

ONCHOCERCIASIS

GUIDELINES FOR STOPPING MASS DRUG
ADMINISTRATION AND VERIFYING
ELIMINATION OF HUMAN ONCHOCERCIASIS



**CRITERIA AND
PROCEDURES**

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CRITERIA AND PROCEDURES



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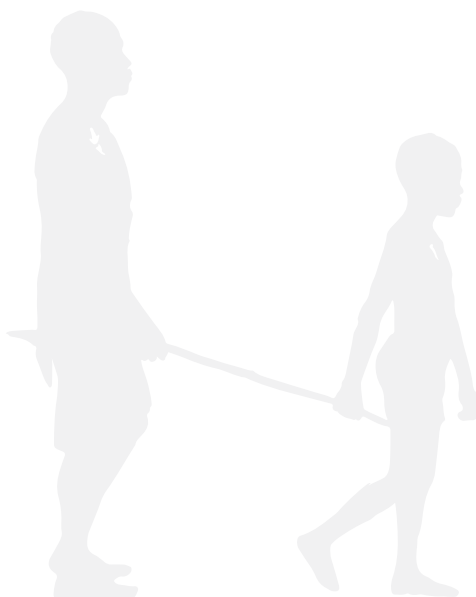
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GLOSSARY

The definitions below refer to the use of terms in these guidelines and may have different meanings in other contexts.

Annual transmission potential

A value calculated as the product of the annual biting rate, the proportion of black flies with infective-stage *Onchocerca volvulus* larvae and the mean number of infective larvae per infective fly. The value refers to the approximate number of infective larvae any one individual may be exposed to in a year. Current evidence suggests that at an annual transmission value of less than 20 in an endemic onchocerciasis focus is not sustainable.

Case of human onchocerciasis

An individual in whom there is evidence of current infection with *Onchocerca volvulus*.

Case definition of human onchocerciasis

An individual who presents with:

- fibrous nodules in the subcutaneous tissue
and
- laboratory confirmation of the presence of *Onchocerca volvulus* microfilariae in skin snips (microscopy or polymerase chain reaction)
or
- the presence of viable *Onchocerca volvulus* adult worms in excised nodules
or
- the presence of living microfilariae in the eye as determined by slit lamp or other examination.

Control

A reduction of the incidence, prevalence, intensity, morbidity and/or mortality of disease as a result of deliberate efforts. Continued interventions may be required to maintain this reduction.

Elimination

The reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts; continued actions to prevent re-establishment of transmission may be required. When elimination of the parasite is confirmed, the endemic area enters the phase of post-elimination surveillance.

Endemic onchocerciasis focus

An area within a country where a local cycle of *Onchocerca volvulus* transmission is maintained and gives rise to local infections; that is, where the basic reproductive rate exceeds 1 (apart from temporal fluctuations). Endemicity is stable where the incidence

of the infection shows little or no increasing or decreasing trend over time. Endemic foci (and transmission zones) can be classified as having (i) active transmission, (ii) suppressed transmission; and (iii) interrupted transmission.

Countries are classified as:

endemic when *Onchocerca volvulus* transmission and infection are present; or

post-endemic when a country with a previous history of endemic onchocerciasis is officially confirmed as having successfully completed a post-treatment surveillance period of at least 3–5 years of interrupted transmission in all its previously endemic onchocerciasis foci.

Eradication

The permanent reduction to zero of the global incidence of infection caused by a specific pathogen as a result of deliberate efforts, with no risk of reintroduction. Sometimes a pathogen may become extinct, or may still be present in confined settings such as laboratories. Eradication requires a formal certification process.

Incidence

The rate at which new cases occur in a given population within a defined time interval.

Interruption of transmission of *Onchocerca volvulus*

The permanent reduction of transmission in a defined geographical area after all the adult worms (and microfilariae) in the human population in that area have died, been exterminated by some other intervention, or become sterile and infertile.

Morbidity

The presence of disease manifestations of the skin (such as dermatitis, especially pruritus and depigmentation) and of the eye (including keratitis, corneal opacities, iridocyclitis, chorioretinitis, optic neuritis and blindness) caused by *Onchocerca volvulus* parasites.

Ov-16

A recombinant *Onchocerca volvulus* antigen to which IgG4 antibodies are produced and are detectable using immunological methodologies. The critical threshold for interruption or elimination of transmission is an upper bound of the 95% confidence interval of less than 0.1% confirmed seropositivity to Ov-16 in children under 10 years of age.

Polymerase chain reaction

A biochemical method in molecular biology to amplify a single or a few copies of a piece of DNA across several orders of magnitude, generating millions to billions of copies of a particular DNA sequence.

Poolscreen

A software program that employs a statistical model to calculate the probability of infection of an individual black fly with *Onchocerca volvulus* from the number of positive pools and the size of the pools using the results of polymerase chain reaction. The model

takes into account the biting rate, the fly density and the infection rate to calculate estimates of annual transmission potential (or seasonal transmission potential) and associated 95% confidence intervals. The critical threshold for interruption or elimination of transmission is an upper bound of the 95% confidence interval of the point estimate of the prevalence of black flies carrying infective larvae of 0.05%, calculated by the results of polymerase chain reaction from testing the head of the vector in which L3s are found.

Post-treatment surveillance

The period of at least 3–5 years after the end of treatment during which ongoing surveillance is conducted to document that interruption of transmission has occurred and there is no recrudescence of infection.

Prevalence

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

Ro (basic reproductive rate)

A measure of the reproductive success of the parasite population. Endemic onchocerciasis requires a basic reproductive rate equal to or greater than 1; any intervention which aims to eliminate onchocerciasis must achieve a state where this rate is below 1 for a sufficient period of time (usually defined by the reproductive lifespan of the parasite). Corresponding values are the threshold biting rate (that is, the vector density below which *Onchocerca volvulus* cannot remain endemic) and the population breakpoint (that is, the parasite density below which onchocerciasis cannot remain endemic).

Seasonal transmission potential

A value calculated as the product of the seasonal biting density, the proportion of flies with infective-stage larvae and the mean number of infective larvae per infective fly. The seasonal transmission potential may be equal to or slightly less than the annual transmission potential.

Sentinel community

A hyperendemic community pre-selected by some programmes where in-depth epidemiological evaluations take place at regular intervals (before treatment starts and at set intervals thereafter).

Suppression of transmission (or conditional interruption of transmission)

The absence of infective larvae (L3s) in the *Simulium* vector population. Infectivity can be suppressed through drug (ivermectin) pressure, despite the potential for re-initiation of transmission through the presence of a population of adult worms capable of producing microfilariae if the drug pressure is removed.

Transmission zone (equivalent to a transmission focus)

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

EXECUTIVE SUMMARY

BACKGROUND

Human onchocerciasis (river blindness) is a disease of the skin and eye caused by *Onchocerca volvulus*, a parasitic worm transmitted by *Simulium* species (black flies) that breed in fast-flowing rivers and streams. The disease is endemic in 31 countries in sub-Saharan Africa, three countries in Latin America and in Yemen. Since 2013, the World Health Organization (WHO) has verified three countries in Latin America as free of human onchocerciasis.

Whilst nodulectomy and vector control have been implemented in the past, the current intervention strategy is based on mass drug administration (MDA) of ivermectin. In Africa, annual community-directed treatment with ivermectin is the main intervention in most areas except in a few foci where semi-annual treatment is implemented. In the Americas, semi-annual ivermectin treatment with a minimum coverage of 85% is the main intervention; recently, quarterly treatment has been implemented in some foci.

Onchocerciasis control programmes carrying out mass treatment with ivermectin have three phases:

Phase 1

The first phase, the intervention or treatment phase, is characterized by regular ivermectin treatment with a minimum requirement of 80% therapeutic coverage. This phase typically lasts at least 12–15 years, corresponding to the reproductive lifespan of the adult worm when exposed to drug pressure. Three countries (Equatorial Guinea, Uganda and the United Republic of Tanzania) supplement MDA with vector control.

Phase 2

The second phase immediately follows the intervention or treatment phase and is therefore also called “post-treatment surveillance”. This phase typically lasts 3–5 years.

Phase 3

The third phase starts at the end of the 3–5 years of post-treatment surveillance and is also known as “post-elimination surveillance”. It follows the confirmation of the initial assessments at the end of phase 2, thereby providing strong evidence that transmission has been permanently interrupted (eliminated) in a country.

An onchocerciasis elimination programme uses several diagnostic tests in vectors (black flies) and in affected communities (humans) to monitor progress. These include:

Entomological evaluation by O-150 PCR technique, to determine the level of infective stage of *O. volvulus* larvae (L3 stage) in female black flies based on amplification of the parasite-specific DNA probes O-150. The upper bound of the 95% confidence interval of the prevalence of infective flies as measured by PCR should be less than one infected black fly for 1000 parous flies ($< 1/1000$) tested, representing a prevalence of less than 0.1% or

one infected black fly in 2000 of all flies examined, equivalent to a prevalence of less than 0.05 %. A minimum of 6000 black flies collected from a transmission zone must be tested and all found to be free of infective larvae to ensure that the upper bound of the 95% confidence interval is met.

Serological evaluation by Ov-16, to determine the presence of IgG4 antibodies to the antigen Ov-16 in children of less than 10 years in order to detect exposure to the *O. volvulus* parasite. Generally, a sample size of 2000 children is needed to detect a prevalence of less than or equal to 0.1 % at the upper bound of the 95% confidence interval. For a finite population with 1100–2000 children to be examined, the number of the sample size of children to be tested has been estimated accordingly in these guidelines. When the eligible population of children less than 10 years of age is below 1100, then all children in that focus should be tested according to the appropriate statistical methods for finite populations.

Parasitological evaluation by skin snip microscopy and DEC patch test can be used to monitor progress during the first (treatment) phase of onchocerciasis elimination programmes, but not to verify elimination.

Skin snip evaluation by PCR, to differentiate actual infection from exposure to the parasite in certain situations where a number of positive tests are found (that is, where Ov-16 seropositivity is 0.1%).

RATIONALE

Although outdated, the guidelines for certification of elimination of human onchocerciasis published by WHO in 2001 were used to confirm the elimination of interruption of transmission in Colombia (2013), Ecuador (2014) and Mexico (2015). Apart from a few foci in Africa (Mali, Senegal, Sudan and Uganda) where transmission of the parasite has been interrupted and MDA subsequently discontinued, a number of countries are planning to determine whether they have eliminated transmission of *O. volvulus*.

Additionally, there was a need to comply with the methods for guideline development according to the international standards as stipulated in the second edition of the WHO handbook for guideline development published in 2014.

SCOPE, PURPOSE AND OBJECTIVES

The criteria outlined in these guidelines are intended for use at the end of the elimination process when programmes decide whether to stop MDA and to begin post-treatment surveillance and monitoring for recrudescence. Interruption of transmission following MDA should be considered as achieved in a country only when adequate post-treatment surveillance has been completed in all endemic foci; elimination of parasite transmission is verified at the end of the 3–5-year surveillance period.

The scope of these guidelines is thus to prepare endemic countries for stopping MDA at the end of treatment (phase 1), in transitioning to post-treatment surveillance (phase 2) and for confirming the interruption of transmission at the end of phase 2 and the beginning of post-elimination surveillance (phase 3).

The purpose is to provide an updated tool for achieving and verifying elimination of transmission of *O. volvulus* at the end of onchocerciasis elimination programmes using mainly MDA.

The objectives are:

- to provide evidence-based recommendations to health providers and policy-makers in order to demonstrate and confirm the interruption of transmission of *O. volvulus* before, during and after post-treatment surveillance; and
- to inform end-users of the procedures required for verifying the elimination of human onchocerciasis.

TARGET AUDIENCE

The target audience of these guidelines is policy-makers in endemic countries, national neglected tropical disease or onchocerciasis elimination programmes and those involved in verification of elimination of human onchocerciasis.

GUIDELINE DEVELOPMENT METHODS

These guidelines were developed in accordance with the second (2014) edition of the WHO handbook for guideline development. Two key questions were formulated and outcomes selected in collaboration with the Guideline Development Group and the guideline methodologist:

1. Which diagnostic tests or combination of tests can validly and reliably be used to demonstrate interruption of transmission of *O. volvulus* for the purpose of stopping MDA?
2. Which diagnostic tests or combination of tests can validly and reliably confirm the interruption of transmission of *O. volvulus* at the end of post-treatment surveillance?

Commissioned experts performed a systematic review of the literature and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the evidence and to formulate recommendations. The GRADE approach designates the body of evidence for each important outcome with a level of confidence or certainty that the effect of a test or approach as measured or known is actually correct. Thus each recommendation is accompanied by an assessment of high, moderate, low or very low certainty that the supporting evidence provides the correct estimate of effect or association.

The factors considered by the Guideline Development Group when formulating the recommendations during a face-to-face meeting (Geneva, January 2015) included: overall certainty of the balance of benefits and harms of the test or approach; resources required; cost; equity; feasibility; and acceptability. The Guideline Development Group formulated a strong recommendation when its members were confident that the desirable consequences outweighed the undesirable effects of the intervention, whereas a conditional recommendation was issued when it considered that the balance of the potential consequences of a test or approach were less certain. The draft guidelines underwent external peer review before finalization.

DECLARATION AND MANAGEMENT OF INTERESTS

All the participants at the face-to-face meeting completed and signed WHO Declaration of Interest forms, which were reviewed and assessed by the WHO Steering Group. At the end of the assessment, the potential conflict of interest for the guidelines was deemed inconsequential in respect of the two members who declared having received research grants from the drug manufacturer that donated ivermectin, and their involvement with the manufacturer was announced to the members of the Guideline Development Group; to further minimize bias during discussions, and as most members were experts and scientists in the field of onchocerciasis, an independent methodologist with no connection with onchocerciasis activities co-chaired the meeting.

RESULTS OF EVIDENCE RETRIEVAL, SYNTHESIS AND ASSESSMENT

Two prospective observational studies were identified that addressed the key questions and thus formed the basis for the recommendations for demonstrating and confirming the interruption of transmission of *O. volvulus*.

RECOMMENDATIONS

The Guideline Development Group formulated the following recommendations:

To demonstrate the interruption of transmission of *O. volvulus* for the purpose of stopping MDA

1. O-150 PCR (Poolscreen) testing in black flies should be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, high certainty of evidence

2. The Ov-16 serology test should be used in children under 10 years of age to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, low certainty of evidence

3. Skin snip microscopy should not be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA. Skin snip microscopy may be used in a transition to using Ov-16 serology; during such transition, skin snip microscopy and Ov-16 serology should be used in parallel. Skin snip microscopy, if used, should be applied with a sample size providing adequate statistical certainty that programmatic goals have been reached.

Conditional recommendation, low certainty of evidence

4. Assessment of ocular infection should not be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, low certainty of evidence

To confirm the interruption of transmission of *O. volvulus* at the end of the post-treatment surveillance period leading to the elimination of human onchocerciasis

5. O-150 PCR (Poolscreen) testing in black flies should be used to confirm the interruption of transmission of *O. volvulus*.

Strong recommendation, high certainty of evidence

6. The Ov-16 serology test should be used in children to confirm the interruption of transmission of *O. volvulus* when the result of O-150 PCR (Poolscreen) testing in black flies is at or near the threshold (that is, less than 1 L3 infective larvae of *O. volvulus* parous fly or 1 out of 2000 total flies).

Conditional recommendation, low certainty of evidence

7. Assessment of ocular infection should not be used to confirm the interruption of transmission of *O. volvulus*.

Strong recommendation, low certainty of evidence

STANDARD OPERATING PROCEDURES FOR STOPPING MDA AND VERIFYING ELIMINATION

Once onchocerciasis mapping is completed in a country, the programme should select sentinel villages close to vector breeding sites. Stopping MDA will be considered only after continuous MDA implementation with a minimum therapeutic coverage in the transmission zone of 80% during phase 1 (treatment phase) indicates it is safe to do so.

Four steps are required in order to stop MDA during phase 2 (post-treatment surveillance):

Step 1

The health ministry establishes an oversight committee independent from the national programme to address matters concerning onchocerciasis elimination.

Step 2

The committee advises the country to stop MDA according to the recommendations contained in these guidelines. It considers the status of treatment for lymphatic filariasis and/or any recrudescence issues of each focus, including cross-border risk with neighbouring countries, to determine the length of post-treatment surveillance that can extend the 3–5 year period. Only the entomological PCR-O150 DNA test should be used to make such a decision. However, the Ov-16 serology test could be used if insufficient black flies are collected.

Step 3

The committee advises the national programme to prepare the country report once all the foci have completed the post-treatment surveillance period.

Step 4

The country submits its report to WHO through the appropriate WHO regional office. After receipt of the country report, WHO constitutes an international verification team

to conduct the verification of elimination according to the format included in *Annex 6*. The collection, methodology, data reporting and analysis of assessments in black flies are described in *Annex 7*.

Based on the judgement of the international verification team, the WHO Director-General issues the acknowledgement letter declaring the elimination of human onchocerciasis. Post-elimination surveillance (phase 3) then follows until onchocerciasis has been eliminated in the entire region.

POST-ELIMINATION SURVEILLANCE

Post-elimination surveillance by O-150 PCR assessment of black flies is regularly undertaken in countries where WHO has verified elimination until the risk of recrudescence of the disease no longer exists in any country in that region.

FUTURE CONSIDERATIONS

The discovery of new diagnostic tools or interventions and improved metrics generated by modelling-based research activities on onchocerciasis and lymphatic filariasis may justify a revision of these guidelines by 2020.

1

BACKGROUND

1.1 INTRODUCTION

Human onchocerciasis, a vector-borne disease, is endemic in 31 countries in sub-Saharan Africa, three countries in Latin America and in Yemen. WHO has verified the elimination of transmission of the parasite in Colombia, Ecuador and Mexico respectively in 2013, 2014 and 2015 and declared them free of the disease. The infection is caused by *Onchocerca volvulus*, a filarial nematode (1,2). Chronic infection causes itching and disfiguring lesions of the skin and produces eye lesions that can lead to irreversible blindness. Because the vectors (black flies of the genus *Simulium*) are insects that breed as larvae in fast-flowing rivers and streams and bite humans near these sites, the disease is also known as river blindness. In the Americas, the disease is sometimes referred to as Robles' disease after Dr Rodolfo Robles, the Guatemalan physician who first documented the causal relation of *O. volvulus* with vision loss and blindness.

1.2 CONTROL AND ELIMINATION OF HUMAN ONCHOCERCIASIS

In Africa, the blindness and the severity of skin lesions have severe socioeconomic consequences. Historically, river blindness has led to the desertion of large areas of fertile land adjacent to vector breeding sites, impeding the economic development of affected countries (3).

Control of morbidity from human onchocerciasis and interruption of transmission of the causative parasite have commanded attention and been addressed in several different ways. Control strategies have included removal of nodules (nodulectomy), vector control and, more recently, mass drug administration (MDA) with ivermectin (4,5). These interventions have varied among regions of the World Health Organization (WHO) in time and place,

with varying degrees of success; all have been well characterized and documented in the peer-reviewed literature (6). Currently, nearly all programmes use MDA with ivermectin, administered once, twice or four times a year (7,8).

In the WHO African Region, annual or semi-annual distribution of ivermectin is used to sustain the successes of the Onchocerciasis Control Programme in West Africa (OCP) and is distributed annually in community-directed country programmes. Community-directed treatment with ivermectin is the main intervention of the African Programme for Onchocerciasis Control (APOC) established in 1995, which covers all of the non-OCP countries where the disease is endemic. These programmes, initially aimed at controlling blindness, have operated under World Health Assembly resolutions WHA47.32 and WHA62.1 adopted in 1994 and 2009 respectively (9).

In the WHO Region of the Americas, semi-annual mass treatment using ivermectin with a minimum expected coverage of 85% of the eligible population in all endemic communities is the strategy adopted by all endemic countries; quarterly treatment is provided in selected areas. In 1991, resolution CD35.R14 of the XXXV Directing Council of the Pan American Health Organization called for the elimination of morbidity due to onchocerciasis by 2007 (10). The OEPA was established in 1992 to consolidate the efforts of partner agencies with a view to eliminating the disease and providing technical and financial assistance to national programmes. This goal was reaffirmed in resolutions CD48.R12 and CD49.R19 endorsed in 2008 and 2009 respectively. The OEPA now operates under resolution CD49.R19, which calls for the regional elimination of ocular morbidity caused by onchocerciasis and interruption of transmission of the causative parasite by 2015 (10).

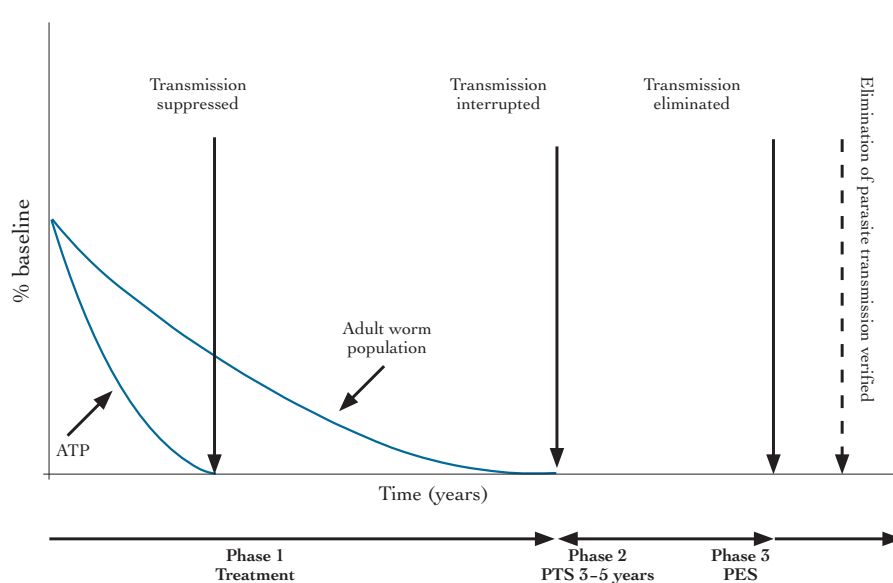
1.3 ONCHOCERCIASIS ELIMINATION PROGRAMMES AND THEIR PHASES

The advent of ivermectin, an effective microfilaricide suitable for large-scale use in rural areas, has enhanced prospects for control or elimination of the disease in many areas, including Africa. The medicine is provided free of charge by Merck & Co., Inc. under the Mectizan Donation Program. Given as an oral dose, ivermectin temporarily lowers skin loads of microfilarial *O. volvulus* to levels below those required for effective transmission by *Simulium* species (black flies). Ivermectin also has a demonstrated microfilarial suppressant activity in adult female worms and a deleterious impact on adult worms, especially when given multiple times per year (11).

Studies in several endemic onchocerciasis foci in Africa and the Americas have shown that sustained, high level coverage with ivermectin is 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 coverage with ivermectin has been achieved over a sufficiently long period of time to effect interruption of transmission and reduce morbidity (5).

Onchocerciasis control programmes carrying out mass treatment with ivermectin have three phases (Figure 1).

Figure 1 Phases in the elimination of human onchocerciasis



ATP, annual transmission potential; PES, post-elimination surveillance; PTS, post-treatment surveillance

Phase 1 The first phase – the intervention or treatment phase – is mainly characterized by regular treatment with ivermectin MDA. Each treatment round requires a minimum of 80% therapeutic coverage of the eligible population (12,13). Treatment eventually leads to a suppression or near-suppression of the annual transmission potential of the vector and thus to a temporary suppression of transmission. However, the population of adult worms may still be at a point of potential recovery should treatment be withdrawn.

If effective MDA continues at the proper interval, this temporary suppression of transmission gives way to interruption of transmission. This phase typically lasts for at least 12–15 years in the case of annual treatment, corresponding to the reproductive lifespan of the adult parasite when exposed to drug pressure. At the end of the first phase most if not all adult worms should have died or become infertile. Importantly, some adult worms and/or microfilariae may persist, but the minimal level of transmission that may occur will not maintain the infection (that is, any transmission is below the threshold necessary to maintain the parasite population [$R_0 < 1$], indicating that elimination of the parasite is imminent).

At some point during phase 1 the infection reaches a state of transmission interruption in which no evidence of ongoing transmission or new infections can be demonstrated. This is a critical time as the programme decides whether to suspend treatment.

Phase 2 The second phase – post-treatment surveillance – occurs when interventions are stopped. During this period, the national programme conducts periodic assessments to ascertain that transmission remains interrupted for a minimum period of 3 years, or up to 5 years depending on the specific parameters of each focus. This timeframe is critical in those areas at highest risk of recrudescence of infection, especially in (i) areas with historical prevalence of intensity of infection bordered by foci with ongoing transmission or (ii) areas with low coverage or few treatment rounds; and (iii) areas of political instability. Periodic assessments can be conducted during this phase by focus, by transmission zone or by country. Isolated foci or transmission zones in the same country may be evaluated at different times if MDA activities are not implemented or progressing in a synchronized manner.

1.4 DIAGNOSTIC TESTS

Any diagnostic tests used to monitor epidemiological progress towards transmission end-points during post-treatment surveillance should be statistically sound and include well established, validated numbers of required samples of the vectors and/or those of the affected human population. The samples should be examined, with identification of correct target populations to be tested and the range of acceptable values including confidence intervals.

1.4.1 Entomological evaluation by O-150 PCR technique

Entomological evaluation by O-150 PCR is a diagnostic technique that aims to determine the level of infective-stage *O. volvulus* larvae in the vector population as analysed by polymerase chain reaction (PCR) technique based on amplification using *O. volvulus*-specific DNA targeting probes O-150 repeat family sequence (14–17). The flies must be collected during daylight hours when parous flies are most abundant (implying knowledge of their diurnal biting cycle for each species or cytoform concerned) and during the peak transmission season of the year (to optimize the collection of infected specimens).

Flies are pooled by collection site into pools containing no more than 200 individuals, and the heads and bodies are separated and examined individually. The bodies (thorax and abdomen of black flies), which may contain *O. volvulus* DNA from microfilaria or L2 stages, may be used to assess if any parasite remains in the human population using black flies as an alternative to skin snipping (xenodiagnosis). However, as bodies carry only immature larval stages, a positive result in bodies is not necessarily indicative of ongoing transmission, which requires the presence of infective-stage larvae (L3) in the head of the vector. Thus, if any evidence for parasite–vector contact is found in the analysis of body pools from a given area, all head pools from that area must be tested to gain as accurate an estimate of the prevalence of flies carrying infective-stage larvae as possible.

The criteria used for entomological assessment are:

- an upper bound of the 95% confidence interval of the prevalence of flies carrying infective larvae (L3) in the head of less than 0.1% ($< 1/1000$) in parous flies; or
- an upper bound of the 95% confidence interval of the prevalence of L3 of less than 0.05% ($< 1/2000$) in all flies (assuming a parity rate of 50%).

These criteria were first applied by the former OCP in West Africa (18,19), then operationalized in the OEPA (20,21) and in recent APOC evaluations in West Africa (22,23).

For the sample size, sufficient flies must be tested to ensure that the upper bound of the 95% confidence interval for the prevalence of infective flies is less than 0.05%. This level of statistical confidence requires that a minimum of 6000 flies must be collected from a transmission zone and all must be shown to be negative by PCR for parasite infective larvae. In areas where collection of such a large number of flies is not feasible, as many flies as possible should be collected over a period of time and tested to ensure that the upper bound of the 95% confidence interval for the annual transmission potential or the seasonal transmission potential falls below an acceptable level.

Estimates of the annual transmission potential necessary to maintain the parasite have ranged from 2 to 54 L3/person/year using mathematical models (15,24), and from 8 to 18 L3/person/year using field observations (25,26). Furthermore, previous estimates were developed before the advent of ivermectin, and the concept of few to no microfilariae in the skin as a result of MDA with ivermectin would suggest that the data used are not entirely comparable to the present situation. Nonetheless, setting an annual transmission potential with an upper bound of the 95% confidence interval of less than 20 has been successfully operationalized in the Americas where a variety of *Simulium* species with differing vectorial capacities serve as vectors; results to date indicate that this is a suitable cut-off point (20). However, such thresholds may be different for African settings and further clarification is awaited.

In the event that no flies are collected because the vector has been eliminated or has disappeared as a result of environmental changes, as in certain foci in Uganda where *S. neavei* was the vector (27), the absence of larval stages of *S. neavei* species on the phoretic crab in surveys and from flies collected in a defined focus is a substitute indication of interruption of transmission.

1.4.2 Serological evaluation by Ov-16

The *O. volvulus* Ov-16 antibody test (28,29) can be performed on finger-prick blood samples and is a proven, valuable and minimally invasive assay (9,41,42). The test determines the presence of IgG4 antibodies to the antigen Ov-16 and is useful for detecting the exposure to the *O. volvulus* parasite.

During the few past years this serological test has been operationalized in Latin America (11,20,21, 30–33) and in Africa (27,34). Children under 10 years of age were included in the evaluation surveys, which determined exposure to the parasite with a sufficient sample size to detect a prevalence of less than 0.1% at the upper bound of the 95% confidence interval.

Generally, a sample size of 2000 children of less than 10 years is required for Ov-16 serology testing in order to meet this criterion (35). Children are selected by a multistage stratified sampling method scheme applied to the local lower administrative unit level. For example, if the local lower administrative unit contains 20% of the total estimated population of the focus (transmission zone), a subsample of 400 children will be enrolled from that administrative unit.

In small foci where there are fewer than 2000 children under 10 years of age, the sample sizes must be tested to ensure that the prevalence of Ov-16 in the target population of children is equal to or less than 0.1% (Table 1).

Table 1 Proportion of finite target population that must be tested to conclude that the prevalence in the entire target population is $\leq 0.1\%$ when none of the sample tested is positive

Total population size (children < 10 y)	Maximum number of positives allowed in total population of children < 10 y	Actual allowed upper bound of prevalence (%)	Number of sample size to be tested
1750	1	0.057	1663
1500	1	0.067	1425
1250	1	0.080	1188
1100	1	0.090	1045

When the eligible population of children is fewer than 1100, essentially all eligible children should be tested. In these situations, efforts should be made to calculate the confidence interval using statistical methods appropriate for finite populations. Sampling should be representative of the entire transmission zone, and analysis should allow for stratification by age.

Because the Ov-16-based serological test may detect recent as well as historic exposure, other confirmatory tests are still needed to distinguish new patent infections from exposure. Efforts are under way to develop such tests, which should be incorporated into the evaluation process of programmes as they become available.

1.4.3 Parasitological evaluation by skin snip microscopy and DEC patch test

Skin snips and the DEC patch test are useful tools for monitoring progress as an elimination programme is implemented and moves towards that goal during treatment (phase 1). A detailed description of the procedures and sample size is found in the APOC manual on evaluating the impact of community treatment with ivermectin using the skin snip method (36). However, a test capable of detecting any new patent infection with a high positive predictive value is still needed.

1.4.4 Skin snip evaluation by PCR

A PCR test on skin snip is indicated in some limited situations where few serologically positive children (Ov-16 > 0.1%) are detected in order to confirm actual infection rather than exposure to the parasite. Serologically positive children found negative by PCR testing of skin snips are considered negative for patent infection with *O. volvulus* and are accepted as not contributory to the 0.1% threshold calculation. Since these children would be considered as *O. volvulus* “exposed”, ethically, the programme should re-examine them 1–1.5 years later to determine if they have developed patent infection. If so, they should be treated accordingly.

2

RATIONALE

The original (2001) WHO guidelines for certification of elimination of human onchocerciasis included the following criteria: (i) an absence or near absence of infective-stage *O. volvulus* in the vector as determined by the O-150 PCR (Poolscreen) test with a minimal sample size of 10 000 black flies; and (ii) an absence of detectable infection based on skin snip microfilariae, DEC patch test, nodule detection and serological testing of untreated children reaching 5 years of age or in untreated new residents who have migrated into an endemic area where transmission has been interrupted. A five-year cumulative incidence rate of less than 1 new case per 1000 susceptible children or individuals provided an acceptable sample size (37,38).

Since 2007, these criteria and the respective diagnostic tools have been operationalized in Latin America and in Africa.

In the Region of the Americas, elimination has been the main goal of the OEPA since its inception in 1991 and has been achieved in three formerly endemic countries since then (39). At the end of 2014, transmission is believed to have been interrupted in 11 of the 13 endemic foci, with only the twin foci on the Brazil–Venezuelan border remaining with active transmission. Consequently, WHO has verified elimination of human onchocerciasis in Colombia in 2013 (40), Ecuador in 2014 (41) and Mexico in 2015 (42) on the basis of the original guidelines.

In the African Region, the shift from control to elimination programme in 2009 led to significant operational changes and implications (12,13,43,44) as well as a renewed approach and criteria to monitor the progress, impact and outcome of the programme using the lessons learnt over the past decade in the Americas (11,30–33) and, more recently, in Africa (22,34,45,46).

In addition to these lessons learned during the operationalization of the criteria and procedures within the old WHO guidelines, there was a need to develop an evidence-informed guideline using transparent and explicit methods for assessing the evidence and for formulating recommendations as stipulated in the *WHO handbook for guideline development* (47).

These guidelines are therefore intended to update the criteria used in the WHO 2001 document and to adhere to WHO's standards and procedures for developing guidelines since 2007. By doing so, countries in which onchocerciasis is endemic will have appropriate tools at their disposal for guidance on when and how to stop MDA and to conduct post-treatment surveillance until confirmation of the elimination of onchocerciasis, to be followed by verification of elimination by WHO.

3 PURPOSE AND OBJECTIVES

The purpose of these guidelines is to provide evidence-based recommendations that warrant the discontinuation of MDA and the verification of elimination of transmission of *O. volvulus*. Information is provided on how to monitor and assess onchocerciasis in order to demonstrate that transmission of *O. volvulus* has been interrupted in areas previously identified as endemic.

The objectives are:

- to provide national onchocerciasis elimination programmes and external agencies with the recommendations required to demonstrate and confirm the interruption of transmission of *O. volvulus* over a specified period of time; and
- to inform those involved in national onchocerciasis elimination of the required procedures for verifying elimination of human onchocerciasis.

4

TARGET AUDIENCE

These guidelines are primarily targeted at national neglected tropical disease or onchocerciasis elimination programme managers within health ministries in anticipation that the recommendations will be adopted as national policies by policy-makers. They are intended also as guidance for those involved in verifying elimination of human onchocerciasis.

5

METHODS

5.1 DEVELOPMENT PROCESS

A Guideline Development Group comprising seven members from leading stakeholders with expertise of onchocerciasis in Africa, the Americas and Yemen was formed. In addition, two methodologists were commissioned to retrieve, synthesize and assess the evidence, a process preceded by formulating key questions and selecting outcomes in collaboration with the members of the Guideline Development Group and a WHO Steering Group. The methodologists reviewed the literature systematically and assessed the quality and certainty of evidence according to the GRADE approach (48). They also prepared the decision tables, which guided members of the Guideline Development Group to formulate recommendations during a face-to-face meeting (Geneva, January 2015) co-chaired by a third independent methodologist familiar with WHO's procedures and standards for developing guidelines and one member of the Group. The draft guidelines were reviewed by five external peers with diverse expertise and field experience in onchocerciasis, lymphatic filariasis and malaria, and their comments helped to refine the final document.

5.2 GUIDELINE QUESTIONS

Two key questions were formulated as follows:

- Which diagnostic tests or combination of tests can validly and reliably be used to demonstrate interruption of transmission of *O. volvulus* for the purpose of stopping MDA (KQ1)?
- Which diagnostic tests or combination of tests can validly and reliably confirm the interruption of transmission of *O. volvulus* at the end of post-treatment surveillance (KQ2)?

Members of the Guideline Development Group contributed electronically to the development of these key questions by providing details of the type of tests to be used, their critical thresholds and the optimal time-point of their use as summarized in *Table 2* and in *Annex 1*.

Table 2 Diagnostic tests for measuring interruption of transmission and confirming elimination of transmission of *Onchocerca volvulus*

Test	Threshold	Time-point
O-150 PCR in black flies (head)	< 1/1000 (0.1%) parous flies or < 1/2000 (0.05%) in all flies assuming a 50% parous rate A 95% CI is used	Peak transmission season
Ov-16 serology in children (< 10 y)	< 0.1% A 95% CI is used	In same quarter of year as flies are collected
Skin snips (PCR)	Only done on those children who test Ov-16 positive	As soon as possible after serological results are known

CI, confidence interval; PCR, polymerase chain reaction; y, years

5.3 SYSTEMATIC REVIEW

The commissioned methodologists conducted the review of the literature to answer two key questions (KQ1 and KQ2). The eligibility criteria comprised:

Population

The eligible populations for inclusion in the review were human populations at risk for onchocerciasis as well as black flies in endemic regions. Black flies (*Simulium* species) were considered a population because they are the vector of *O. volvulus*.

Intervention (diagnostic tests)

The search included studies on populations where diagnostic tests for measuring the elimination of *O. volvulus* have been implemented individually or in various combinations.

Control (diagnostic test accuracy reference standard or other test)

Evidence from studies with a known and validated reference standard or comparison of two versions of a similar test was also included in the review.

Outcomes

The main outcome was the absence of recrudescence of infection; that is, the negative test at the time-point of KQ1 predicts a negative test at the time-point of KQ2.

Timing

The first question (KQ1) determined the interruption of transmission, hence the end of MDA, whereas the second question (KQ2) confirmed the end of post-treatment surveillance.

Setting

Areas endemic for onchocerciasis for which populations at risk have received MDA and are being evaluated in order to demonstrate or confirm the interruption of *O. volvulus* transmission.

The details of the search strategy are included in *Annex 2*.

5.4 FORMULATION OF RECOMMENDATIONS

The experts commissioned by the Guideline Development Group conducted a systematic review of the literature using the GRADE approach to assess the quality of the evidence and to formulate the recommendations. The GRADE approach designates the body of evidence for each important outcome with a level of confidence or certainty that the effect of a test or approach as measured or known is actually correct. Thus each recommendation is accompanied by an assessment of high, moderate, low or very low certainty that the supporting evidence provides the correct estimate of effect or association.

The co-chair led the Guideline Development Group through the process of formulating the recommendations. Members were asked to review each of the key questions and to formulate recommendations based on the evidence identified by the systematic review. The discussion was structured around decision tables that were prepared a priori, and contained the following criteria: accuracy of the diagnostic tests; overall certainty of the evidence; resources required; cost; equity; feasibility; and acceptability of the test or approach. After judging the various criteria, the members agreed on the balance of consequences, the direction and strength of the recommendation, and its wording.

A strong recommendation was formulated when members were confident that the desirable effects of adherence to the recommendation outweighed the undesirable effects (or vice versa). A conditional recommendation was formulated when desirable effects of adherence to the recommendation probably outweighed the undesirable effects (or vice versa).

The recommendations were formulated by consensus among the members. When consensus could not be reached, votes were taken by hand-raising at the Chair's discretion. A strong recommendation was adopted if supported by at least a two-thirds' majority. As members raised points that were relevant but not directly related to criteria that did not directly affect the recommendation, the co-chair attempted to classify them as conditions or key remarks to support the recommendation statement, implementation considerations, monitoring considerations or implications for future research. He offered a neutral recommendation as a starting point for discussing the recommendation statement.

The draft guidelines underwent external peer review before finalization: no changes could be made in the recommendations during this process, however several clarifications were added.

6 DECLARATION AND MANAGEMENT OF INTERESTS

All seven members of the Guideline Development Group and the three methodologists who participated in the face-to-face meeting completed and signed WHO Declaration of Interest forms (*Annex 4*).

Of the seven members with longstanding involvement in onchocerciasis control or elimination programmes or research activities, two reported having received research grants or consulting fees from either the Mectizan Donation Program or the Bill & Melinda Gates Foundation. Two members of the WHO Steering Group reviewed and assessed these two cases and concluded that these declared interests were not a significant conflict of interest and these individuals therefore participated fully in the guideline development process.

The two systematic reviewers and the guideline methodologist were neither voting members of the Guideline Development Group nor onchocerciasis experts; they declared no conflicts of interest. However, they participated in the meeting at which recommendations were formulated (the guideline methodologist was co-chair) to ensure that the evidence was evaluated objectively and that the recommendations accurately reflected the evidence.

7 RESULTS OF EVIDENCE RETRIEVAL, SYNTHESIS AND ASSESSMENT

Overall, there was little direct comparative scientific evidence on the use of different tests for verification of elimination of human onchocerciasis. The best available evidence was provided by two prospective observational studies that provided data from interruption of transmission leading to cessation of treatment. Multiple studies of diagnostic test accuracy comparing various tests were located but these were generally done in populations with high prevalence of onchocerciasis (which does not reflect the situation close to interruption of transmission with a low prevalence of onchocerciasis). This is particularly important because the standard reference test used in these studies (skin snip microscopy) does not perform well in populations with low disease prevalence. Moreover, comparative studies of diagnostic test accuracy were performed to assess test accuracy, but not to demonstrate interruption of transmission or elimination.

For demonstrating interruption of transmission or elimination of *O. volvulus*, the quality of the evidence for entomological assessment through O-150 PCR (Poolscreen) of black flies was rated high, whereas for epidemiological assessments such as Ov-16 serology, skin snip microscopy and ocular morbidity (slit lamp) it was low. The systematic reviews and the assessments of the certainty of the evidence are included in *Annex 2*.

8 RECOMMENDATIONS

8.1 DEMONSTRATION OF THE INTERRUPTION OF TRANSMISSION OF *O. VOLVULUS* FOR THE PURPOSE OF STOPPING MDA

8.1.1 O-150 PCR (Poolscreen) testing in black flies

O-150 PCR (Poolscreen) testing in black flies should be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, high certainty of evidence

8.1.1.1 Background

Onchocerciasis is a vector-borne disease, where humans are the only natural vertebrate host, and infection rates and intensity are determined by the degree 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 capacity and blood-feeding characteristics of local black fly populations, with the seasonal abundance of the vector and with differences in the human host responses to the parasite. These factors, together with those related to environmental, geographical, social and demographic influences, increase the complexity of the epidemiology of the disease in the different areas of its distribution. The original WHO guidelines on the certification of elimination of human onchocerciasis issued in 2001 (37,38) required a sample size of 10 000 black flies, which was operationalized at a minimum of 6000 black flies in Latin America and a few countries in Africa.

8.1.1.2 Summary of the evidence

The systematic review conducted on the use of O-150 PCR (Poolscreen) testing in black flies to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA identified two observational studies (33,46) and 15 studies of diagnostic test accuracy (29,49,50–62), which provide limited evidence on the comparative use of tests (*Annex 3.1*).

Based on those two observational studies, the O-150 PCR (Poolscreen) for black flies test was rated very accurate with a high certainty of evidence. Following historical data from Mali, this PCR test could distinguish *O. volvulus* from the cattle parasite *O. ochengi*, which could not be done by simple dissection of black flies.

8.1.1.3 Rationale for the recommendation

The rationale for the strong recommendation was based primarily on the specificity of the PCR testing, which is higher than that for the dissection of the black flies. In addition, larger pools of flies are more cost-effective than smaller pools for the overall costs of the programme.

Nevertheless, a few factors could affect the feasibility of implementing PCR in the community, including (i) the existence of a procurement and supply policy; (ii) support from the Ministry of Health; (iii) support from the frontline health facilities; and (iv) health workers' attitudes, motivation and outreach on the basis of one study in Africa (66). In this case, the value of properly informing and empowering communities to enlist them as crucial allies in disease control efforts can facilitate the acceptability of the test by showing the benefits of the intervention.

Overall, the desirable consequences clearly outweighed any undesirable consequences in both Latin America and Africa.

8.1.1.4 Implementation considerations, including monitoring and evaluation

The existence of regional laboratories serving the largest possible administrative area is the main prerequisite for implementation of this test.

Sampling should be appropriately conducted according to APOC standard operating procedures on entomological evaluation.

Laboratory quality control should be regularly monitored to ensure high-quality, reliable test results.

The test should be conducted annually up to the end of post-treatment surveillance.

8.1.1.5 Research priorities

More investigations should be carried out to define appropriate and standardized protocols for fly catching.

8.1.2 Ov-16 serology testing in children less than 10 years of age

The Ov-16 serology test should be used in children less than 10 years of age to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, low certainty of evidence

8.1.2.1 Background

In areas where onchocerciasis is endemic, infected individuals harbour both adult (macrofilariae) and immature (microfilariae) worms. Following an appropriate period of MDA with ivermectin (that is, corresponding to the lifespan of the *O. volvulus* parasite

under recurrent treatment), infected subjects are believed to be free of any microfilariae in their skin or eye. Consequently, children born by the end of MDA implementation are not exposed to *O. volvulus* parasites, justifying the indirect method of determining the interruption of transmission of onchocerciasis. Towards that end, the Ov-16 serology test aims to determine the level of detectable onchocercal infection in children and migrant individuals in an endemic area during the post-treatment surveillance phase as stipulated in the 2001 WHO guidelines for certification of elimination of human onchocerciasis (37,38).

8.1.2.2 Summary of the evidence

The systematic review conducted on the use of the Ov-16 serology test in children to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA identified the same two observational studies (33,46) and 15 studies of diagnostic test accuracy (29,49,50–62) above, which provide limited evidence on the comparative use of tests for the determination of interruption of *O. volvulus* (Annex 3.2).

The Guideline Development Group rated the Ov-16 serology test as accurate, with a low certainty of evidence. Studies were mostly performed in populations with high onchocerciasis prevalence, and the reference standard used (generally skin snip microscopy) is an imperfect test in low prevalence settings at this stage of the programme (63). In addition, interruption of transmission demonstrated by Ov-16 serology testing was not confirmed during and after post-treatment surveillance using the same test.

8.1.2.3 Rationale for the recommendation

Apart from the costs of a plate reader for ELISA testing, estimated at approximately US\$ 5000, Ov-16 serology testing can easily be used in the field with strong community participation (64–68) and support from nongovernmental development organization partners alongside other programme assessments such as transmission assessment surveys for lymphatic filariasis (69). One ELISA test costs about US\$ 0.15, which is cheaper than the cost of continuing MDA.

Compared with skin snipping the ELISA (finger-prick) test is considered to be minimally invasive and hence more acceptable in some settings.

The Guideline Development Group concluded that the desirable consequences clearly outweighed any undesirable consequences in most settings.

8.1.2.4 Implementation considerations, including monitoring and evaluation

Despite the simplicity of the Ov-16 serology test, challenges include the need for 2 days to test an average acceptable sample, which sometimes is difficult to obtain. Therefore, Ov-16 serology should be used in conjunction with the PCR test in black flies.

Other implementation challenges are related to sampling where obtaining the minimum sample size of 2000 children in an endemic focus is not possible.

The Ov-16 serology test should be conducted annually until the end of post-treatment surveillance in conjunction with O-150 PCR in black flies.

8.1.2.5 Research priorities

Two main topics need to be addressed. First, the sero-reversion of Ov-16 responses by age and over time should be investigated. Second, the new Ov-16 Rapid Test should be validated as a possible replacement of the standard test.

8.1.3 Skin snip microscopy

Skin snip microscopy should not be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA. Skin snip microscopy may be used in a transition to using Ov-16 serology; during such transition, skin snip microscopy and Ov-16 serology should be used in parallel. Skin snip microscopy, if used, should be applied with a sample size providing adequate statistical certainty that programmatic goals have been reached.

Conditional recommendation, low certainty of evidence

8.1.3.1 Background

The Ov-16 serology test and skin snip microscopy were both listed in the original (2001) WHO guidelines for certification of elimination of human onchocerciasis as diagnostic tests to be used in determining the absence of detectable *O. volvulus* parasites in humans (37,38). Since 2005, skin snip microscopy has been extensively used to follow up trends towards elimination in several APOC projects using community-directed treatment with ivermectin across Africa.

8.1.3.2 Summary of the evidence

The systematic review conducted on the use of skin snip microscopy to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA recorded two observational studies. The Guideline Development Group was divided on the accuracy of the evidence: three members voted that skin snip microscopy is very inaccurate, two voted that it is inaccurate and two considered the test accurate. Although specificity is 100%, the main challenge with skin snip microscopy at this stage of the programme is its low sensitivity (estimated at 20%). Additionally, skin snipping of humans seems to be redundant in the presence of O-150 PCR testing in black flies. Consequently, a majority of the GDG (five “yes” votes out of seven) concluded that the test was not relevant based on the low certainty of evidence (*Annex 3.3*).

8.1.3.3 Rationale for the recommendation

Currently, skin snip microscopy is widely used in Africa as a monitoring and evaluation tool to assess progress towards onchocerciasis elimination. Although skin snip microscopy is 10 times less expensive than O-150 PCR testing on skin snips, its sensitivity substantially decreases as the programme reaches the end of the treatment phase, making it inappropriate for use at this stage. Furthermore, a high rate of refusal has been observed in some communities as the manifestations of the disease decrease with the number of years of MDA implementation. However, as the test has been performed for many years, its acceptability is high in some settings.

Given the initial lack of consensus among the Guideline Development Group on the balance of desirable and undesirable consequences of skin snip microscopy for demonstrating the interruption of transmission after MDA, a vote was held. Five out of seven members supported a conditional recommendation against skin snip microscopy. The voting results allowed the adoption of a conditional recommendation against skin snip microscopy.

8.1.3.4 Implementation considerations, including monitoring and evaluation

Skin snip microscopy is currently used as a tool for monitoring and evaluation during phase 1, which is an appropriate context as sensitivity is still relatively high because the prevalence is still also high. Therefore, the use of skin snip microscopy was considered acceptable as a transitional test while Ov-16 serology testing is being introduced.

8.1.3.5 Research priorities

The acceptability of skin snip microscopy in settings of low prevalence should be investigated, as a high rate of refusal has been observed in some settings.

8.1.4 Ocular infection

Assessment of ocular infection (that is, the presence of microfilariae in the anterior chamber) should not be used to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA.

Strong recommendation, low certainty of evidence

8.1.4.1 Background

Identification of microfilariae in the anterior chamber during ophthalmological assessment is a pathognomic sign of onchocerciasis and was included among the diagnostic tests to be used in the original (2001) WHO guidelines for certification of elimination of human onchocerciasis in order to determine the absence of detectable *O. volvulus* parasite in humans (37,38). It requires an experienced ophthalmologist with good knowledge of onchocerciasis-related eye lesions using slit lamp biomicroscopy.

8.1.4.2 Summary of the evidence

As for other diagnostic tests, the systematic review conducted on using ophthalmological assessment to demonstrate the interruption of transmission of *O. volvulus* in a human population receiving MDA against onchocerciasis for the purpose of stopping MDA recorded two observational studies, of which only one study allowed the evidence for this diagnostic test to be assessed. Testing for ocular infection was considered inaccurate, with a low certainty of evidence (Annex 3.4).

8.1.4.3 Rationale for the recommendation

In addition to the high cost of the equipment needed for this diagnostic test, the Guideline Development Group noted the difficulties involved in implementing ophthalmological

assessments in the final phase of elimination, particularly in settings of low endemicity, given the specialized technical expertise required. After considering its high cost and the need for specialized personnel to conduct the assessment, ocular infection assessment was considered inappropriate despite the fact that local communities appreciate the delivery of eye examination most of the time at no cost. Consequently, the undesirable consequences of ocular infection assessment clearly outweigh any desirable consequences, justifying this recommendation.

8.2 CONFIRMATION OF INTERRUPTION OF TRANSMISSION OF ONCHOCERCA VOLVULUS AT THE END OF POST-TREATMENT SURVEILLANCE

Post-treatment surveillance lasts on average 3–5 years. The following diagnostic tests are typically implemented at the end of this period to confirm the interruption of transmission of *O. volvulus* and hence the elimination of human onchocerciasis.

8.2.1 O-150 PCR (Poolscreen)

O-150 PCR (Poolscreen) testing in black flies should be used to confirm the interruption of transmission of *O. volvulus*.

Strong recommendation, high certainty of evidence

8.2.1.1 Rationale for the recommendation

Since the aim of the diagnostic test at this stage of the programme is to assess the risk of recrudescence of infection by the presence of the infective stage of *O. volvulus* parasites in black flies, the Guideline Development Group agreed to use the O-150 PCR (Poolscreen) test under the same conditions during the initial phase of post-treatment surveillance. This is why the criteria used for evidence assessment of O-150 PCR testing as well as its implementation considerations and research priorities are the same at the beginning and at the end of post-treatment surveillance.

8.2.2 Ov-16 serology testing in children less than 10 years of age

Ov-16 serology testing should be used in children less than 10 years of age to confirm the interruption of transmission of *O. volvulus* when the results of O-150 PCR (Poolscreen) testing in black flies are at or near the threshold.

Conditional recommendation, low certainty of evidence

8.2.2.1 Rationale for the recommendation

As is the case for the O-150 PCR test used to confirm the interruption of transmission, the evidence assessment of the Ov-16 serology test as well as its implementation considerations and research priorities are the same at the beginning and at the end of post-

treatment surveillance. Nevertheless, it is used only under certain conditions, justifying the conditionality of this recommendation. The first condition is when the result of PCR equals the threshold, meaning one positive infective black fly out of 1000 parous flies or 2000 total flies examined. The second condition is when the result of PCR is near that threshold, meaning 2 or 3 positive infective black flies out of 1000 parous flies or 2000 total flies examined.

8.2.3 Ocular infection

Ocular infection (that is, the presence of microfilariae in the anterior chamber) should not be used to confirm the interruption of transmission of *O. volvulus*.

Strong recommendation, low certainty of evidence

Ocular infection (that is, the presence of microfilariae in the anterior chamber) should not be used to confirm the interruption of transmission of *O. volvulus*.

Strong recommendation, low certainty of evidence.

8.2.3.1 Rationale for the recommendation

As indicated for the rejection of ocular infection assessment at the beginning of post-treatment surveillance to determine the interruption of transmission of *O. volvulus* for the purpose of stopping MDA, its implementation to confirm elimination of human onchocerciasis is inappropriate at the end of post-treatment surveillance (see also recommendation 8.1.4).

9 STANDARD OPERATING PROCEDURES FOR STOPPING MDA AND VERIFYING ELIMINATION OF TRANSMISSION

9.1 INTRODUCTION

Once an endemic country has been completely mapped, with all the endemic communities identified and stratified according to their level of endemicity (hypoendemic, mesoendemic, hyperendemic or non-endemic), the national programme typically launches an elimination intervention mainly based on MDA during a number of years. This is known as phase 1 or the intervention (treatment) phase (*Figure 1*). Theoretically, this phase lasts 12–15 years, corresponding to the lifespan of the adult female worm whose death will lead to the permanent interruption of transmission.

At the end of mapping, sentinel communities are selected and monitoring and evaluation activities are regularly conducted to assess the impact of the programme after baseline data have been determined. These in-depth parasitological (skin snip), entomological and serological surveys are done every 4–5 years according to the existing procedures of regional onchocerciasis programmes (36,70,71). The programme should continue treatment with ivermectin with at least 80% coverage of the eligible population each year (assuming MDA is performed annually) until the infection has been interrupted. At this stage, the country will consider stopping the intervention (MDA mainly) and start post-treatment surveillance.

9.2 POST-TREATMENT SURVEILLANCE (PHASE 2)

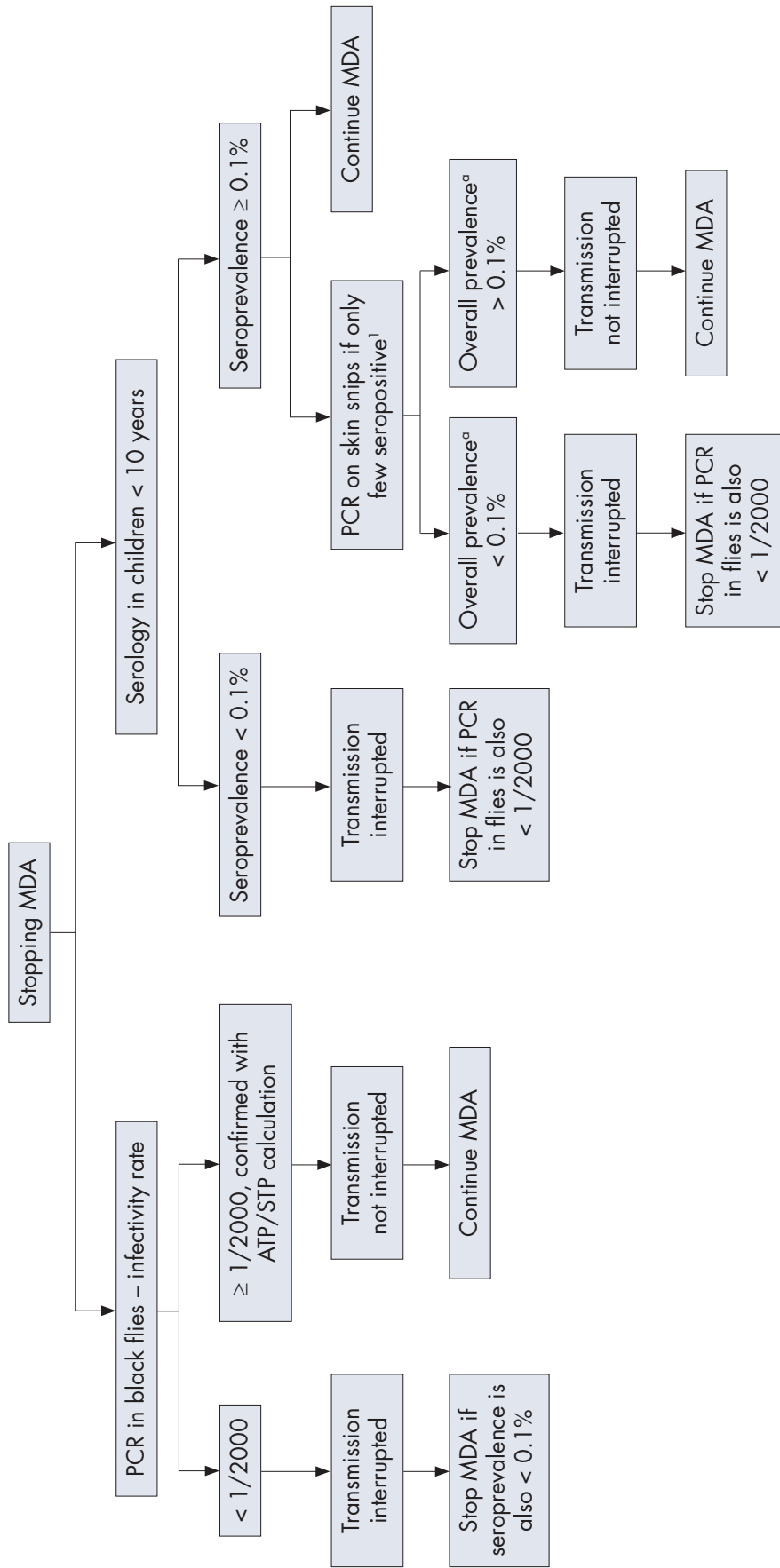
9.2.1 Step 1

Before initiating post-treatment surveillance, the health ministry establishes a national oversight committee to review programme data and validate that the criteria for interruption of transmission have been met. The committee should be independent from the national programme and comprise national and international experts, in accordance with practice in some countries in Africa (72). This committee can be embedded in any existing national committee for neglected tropical disease activities or onchocerciasis-specific matters.

9.2.2 Step 2

During an annual meeting, the national oversight committee advises its respective health ministry to stop MDA according to the recommendations contained in these guidelines. The decision to stop MDA, based on the results of entomological (O-150 PCR Poolscreen) and serological (Ov-16) testing, is summarized by the decision tree in *Figure 2*. These tests are conducted 12 months after the last round of MDA and at the peak period of parasite transmission. After a PTS period of 3–5 years, and on the advice of the national oversight committee, interruption of transmission is confirmed, by entomological (O-150 PCR Poolscreen) test and if necessary, by additional serological (Ov-16) testing. An algorithm on O-150 PCR testing has been incorporated into a flow chart of programmatic decision points including reimplementing of programme measures (*Figure 3*).

Figure 2 Decision tree for stopping MDA as elimination programmes transition from phase 1 (treatment) to phase 2 (post-treatment surveillance) using both PCR in black flies and serology in children aged under 10 years

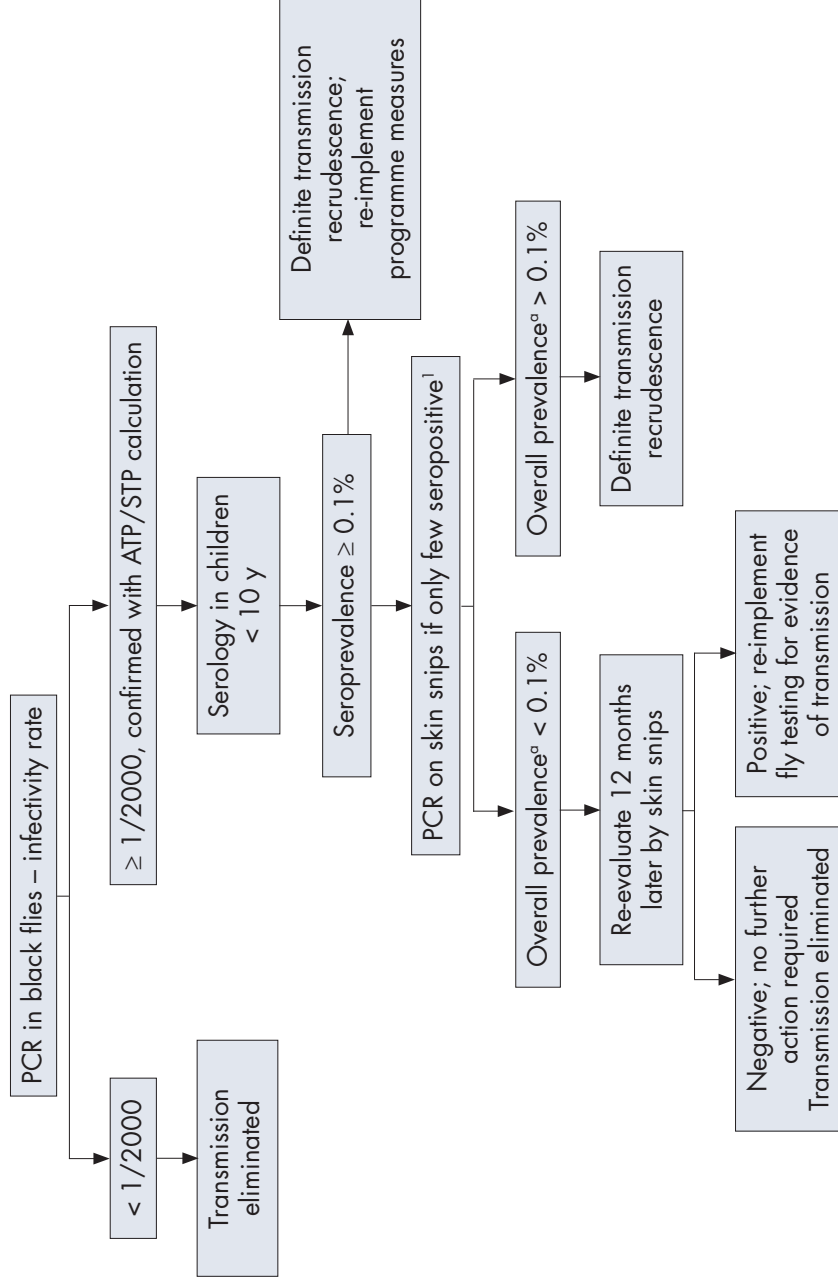


ATP, annual transmission potential; MDA, mass drug administration; PCR, polymerase chain reaction; PTS, post-treatment surveillance; STP, seasonal transmission potential

¹ Few is defined here as below 10.

^a Overall prevalence: the number of seropositive children minus the number of seropositive children who tested negative at PCR on skin snips, divided by the number of children who were tested for serology.

Figure 3 Post-treatment surveillance decision tree for the detection, confirmation and response to a potential recrudescence event (modified from Program Coordinating Committee and OEPA Staff, 2012 (20))



ATP, annual transmission potential; MDA, mass drug administration; PCR, polymerase chain reaction; PTS, post-treatment surveillance; STP, seasonal transmission potential

¹ Few is defined here as below 10.

^a Overall prevalence: the number of seropositive children minus the number of seropositive children who tested negative at PCR on skin snips, divided by the number of children who were tested for serology.

The 3–5 years of post-treatment surveillance can be extended in areas where lymphatic filariasis is coendemic and ongoing treatment for this disease may continue after the decision to stop MDA for onchocerciasis has been justified (73). Furthermore, because the risk of reintroduction of infection exists it is likely that within a single country, or among WHO regions, interventions may stop at different times. The two most relevant risk factors for reintroduction of infection are dispersal of infected flies, which may be transported via wind currents from endemic areas, and infected persons emigrating from endemic areas with active transmission to cleared areas. Referring to migration, other factors such as political instability in neighbouring countries may also increase the risk of recrudescence of parasite transmission, highlighting the need to address cross-border issues.

Under normal circumstances, post-treatment surveillance ends in 3–5 years. This supports the three recommendations on confirmation of the interruption of transmission (see sections 8.2.1–8.2.3). This is based on O-150 PCR testing. In the case of insufficient or absence of flies, then the Ov-16 serology test should be used.

9.2.3 Step 3

At the end of post-treatment surveillance, the independent national oversight committee reviews all the data assembled by the country programme, either countrywide or by individual foci or transmission zone. Once the committee has made its assessment and is satisfied that its findings agree with the present verification guidelines and that the risk of re-introduction or recrudescence of infection no longer exists, the secretariat of the national programme prepares a country report (dossier) according to the format in *Annex 5* and contacts WHO to begin the verification process.

9.2.4 Step 4

The Ministry of Health submits the dossier to WHO through the Country Office and the Region, in order to start the verification process by an international verification team.

9.3 THE INTERNATIONAL VERIFICATION TEAM

After receipt of the country report, WHO constitutes an international verification team to independently assess the dossier on its behalf, including a country field visit, and recommends to WHO that it either supports or rejects the national assessment of transmission interruption and therefore the national claim of interruption of transmission of the onchocercal parasite.

9.4 ACKNOWLEDGEMENT OF ELIMINATION

Elimination status can be granted to a country only by the WHO Director-General after all detected foci under long-term, continuous ivermectin treatment have been verified as free of transmission, and after sufficient evidence has been provided that all areas of potential transmission have been identified, and therefore that transmission of *O. volvulus* can be excluded to occur any longer in that country based on the report of the international verification team.

9.5 CONCLUSION

Elimination of transmission of *O. volvulus* cannot be verified until a sufficient number of years of treatment with ivermectin and post-treatment surveillance has been concluded.

In certain situations where transmission continues in neighbouring countries, WHO may decide not to grant a country acknowledgement of elimination until areas immediately surrounding that country have interrupted transmission.

10 POST-ELIMINATION SURVEILLANCE (PHASE 3)

If elimination is documented through (i) appropriate testing of black flies and (ii) corroborated through serological evaluation of children under 10 years of age as necessary, the national programme establishes a post-elimination surveillance system to detect possible renewal of parasite transmission (recrudescence or reintroduction) both in previously endemic and in non-endemic areas as well as in areas where imported cases might be expected to occur. Such post-elimination surveillance can be centred on entomological assessments by the demonstration of the absence of infective-stage larvae of *O. volvulus* in the vector population as determined by O-150 PCR using *O. volvulus*-specific DNA probes. Such assessments should be conducted at regular intervals until elimination is verified in all countries in the relevant WHO region, or at least until any risk of recrudescence or reintroduction can substantially be excluded.

11 FUTURE CONSIDERATIONS

11.1 REVISION

It is anticipated that new discoveries, such as improved diagnostic assays or new interventions, will be forthcoming. These innovations should be tested and validated under field conditions for applicability and, if shown to be suitable, incorporated into the revised version of these guidelines for future consideration by 2020.

In addition, further clarification on co-endemicity of onchocerciasis and lymphatic filariasis will likely emerge over the ensuing years as more and more programmes encounter this situation and specific lessons are drawn.

11.2 MODELLING

The metrics derived for the control of onchocerciasis have been supported extensively by both field and modelling-based research. The models most widely used by control programmes are ONCHOSIM (74), SIMON (75) and the EuSimon model refined for the Americas and currently used by the OEPA. Various independent approaches have examined several questions relevant to elimination, such as the persistence of onchocerciasis under different ecological conditions or the feasibility of elimination under vector control and MDA (76–82). Although these investigations have improved understanding of onchocerciasis control and elimination, current and future strategies still face new challenges that must be addressed. These include the potential effect of macrofilaricides on long-term mass distribution of ivermectin and the extent to which this intervention shortens the duration of annual, twice yearly or quarterly MDA until elimination. The refinement of these models by sufficient, good-quality data will improve the prediction of elimination of human onchocerciasis in the future.

12 DISSEMINATION AND EVALUATION OF THE EFFECT OF IMPLEMENTING THE GUIDELINES

These guidelines will be issued and launched at a suitable event on control and elimination of neglected tropical diseases, for maximum visibility.

The WHO secretariat will work closely with neglected tropical disease focal points in the regional offices in Africa, the Americas and the Eastern Mediterranean, in collaboration with their counterparts within country offices of all onchocerciasis-endemic countries, to ensure wide dissemination of the guidelines to end-users, including national programme managers and their respective implementing partners. The guidelines will also be available electronically on the WHO website in an easily downloadable version.

The effect of implementation will be evaluated by the number of foci that have met the elimination targets of the WHO Roadmap on neglected tropical diseases (83) on an annual basis by using these guidelines.

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