 1991).

A deterministic and general model framework has consequently being developed, which can be tailored to incorporate parameters describing microfilarial establishment and vector survival for 'armed' or 'unarmed' vectors (Basañez 1996). In humans, L₃ establishment is a decreasing function of the annual transmission potential (Dietz 1982) with two possible scenarios: - limitation in the human (portraying the acquisition of solid protective immunity as transmission intensity increases), or asymptotic proportionality (i.e. a small yet constant proportion of L₃ larvae succeed in reaching maturity as immunity is not completely protective) (Basañez & Boussinesq 1999). The parameter value describing L₃ establishment in humans for settings with intense transmission is remarkably similar to that derived by the ONCHOSIM approach (Habbema et al. 1996). Expressions for the basic reproductive ratio (R₀) and for the critical vector density have been derived. For macroparasites, R₀ is the average number of mature female worms produced by an adult female during her reproductive life-span in the absence of density-dependent constraints (Anderson & May 1991). The critical biting rate is the average number of bites per person per unit time above which R₀ is greater than 1. The relationship between R₀, mf prevalence and annual biting rate will be presented. This illustrates that hypoendemic communities, defined as those with mf prevalence ≤ 20%, may not be truly endemic, and that the critical biting rate, dependent on the proportion of blood-meals taken on humans, is on average ten times as high for vectors with cibarial armature as for those without armed cibarium. For epidemiological settings with the latter type of vectors

1 Amazonian Centre for Research and Control of Tropical Diseases (CAICET), Amazonas, Venezuela.
(and setting the mating probability equal to 1), there is a single locally and globally stable endemic equilibrium when vector density is above the threshold biting rate. For settings with the former type of vector, in addition to the stable equilibrium there arises a second, unstable, equilibrium or transmission breakdown point. This translates into a critical mf load per person and a critical annual transmission potential below which the parasite cannot sustain itself in the host population. However, the magnitude of this critical infection intensity in humans and flies and, therefore, its epidemiological significance, decreases as vector density increases (Basáñez 1996).

For the Amazonian focus, the host age-profiles of mf infection for varying levels of endemicity will be presented as determinants of the relationship between community microfilarial prevalence and prevalence in the indicator group for rapid epidemiological assessment (Vivas-Martínez et al. 2000a, 2000b); the relationship between mf prevalence and intensity will be compared between the northern and southern Venezuelan foci, and the relationship between ocular disease, mf prevalence, and intensity of transmission will be presented for a variety of studies comparing African savannah with Central and South America. Intensity of transmission is best measured as the annual transmission potential: the no. of L3 larvae potentially received per unit time by a person fully exposed to vector bites in a particular locality. Since PCR-based analysis of pools of flies yields information on the proportion of infected/infective flies but not on the mean no. of larvae/fly, the analysis of larval distribution in simulid populations can be used to derive an expression for the intensity of infection in the vectors as a function of the proportion infected and the over-dispersion parameter. This procedure will be illustrated with *S. ochraceum* in Mexico and Guatemala, and with *S. guianense* in the Amazonian focus (Basáñez et al. 1998; Gowtage-Sequeira 2000). Finally, the application of the model to the evaluation of the Mexican control programme will be presented and various control scenarios discussed: only nodulectomy; only ivermectin, and a combination of worm removal and the microfilaricide (Basáñez & Ricárdez-Esquina 2000). Model outcomes mirrored observed data best when it was assumed that ivermectin irreversibly affects adult worm fecundity as it has been suggested by other workers (Plaisier et al. 1995).

References:


*Address from November 2000: Imperial College of Science, Technology and Medicine, Department of Infectious Disease Epidemiology, St Mary's campus, Norfolk Place, London W2 1PG, UK.*

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REPORT OF A ROUND TABLE DISCUSSION ON:

"HOW FAR CAN WE GO TOWARDS ELIMINATION OF HUMAN ONCHOCERCIASIS?"

At the conclusion of a WHO Meeting on "Criteria for certification of interruption/elimination of human onchocerciasis transmission", held in Geneva on 28-29 September 2000, the participants were invited to express their personal views at a Round Table discussion on "How far can we go towards elimination of human onchocerciasis".

The present document presents the various speakers' own summaries of their contributions to the discussion. The views expressed are not necessarily those of the World Health Organization.

1. Dr K. Yankum Dadzie, former Director of the FAO/UNDP/World Bank/WHO Onchocerciasis Control Programme in West Africa (OCP), Pazzallo, CH.

Human onchocerciasis has currently been eliminated from the greater part of the original area in the OCP and, without doubt, can be eliminated from almost the whole of Latin America. As regards global eradication, there is doubt whether it can be attained through the application of current tools, which are as follows.

1. Current tools for control

1. 1. Vector control by larviciding. Larviciding can eliminate the vector in isolated areas and interrupt transmission effectively in such foci, as was done in the past in the Kodera River valley in Kenya, and is currently being carried out in some selected foci in APOC countries.

OCP experience demonstrates that aerial larviciding is very effective in interrupting transmission within a relatively short period of time. Although the OCP operation has been successful and cost-effective in controlling transmission over large areas and thus eliminating onchocerciasis as a disease of public health importance and a barrier to socio-economic development, it has also been expensive and it is virtually certain that it will never be repeated elsewhere. Furthermore, in areas with complex breeding sites and difficult terrain, such as in Bui river basin in Ghana and the Kara, Keran and Mo river basins in Togo, the effect of vector control becomes limited.

1. 2. Chemotherapy. Ivermectin (as Mectizan®), given twice a year was first shown to interrupt transmission in Latin America in areas where the vector (S. ochraceum) is an inefficient transmitter. Later, reports from Ecuador (where the main vector, S. exiguum, is an efficient vector) and recently also from the OCP area (where all the vectors are efficient) show that ivermectin given 6-monthly can also interrupt transmission in areas where efficient vectors are responsible for transmission. It therefore appears that the efficiency of the vector does not limit the effectiveness of ivermectin in interrupting the transmission of human onchocerciasis.

However, certain factors are necessary to ensure that ivermectin effectively interrupts transmission. These include the following.

(a) Adequate treatment coverage of the population, defined as at least 65% of the total population of the communities under treatment.

(b) Adequate and continued compliance of the population. (The duration of ivermectin treatment for interrupting transmission is estimated to be at least 12 years and is likely to be much more in hyperendemic areas. This long duration is enough to cause concern as regards the compliance of human populations.)
(c) Migration of the human and vector populations.

(d) Inability to treat human populations due to wars, disturbances or other conflicts, and natural disasters.

(e) Development of resistance to ivermectin, which may have to be reckoned with after perhaps 20 – 30 years of usage.

Although, with a great effort, most of these factors could be overcome, the relevant cost/benefit ratio could escalate and be a matter of concern capable of compromising the level of financial resources that can be mobilised to support a sequential programme of country-wide elimination leading to global eradication.

2. Tools needed in the future

In order to achieve global eradication, therefore, more effective and better tools, specifically a safe and effective macrofilaricide, need to be found. However, the resources earmarked for the search for a macrofilaricide are dwindling, partly as a result of the success of the present control efforts. There is therefore a need to change the approach. I believe that broadening the portfolio to address an integrated research and control effort against all helminthic diseases, or even perhaps against all parasitic diseases, might succeed in mobilising the required resources. It is only within such a context that there can be some hope of pursuing the research that is necessary for developing the appropriate tools which can be applied to eradicate human onchocerciasis globally.

Although for the present, the prospect for global eradication of human onchocerciasis is not so bright, we should be optimistic and pursue the research that should provide the effective tools to make it possible. It is global eradication that will finally secure the already great achievements of local elimination of the parasite (as in Kenya) and of elimination of the disease as a public health and socio-economic problem (as in the OCP).

2. Dr Daniel Etya'Alé. Prevention of Blindness and Deafness (PBD), Management of Non-communicable Diseases (MND), Non-communicable Diseases and Mental Health (NMH), WHO, Geneva, CH.

Current efforts have focused essentially on eliminating onchocerciasis as a public health problem. Eliminating the infection altogether is something for which many gaps still exist regarding what knowledge and strategies will be needed to reach this goal.

The following are just a few examples:

(a) In the absence of a safe macrofilaricide, what levels of both geographic and therapeutic coverage do we need to aim for in order to achieve the elimination of human onchocerciasis and its causative parasite, and for how long?

(b) How soon can we have clear answers to those questions, and how could mathematical models (both old and new) help in quickly providing us with these answers?

(c) To achieve the elimination of *Onchocerca volvulus*, current activities (chemotherapeutic or antivectorial) will need to be scaled up quite significantly, for instance by extending to hypoendemic areas, currently not covered in existing programmes, except in parts of OEPA.

This being the case, the next logical questions will then be:

(d) To what extent do we need to scale up our operations, and what would be the implications of such upscaling in terms of advocacy, training and retraining, additional resource mobilisation, etc.?
Or put differently,

(e) How feasible operationally, would such an upscaling be, given current efforts and the constraints of existing control programmes?

If we are serious about elimination, these are some of the questions that will need to be answered first. There are probably many others.

3. Dr Marc Karam, Certification of Eradication and Elimination, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS), WHO, Geneva, CH.

The recent history of the Onchocerciasis Control Programme (OCP) in West Africa has been marked by success. Unlike some other programmes and despite the scarcity of tools when it began, it has been able to overcome many problems. Initially, with only one insecticide available for vector control, the OCP was facing a tremendous challenge of insecticide resistance. However, alternative products were developed and provided the means to control pockets of resistance when needed.

With ivermectin, another powerful tool, OCP was able to modify its strategy by adding chemotherapy to the sole vector control approach. With this combination, the programme reached its objectives, i.e., control of the disease as a public health problem and as an obstacle to socio-economic development. Although the results obtained in some parts of the original area of OCP were beyond expectations, there are still some pockets with the potential for recrudescence of transmission, despite the combination of vector control and ivermectin treatment. With this in mind, the total elimination of onchocerciasis in Africa is unlikely to be attained.

A safe macrofilaricide could, theoretically, be the ultimate solution to the total elimination of onchocerciasis. This, however, would require administering the drug to all onchocerciasis foci irrespective of their level of endemicity. One has to remember that other diseases, such as yellow fever, tetanus, etc., are still transmitted despite the availability of excellent vaccines. Therefore, the availability of a macrofilaricide would not necessarily equate to the total elimination of the disease, at least in Africa.

4. Dr Hans Remme, Filariasis, Intervention Development and Evaluation (IDE), Research and Development (TDR/CRD), Communicable Diseases (CDS), WHO, Geneva, CH.

The extensive experience with onchocerciasis control in Africa since 1975 makes it possible to give a fairly informed answer to the question of whether eradication of onchocerciasis is feasible with the currently available control tools. These experiences include many successes and pleasant surprises, as well as failures and serious disappointments.

The principal success story has been the elimination of onchocerciasis as a public health problem in the OCP, and the almost complete elimination of *O. volvulus* from most of the original OCP area. However, the OCP also revealed several major problems affecting the control of onchocerciasis transmission, notably the impact of long-distance migration of infective vectors (up to 500 km) and the fact that endemic foci can cover enormous areas.

Since the registration of ivermectin in 1987, much has been learned about its safety, and its efficacy in controlling ocular and skin disease. This indicated that control of the disease as a public health problem was feasible with annual mass treatment, provided that adequate treatment coverage in the range of 65-70% of the total population (or about 80-85% of those eligible to take the drug) could be maintained.

Mass treatment also reduced transmission significantly but the remaining level was still unacceptably high. A pleasant surprise came when follow-up parasitological data from five
annual treatments in the Asubende focus in Ghana were analysed in the ONCHOSIM model. The analysis indicated that the initial assumption that ivermectin had no effect on the productivity of the adult worm was not consistent with the observed trends, and it was likely that each annual treatment resulted in as much as a 30 per cent reduction in productivit.

Furthermore, preliminary results from the isolated Mako focus in Senegal, where 6-monthly ivermectin treatment has been given on an experimental basis, suggest that transmission may have been interrupted after 9 years of intervention. This is expected to be confirmed by a detailed entomological evaluation made this year (2000).

Other good news was the popularity of ivermectin among endemic populations and the development of an approach to drug distribution, namely Community-Directed Treatment with ivermectin (CDTI), which has proven very effective and promises to sustain high treatment coverage.

But there have also been major problems. In one focus in central Togo, 24 years of vector control, combined with ivermectin treatment during the last 10 years, has failed to control onchocerciasis, and, in some of the villages in this area, the endemicity level is still so high that the disease is remains as a public health problem. In Asubende, after 12 years of combined vector control and ivermectin treatment, transmission is still not interrupted and the prevalence of microfilariae remains above 30 per cent. Particularly alarming was the finding in the Bougouriba valley, the only focus where recrudescence after the cessation of vector control has been detected to date. There the speed of recrudescence was much faster than had been predicted, and this experience also showed that, even after very low prevalence levels had been achieved, it is very difficult to control transmission using ivermectin treatment alone in a previously hyper-endemic focus where the vector density remains very high.

To these problems should be added other obstacles to achieving adequate treatment coverage over a long period. One such is the problem of heavy Loa loa microfilarial infections in parts of the Cameroon Republic. Another is maintaining treatment during military or natural emergency situations.

In my opinion, it will be possible with current tools to control onchocerciasis as a public health problem throughout most of the endemic areas in Africa; and it may even prove possible to eliminate the parasite from some isolated foci, especially where transmission is not too intense. But to expect that it will be possible, using ivermectin treatment alone, to eliminate onchocerciasis from all of Africa, including the vast hyper-endemic foci in the west and central parts of that continent, seems to me completely unrealistic. The elimination of onchocerciasis from Africa will require the development of more effective intervention tools than we have at present. Why aim for failure when success, in terms of elimination of onchocerciasis as a public health problem, is within reach?

5. Dr Richard Collins, University of Arizona, Tucson, Arizona, USA.

Several important differences, both biological and human, between onchocerciasis in Africa and the Americas make elimination using ivermectin more likely in Latin America. As a species, Onchocerca volvulus evolved from ungulates and became adapted to man in Africa over thousands of years. As a result, the host-parasite relationships in Africa are more stable and deeply entrenched than in Latin America, where African slaves introduced it no more than 500 years ago. When the parasite was introduced into an area in the Americas where a competent vector occurred in sufficient numbers, a local transmission cycle developed and the disease became endemic. Many of these areas are relatively small and well circumscribed around streams that provide larval development sites for vectors. Transmission within most endemic areas is less intense than in Africa. For example, the rates of L3 transmission (ATP or MTP) and the reproductive ratios (Ro) are lower in the Americas than in Africa, for areas of comparable human endemicity. Also New World vectors do not migrate long geographic extent of endemic foci in Latin America and it also reduces the probability of re-introduction of the parasite into areas where transmission has been suppressed.
On the human and programmatic side, Latin American countries have organized health delivery programmes and all endemic countries are now distributing ivermectin to their endemic communities. Most communities are relatively easy to reach (the Amazon basin foci are an exception). OEPA provides technical assistance to country programmes and a region-wide perspective to the elimination effort, as well as co-ordination with the Mectizan Donation Program, other institutions such as PAHO and WHO, and with financial donors through the Carter Center. OEPA's continued existence is crucial to the elimination effort.

The elimination strategy in the Americas is long-term (15 years minimum) distribution of ivermectin to all endemic communities twice a year. As a scientific and technical question, there is no longer any doubt that this can completely interrupt parasite transmission, often after as few as four treatment cycles (2 years). This has been demonstrated in a research setting in Guatemala as well as in an operational programme in Ecuador. The key is coverage both of depth and extent. Depth of coverage should be at least 85% of the population eligible to take ivermectin for each treatment round, and all endemic communities must be identified and treated in order for the strategy to succeed at a national or regional level.

An overview of recent (1998-2000) entomological assessments of parasite transmission country-by-country indicates some success, as well as problems.

Mexico has completed 10 years of semi-annual treatments, which have made important progress in the elimination of ocular morbidity. However, coverage (both in depth and extent) has not been sufficient to interrupt transmission in either Oaxaca or Chiapas. Part of the problem is that the Mexican brigades persist in doing physical examinations and skin snips in conjunction with ivermectin distribution. This reduces depth of coverage in many communities and results in the refusal of others to participate.

Guatemala has recovered from decentralization of its health delivery services and resumed ivermectin distribution in 1997-98. As a result, transmission has been interrupted in one sentinel community (Los Andes) and suppressed in others.

Colombia (with one endemic community) has completed eight treatment cycles to date with ~87 per cent coverage and can look forward to assessing parasite transmission next year using standard entomological guidelines developed by OEPA.

Ecuador has completed 10 years of treatment and is assessing transmission in its sentinel communities using PCR technology during the 2000 transmission season (March – July). Venezuela recently (1999) started treatment in both its northern and southern foci. The southern focus in the Amazon Basin region is contiguous with the foci in Brazil where, because of the migratory human populations and remoteness, regular treatments are difficult.

In Brazil, missionary groups and the Ministry of Health are collaborating to achieve semi-annual treatments in its three principal endemic communities.

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 absentee and people refusing the drug; learning why people refuse and making adjustments etc.
6. Dr María-Gloria Basáñez, Departmental Lecturer in Infectious Disease Epidemiology, The Wellcome Trust Centre for Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, U.K.

In general, I agree with the previous speakers, who expressed, on the one hand, the hope and optimism about eliminating onchocerciasis wherever possible, and, on the other hand, the cautionary scepticism about regional or global eradication of the parasite.

My main reservation about eliminating the infection wherever possible is that in low intensity foci, there may be a law of diminishing returns when one tries to get that much further towards elimination. In situations where onchocerciasis was never a truly severe public health problem, does it really pay off to invest further and further in elimination and costly surveillance? How does this tally with the over-stretched health budgets of many developing countries?

In all my interventions, a prime consideration has been the costing of the control programmes. In areas where intensity of infection and morbidity are high, the intervention programme can reduce the burden of new disease relatively quickly. Surveillance pays off because the infection can spread again (the parasite population has a high value of the basic reproductive number under the prevailing conditions). What is the cost-effectiveness per heavily infected community treated? I think this question warrants to be addressed. A further consideration is that the existence of untreated, susceptible parasite populations may delay the emergence of ivermectin resistance.

Finally, there may be an overall health benefit obtained by treating heavily infected communities. Ivermectin acts on various macroparasitic agents. Onchocerciasis infection is immunosuppressive, and there is mounting evidence that this is not only addressed against specific parasite antigens but also against heterologous antigens (e.g. BCG and tetanus toxoid vaccination). There is also evidence now emerging of a relationship between helminth infection and the rate of progression towards AIDS in individuals co-infected with intestinal worms and HIV. If this is the case, treating with ivermectin may restore, albeit temporarily, a more healthy immune balance of the host. Repeated treatment may keep patency at bay and improve cellular immune responses. These, as opposed to antibody-driven responses, are characteristic of the putative immune individuals in onchocerciasis and lymphatic filariasis. I argue that in the future, models of infectious disease should not only address the population biology of causal agents taken in isolation but the ‘community ecology’ of real-life co-infection.

7. Dr Tamara Mancero, Ministerio de Salud Pública, Quito, Ecuador.

In the Americas, there are some in-country differences that affect the possible elimination of the onchocerciasis. In Venezuela and Mexico, the endemic foci inside each country are very different and each can be evaluated separately. In Ecuador on the other hand, evaluation has to be done for the whole country. Owing to migration inside the endemic area, and to the geographical characteristics and the primary health care strategy therein, it is very difficult to individualise the foci. The exercise of pre-certification of onchocerciasis, undertaken now with OEPAs’s support, is helping Ecuador to prepare the country for a possible certification of elimination of the disease. Further analysis of the data already obtained will permit the programme to define the gaps in our knowledge and to undertake all necessary research. Until the interruption of transmission is demonstrated, all immigrants entering the endemic area should be treated.

The American programmes still have still a lot to learn from those in Africa, and more effort is needed so that each continent may benefit from the other’s experience. Ecuador has developed an information system that includes detailed data on onchocerciasis, which may be useful for mathematical modelling (by Onchosim for example) worldwide.
8. Dr Markus J. Behrend, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS), WHO, Geneva, CH.

I should like to emphasize that, at least in Latin America, clearly separate foci of onchocerciasis within a single country can be evaluated and monitored independently, and that they may also be placed at different points on the "elimination time frame". The guidelines should provide tools for technical evaluation at focus level, although it should be made clear that final certification will only be provided by WHO to the country as a whole. This would mean, for example, that an isolated focus, in which the interruption of transmission has been confirmed, could in theory stop intervention (ivermectin treatment) and enter into pre-certification. This could be officially acknowledged by WHO (as being an important achievement for the country concerned), although the country could only be finally certified as "post-endemic" after all the known national foci have successfully passed through the pre-certification exercise.


I am quite hopeful about the elimination of onchocerciasis from the Americas. I believe the focus in Colombia (which is trivial) and that in Ecuador will be eliminated in the near future. The same applies to the Oaxaca focus in Mexico, provided that all persons eligible to take ivermectin are treated regularly and that the Brigades do not antagonise the population by insisting on treating only those persons who are found to have positive skin snips or nodules.

Success should be achieved, though rather more slowly in the other Latin American countries and foci, although I am doubtful about successful elimination in the Amazon/Orinoco rainforest foci, where it will be difficult to obtain regular and adequate coverage of the migratory and very primitive Amerindian tribes in the area.

In Africa, where the problem has been reckoned at some 30 times what it is in the Americas, the present control programmes, based largely on ivermectin, can be expected to control eye and skin lesions and to prevent the devastating socio-economic consequences of onchocerciasis, but it is hard to envisage the prospect of elimination with the tools that we have at present.

I am not unduly worried about the possibility of resistance developing to ivermectin. The generation turnover time for *Onchocerca volvulus* is of the order of 9-12 months, which is 3-4 orders of magnitude greater than the 20-minute generation time of those bacterial populations in humans that have developed resistance to antibiotics. Also, there is without doubt more to be learned about the possible, slow, long-term macrofilaricidal or embryonic suppressive properties of ivermectin.

However, I still believe that the best hope for the elimination of onchocerciasis in Africa must depend on the finding of an effective macrofilaricide for *O. volvulus* and one that can be safely used on a large scale.

Over the last 20 years, WHO/TDR/OCP and others have put much effort into the search for such a drug and, for this purpose, they developed and established first a tertiary screen based on *O. gibsoni* in cattle at Townsville in Australia and, later, an improved screen using *O. ochengi* in cattle, at Wakwa in the Cameroon Republic. I am therefore very disappointed, to say the least, to learn that, on the advice of its relevant Steering Committees, WHO/TDR has decided, allegedly on grounds of financial constraint, to abandon the *O. ochengi/cattle* screen and to jump straight from the primary/secondary rodent screens to trials in human volunteers. At a time when many veterinary anthelmintics are available that need to be tested against *Onchocerca*; when moxidectin is available as a promising drug needing further assessment; and when the use of drugs against the rickettsia-type organisms (*Wohlbachia* spp) in *O. volvulus* (on which that parasite's survival may well depend) is curing out for investigation, it seems hardly the moment to abandon the *O. ochengi/cattle* screen. Rather it
should be the time actively to seek funds from newly established sources, which have recently shown willingness to provide considerable support for research and control of tropical diseases.

10. Dr Frank Richards, Technical Director, Global 2000 River Blindness Program, The Carter Center, Atlanta, USA.

I suppose I need to intervene with a positive angle since all the comments up to now have been "cautiously negative" with regards to our ability to eradicate onchocerciasis. Here is why I am "cautiously optimistic."

First, ivermectin is working better than we thought in the beginning. The modellers, fitting their data to the observations, have told us that there may be a 30% impact on fertility of adult worms, either per year, or even per treatment round. That is impressive.

Second, when we started, we thought that only in onchocerciasis transmission areas with inefficient vectors, such as *S. ochraceum*, would it be feasible to interrupt transmission by chemotherapy alone. Now there is evidence presented at this meeting that semi-annual (or more frequent) treatment with ivermectin can interrupt transmission in areas with efficient vectors, such as *S. exiguum* (Ecuador) and *S. damnosum* (Senegal). That is encouraging.

Third, I think there will be an impact of the new Programme for the Elimination of Lymphatic Filariasis (PELF) on onchocerciasis. I think we need to change our orientation regarding this programme. Instead of saying, as we have in the recent past, "What can the established onchocerciasis programmes do to help the nascent PELF in Africa?" we need to reverse the question by asking, "What can the new PELF strategy do for established onchocerciasis programmes". Dr. K. Awadzi has interesting data (albeit in very small numbers of patients) about the impact of low-dose albendazole on developing stages of microfilariae in *O. volvulus* females in nodules. To my mind this suggests that there may be some synergy of ivermectin combined with albendazole against *O. volvulus*, as has been 'shown' for *W. bancrofti*. The full story remains to be told, and more research is needed, but I am optimistic about the impact of the PELF in areas of co-endemic onchocerciasis.

Fourth, there are new drug developments that will lead us to think more about future eradication possibilities. There is moxidectin, which has a much longer half-life than ivermectin, and seems to have activity against some veterinary helminths that are resistant to ivermectin. Can a single dose per year of moxidectin interrupt transmission? There is also the story of the *Wolbachia* rickettsial endosymbionts; kill these and you may kill the adult *O. volvulus* worms. With this new clue, what we need now is to identify safe antibiotics and/or short course regimens that can be given in community-based programmes, and to all age groups.

With these four items that lend a positive outlook, what are the challenges to moving toward eradication of onchocerciasis? They are many.

First, there are concerns about ivermectin resistance emerging. If this is true, then we need, right now and while we still have the opportunity, to change the way we use the tools that we have available to get rid of onchocerciasis. Otherwise, 100 years from now, we may risk being back where we started. In other words, there may be urgency to our decision.

Second, there needs to be a change in APOC strategy so as to reach hypoenemic areas with more than just clinic-based treatment (which latter form of treatment is not supported by APOC anyway). Transmission occurs in hypoenemic areas, so transmission cannot be interrupted if hypoenemic areas are not treated. Here is another way that the PELF will help onchocerciasis control - by extending ivermectin treatment to a number of areas where hypoenemic onchocerciasis is co-endemic with *Wuchereria bancrofti*. 

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Third, if we are to be more aggressive toward the eradication of onchocerciasis, we need to do a better job in communicating to the world the remaining challenges that lie before us. OCP has done too good a job in its public relations campaign; so much so that the world now thinks onchocerciasis is a thing of the past. I don't believe onchocerciasis is a thing of the past, and I think that message is dangerous, particularly if we want to find support and funding for continued research in onchocerciasis. We have heard during this meeting that such support is already drying up.

Fourth, there are some other challenges to the elimination of onchocerciasis: e.g. the difficulties of treatment in areas where heavy microfilarial infections with *Loa loa* are co-endemic; long-term maintenance of treatment coverage; political unrest and conflicts. All these appear greater if we operate in 'elimination-mode' rather than in 'control mode.'

Finally, I must ask Professor David Molyneux why he works so hard and is so positive about interrupting transmission of lymphatic filariasis (LF) with chemotherapy alone, but pessimistic about doing the same for onchocerciasis? For LF elimination in Africa, some of the same key issues remain: - co-endemic, heavy *L. loa* infections; the need for high coverage continued for many years; and delivery of services in areas of conflict. There is also a new challenge in LF, that of reaching more people overall and many of them living in peri-urban or urban centres of transmission. I assume Professor Molyneux's positivity about interruption of LF transmission is because: - (i) DEC has macrofilaricidal effects against LF parasites and can be used in salt (but DEC cannot be used in Africa, where there is onchocerciasis); (ii) the LF adult worms have a shorter life span of 5-6 years (but, if ivermectin is indeed reducing *O. volvulus* fecundity by 30 per cent per round, then that parasite's effective life-span will be short as well); and (iii) LF has already been eliminated from several countries (but China, Japan, and islands in the Pacific are perhaps special cases). My question remains, are the challenges and the biology of these two parasites so different as to give rise to such different strategies, and such different goals (control of morbidity versus interruption of transmission)? I wonder...

11. **Professor David Molyneux**, Professor of Tropical Health Sciences, Liverpool School of Tropical Medicine, Liverpool, U.K.

11. 1. **Comparison between onchocerciasis and lymphatic filariasis in terms of elimination**

There are several technical differences between onchocerciasis and lymphatic filariasis (LF) when it comes to the feasibility of elimination.

(a) The duration of adult worm life is 4-6 years in *W. bancrofti* and *circa* 12-14 years in *O. volvulus*.

(b) LF elimination, at the target drug coverage of 65% of the whole population, is more likely to be sustainable over the shorter 4-6 year period as compared with the 12-14 years needed for onchocerciasis.

(c) A two-drug regimen (ivermectin plus albendazole) will have a very limited likelihood of inducing any resistance to LF and the probable synergistic macrofilaricidal effects are also expected to be significantly greater.

(d) In addition to the Community-Directed Treatment with Ivermectin (CDTI) system adopted by APOC, many other distribution systems (e.g. schistosomiasis control, school health programmes, EPI, leprosy, bednets) could be used in LF campaigns owing to the more extensive distribution of the disease.

(e) There is evidence from areas outside Africa (Costa Rica, Suriname and Trinidad) that single-dose treatment with DEC, or DEC in household salt (China) can eliminate LF or reduce it to a level of limited public health importance. Hence transmission of this parasite is on a knife-edge.
(f) Given the above, and if widespread bed-net use in Africa for malaria control is to be implemented (Roll Back Malaria objective) then, in rural areas with Anopheles transmission, LF elimination as a public health problem will be even more achievable.

(g) I believe that, at least in West and East Africa, LF transmission could be eliminated. I emphasise that the WHA resolution calls for “elimination of the disease as a public health problem” (not elimination of the parasite), hence this is a consistent, technically acceptable position given the caveats we all recognise and the arguments above. In Africa also, neither OCP nor APOC have ever had elimination of the parasite as their Goal. The donors would simply have never signed up to this.

In response to the specific points raised in the first part of Dr Frank Richards’ contribution, I agree entirely with his paras 1 and 2. On para 3, I agree, but the issue here is the extent of the overlap between LF areas and hypendemic onchocerciasis areas. On para 4, I agree that moxidectin is important, but who will pay for the necessary investigations? Likewise, I agree that the Wolbachia story is potentially a great breakthrough (indeed I ought to, as much of the work was done at the Liverpool School).

11.2. Response to Dr Frank Richards’ challenges

1. Resistance. I am not too pessimistic on this front. It is not yet apparent that the filarial life cycles are as amenable to developing resistance as are those of the gastrointestinal nematodes - anyway moxidectin would probably have cross-resistance with ivermectin.

My colleague, Professor Sandy Trees, who is a veterinary surgeon, and his colleagues have been working both on the Wolbachia problem (Langworthy et al., 2000 Proc. Roy. Soc. Lond. B. 267, 1063-1069) and on ivermectin as a prophylactic (see Tchakoute et al, 1999, Parasitology, 118, 195-9). Their studies clearly show that in the cattle/O. ochengi model, monthly ivermectin dosage prevents transmission; and this has led to a recommendation that studies on the timing of ivermectin delivery would be important so that blood levels of ivermectin should peak with the peak season of transmission. Hence the impact of ivermectin would not just be microfilaricidal. Workers in the onchocerciasis field tend to forget that one of the main uses of ivermectin in veterinary medicine is as a preventive for heartworm (Dirofilaria immitis) in dogs, where monthly doses are given. According to Professor Trees, there is as yet no evidence of any resistance of Dirofilaria to ivermectin, despite its long-term and widespread use against this filarial parasite in the U.S.A.

In addition, Professor Trees is in contact with several pharmaceutical manufacturers in the animal health field, all of whom have the intention of developing new generations of avermectin molecules for this market. The next approach to prophylactic use of these products is via topical treatment and already Pfizer have on the market Selamectin (“Stronghold”), which is topically applied as a spot-on for prophylaxis against Dirofilaria, as well as gastro-intestinal parasites, and fleas, lice and mites. Surely this is the direction we should be taking for the development of new strategies for these of compounds. The veterinary pharmaceutical manufacturers are not inhibited by any fears of resistance developing from pursuing their efforts to discover and develop new compounds. (They should know, as they have a commercial interest!) As a result, there is a large range of remarkably effective compounds available for veterinary use - which we could and should exploit in the field of human medicine. A topically-applied prophylactic and curative tool, if demonstrated as being safe for humans, would be an amazing development in onchocerciasis or in LF, yet nobody as far as I am aware in the ‘oncho’ or LF community has even mentioned it.

I am developing with Professor Trees a statement along these lines which, I believe, should be widely circulated before the next meetings of Joint Programme Committee (JPC) of the OCP and the Joint Action Forum (JAF) of APOC. There should be far more new thinking from the community, and particularly from MACROFIL, on these issues. Drug development will not be the answer as presently articulated in human medicine, especially given the availability of products in the animal health market which, historically, have always been the source of those used in human medicine (e.g. ivermectin, praziquantel, and albendazole).
2. **APOC Strategy.** I agree totally.

3. **OCP Strategy.** Donors are the problem here, given that the original OCP mandate has been achieved.

4. **Loiasis.** I agree, but the Central/Equatorial African area will need to be approached with some caution, even in control mode. That is why I believe that, in the LF context, West and East Africa should be the starting points - areas where *Loa* is absent.

As regards the possible elimination of onchocerciasis from Africa the position has been articulated in the response (about to be published) to the recent letter by Richards et al. in *The Lancet*. Owing to lack of space a full case could not be made out but the major issues of maintaining coverage, duration of treatment, costs, conflicts, blackfly migration, additional Mectizan supply costs, need for more NGDOs, extension to hypo-endemic oncho areas and the costs thereof, all of which are covered, are for me major impediments to elimination.

I accept that onchocerciasis can be eliminated from parts of Central and South America by chemotherapy alone but, aside from the isolated and proven local eliminations of onchocerciasis in Africa which have already been achieved (Kenya, parts of Uganda and Tanzania - all *S. neavei* s.l. foci - and Kinshasa), I do not believe this is achievable in Africa. We had hoped Bioko would be another example - an effort that I vigorously endorsed.

The targets set by OCP have been achieved. The APOC strategy, based on CDTI, remains to be proven, at least as far as long-term public health achievements are concerned.

The treatment of the hypo-endemic onchocerciasis areas in Africa remains a key factor and we surely need to validate REMO and then to map them thoroughly. I totally agree with Dr Richards that the LF programme will help considerably here. However, given the public health mandates of OCP and APOC, as presently constituted, hypo-endemic areas will simply not come into the frame.

Finally, although diagnostics may now be available to track the last onchocerciasis cases as one goes into an elimination/eradication scenario; and, whilst I applaud the vision of removing the last adult worm from the last infected individual in Africa, I fear that this view is slightly over-optimistic, even with a macrofilaricide!

**12. Dr Nevio Zagaria.** Coordinator, Strategy Development and Monitoring for Eradication and Elimination (CEE), Control, Prevention and Eradication (CPE), Communicable Diseases (CDS), WHO, Geneva, CH.

Eradication and elimination initiatives have a global dimension which is fascinating and which was tremendously enhanced by the success of the smallpox eradication.

This experience and the only other two on-going eradication efforts (polio and Guinea worm) have clearly indicated that three main factors need to be taken into account in setting up new global initiatives targeting new diseases for eradication or elimination: the technical feasibility, the cost benefit, and the social and political support.

It seems to me that the debate on the eradication of onchocerciasis in the world is at the beginning, but clearly serious concerns have been highlighted by the participants to this round table on all the three main aspects that need to be considered. The biological and the epidemiological diversities of the disease in the Americas and in Africa are only part of the complexity of the debate.
Uncertainties about the role of hypo-endemic areas in onchocerciasis transmission need to be addressed by the research agenda, as well as the real additional benefit of shifting from annual to semi-annual mass treatments regimen with ivermectin outside the Americas. There is a need to evaluate the cost benefit of shifting the target from intensified control aimed at eliminating the public health problems related to onchocerciasis morbidity, towards a campaign which targets the permanent interruption of onchocerciasis transmission. Such a change in campaign objectives would also need to be carefully evaluated in public health terms. We should consider the major implications of the required high mass treatment coverage rates and the necessity to continuously sustain them over a very long intervention period (20 years?).

Finally, the political and societal support factor needs to be addressed properly, with the full involvement of the endemic countries. The importance of this factor has been underestimated for example in the guinea worm eradication campaign, and is one of the main reasons of the delay in respect to the original target date of 1995. Judging what may be priority global public health goods toward which the international community and the endemic countries and communities need to concentrate their respective efforts and energies is not an easy task, but it is at the same time a fascinating challenge for all of us.

For sure the definition of criteria for assessing the impact on onchocerciasis transmission of ivermectin mass treatments, as well as the standardization of the phases and methods to apply these criteria are essential steps, which need to be addressed through a participatory process, as we did during the last two days. A different issue is the opportunity to set up a formal certification process at international level, which still need to be discussed, and for which essential questions have been formulated during our discussion.

There is clearly the need for addressing these issues in further collegial discussions, which should be based on the outcome of the important on-going operational researches.