

Certification of elimination of human onchocerciasis: criteria and procedures

Following a WHO meeting on
“Criteria for certification of interruption of transmission / elimination
of human onchocerciasis”
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GUIDELINES



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NOTES

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 *cum* temporary 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 (OEPA) and in Africa (APOC).

After more than 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 Koderia 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-invade 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 microfilaricide 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 Amazons Region, 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 punctuate 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 Cameroon 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 loiasis 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 macrofilaricide 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 (OEPA 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, OEPA 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 OEPA 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 OEPA 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 microfilariaemia 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. incrustatum*. 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), microfilariaemia 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 (punctuate 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 microfilariae, 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 microfilariae, 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. 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 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.

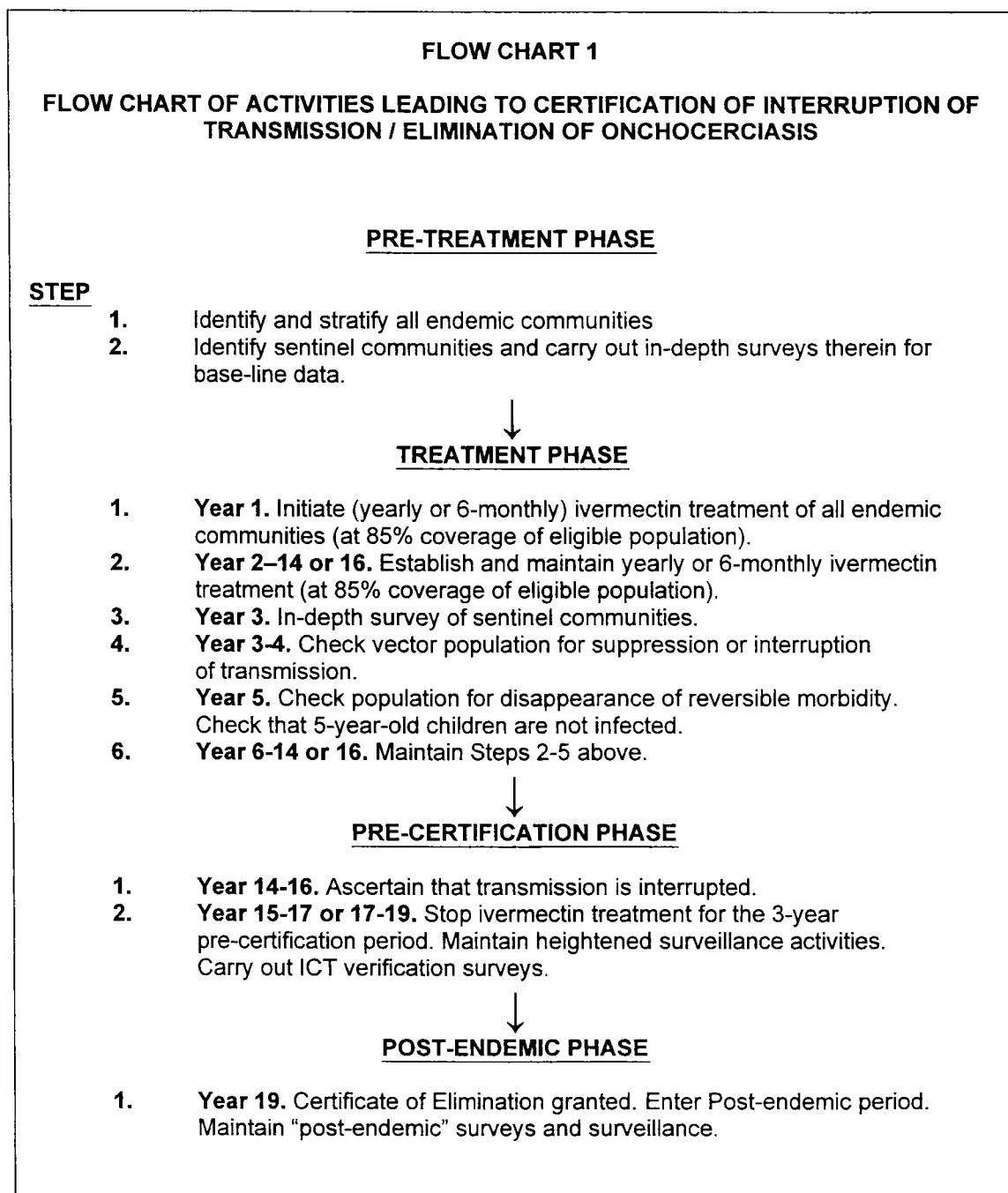
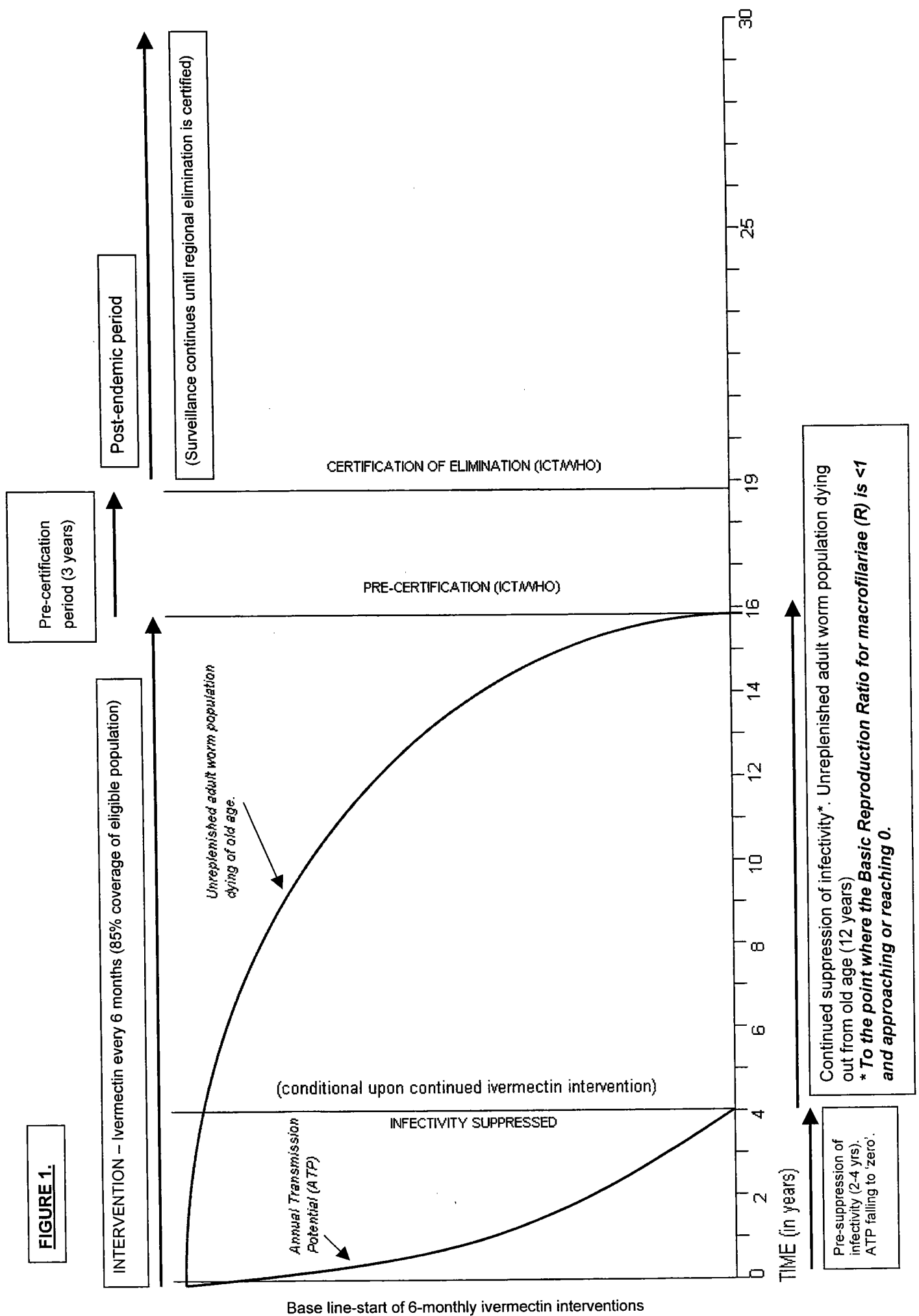


Figure 1 (on next page) shows the time-scale for the theoretical fall-off of the Annual Transmission Potential or ATP to zero (or near zero), together with the theoretical fall-off of the dying and unreplenished adult worm population, both in relation to the timing of the various interventions and certifications.

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.



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.

NOTES

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NOTES

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) (Basáñez 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 co-operate. 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 (R_0) 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).

Assessment method	Large scale treatment	
	Treatment is a "must"	Treatment is highly desirable
Parasitological assessment		
Prevalence of mf in skin snips		
- Males and females of all age	60% and over	40 – 59%
- Males over 20 years	90% and over	70 – 89%
Rapid assessment methods		
Prevalence of nodules in males over 20 years	40% and over	20 – 39%
Prevalence of leopard skin in males over 20 years	20% and over	Not useful

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).

NOTES

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.

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.

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 microfilarial 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 dannosum 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 (Katoli 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, PIP*) can be calculated if the flies' bodies are processed. **PIP** is calculated from fly bodies only because if pools of heads and bodies both test positives, it is 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 examples 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 0.000093 (95% confidence interval of 0.0000024 to 0.00052).

- Transmission potential during June and July is infectivity rate x biting density = $8077 \text{ flies} \times 0.000093 = 0.75$ 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 $0.000093 \times 14,685 \text{ flies} = 1.37$ 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).