



GUIDELINE



ALTERNATIVE MASS DRUG ADMINISTRATION
REGIMENS TO ELIMINATE LYMPHATIC FILARIASIS



World Health
Organization

GUIDELINE

Alternative mass drug administration
regimens to eliminate lymphatic filariasis

Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis

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Abbreviations

AE	adverse event
<i>Brugia</i> spp.	<i>Brugia malayi</i> and <i>Brugia timori</i> species
CFA	circulating filarial antigen
DA	diethylcarbamazine (citrate) plus albendazole
FTS	Filariasis Test Strip (Alere, Scarborough, ME, USA)
GPELF	Global Programme to Eliminate Lymphatic Filariasis
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IA	ivermectin plus albendazole
ICT	immunochromatographic test (BinaxNOW Filariasis ICT, Alere, USA)
IDA	ivermectin plus diethylcarbamazine (citrate) plus albendazole
IgG4	IgG4 antibody to BmR1 antigen of <i>Brugia</i> species
IU	implementation unit
LF	lymphatic filariasis
MDA	mass drug administration
PICO	population, intervention, comparator and outcome
pre-TAS	pre-transmission assessment survey
RCT	randomized controlled trial
SAE	serious adverse event
TAS	transmission assessment survey
WHO	World Health Organization

Glossary

The definitions given below apply to the terms as used in this guideline. They may have different meanings in other contexts and WHO documents. An asterisk (*) next to terms denotes definition of outcomes assessed in the development of recommendations.

adverse event (AE) following mass drug administration (MDA)*

A medical incident occurring after mass drug administration that is suspected to be but is not necessarily caused by the medicines used in the intervention. Some AEs, after investigation, may be found to have been caused by the medicine and are also referred to as adverse drug reactions or side-effects.

Note: AEs are often categorized by severity in clinical studies. While the grade of severity may vary, the following classifications were used for the outcomes reviewed in these comparisons:

- Grade 1 – a mild adverse event that does not interfere with work or school;
- Grade 2 – a moderate adverse event that interferes with work or school for at least 1 day;
- Grade 3 – a severe and undesirable adverse event that interferes with the activities of daily living and requires medical assessment;
- Grade 4 – a potentially life-threatening or disabling adverse event that requires medical evaluation and a serious adverse event report; and
- Grade 5 – a catastrophic adverse event that causes death.

During the process of formulating the recommendations, the following designations were given to the outcomes of adverse event and serious adverse event:

- Critical – serious adverse events (Grade 4 and 5), adverse events (Grade 3 and 4) and adverse events (Grade 2 to 4) in communities with no prior MDA;
- Important – adverse events (Grade 2 to 4) among microfilaraemic persons, any adverse events in microfilaraemic persons and adverse events (Grade 2); and
- Not important – any adverse event not addressed above.

antibody

A protein produced by the human immune system in response to a foreign substance (antigen) to fight off infection. An antibody reacts specifically with the antigen that triggered its formation and its function is to facilitate removal of the antigen from the body.

antigen

Any foreign substance that stimulates the human immune system to produce antibodies.

antigenaemia

Presence of circulating filarial antigen of adult *Wuchereria bancrofti* in human blood.

at-risk population

Total population in the endemic implementation unit(s).

***Brugia malayi* area, *Brugia timori* area, *Wuchereria bancrofti* area**

Geographical areas with established transmission of the disease caused by the respective parasite.

chyluria

Presence of chyle in human urine as a result of organic disease (as of the kidney) or obstruction of lymph flow from ruptured lymph vessels.

circulating filarial antigen (CFA)*

Antigen released by adult *Wuchereria bancrofti* circulating in human blood that can be detected by laboratory immunoassays and rapid diagnostic tests such as the BinaxNOW Filariasis immunochromatographic test (ICT) and the Alere Filariasis Test Strip (FTS).

Designated as an important outcome in the recommendation formulation process.

circulating filarial antigen (CFA) reduction*

Percentage reduction in the prevalence of CFA as detected by the ICT or the FTS.

Designated as an important outcome in the recommendation formulation process.

clinical case of lymphatic filariasis (LF)

Case in a resident of, or long-term visitor to, an endemic area with hydrocele, chylocele, lymphoedema (elephantiasis), chyluria, haematochyluria, haematuria, hypereosinophilia or tropical pulmonary eosinophilia syndrome for which other causes have been excluded.

complete microfilaraemia clearance*

Occurrence of zero microfilariae detected in sampled blood following treatment.

Designated as a critical outcome in the recommendation formulation process.

critical cut-off threshold

The threshold of infection prevalence below which transmission is likely no longer sustainable, even in the absence of control interventions. A value of the number of cases that are antigen-positive or antibody-positive representing this threshold is calculated based on the sample size of the transmission assessment survey.

disability

Inability to adequately or independently perform routine daily activities such as walking, bathing and toileting; also the negative aspects of the interaction between a person with a health condition and his or her context (environmental and personal factors).

drug coverage

Proportion of individuals in a targeted population who swallowed a medicine or a combination of medicines. Drug coverage is expressed as a percentage.

effective coverage

Coverage of medicines during MDA where at least 65% of the total population ingested the medicine or combination of medicines.

elephantiasis

Severe or advanced lymphoedema.

elimination as a public health problem

The achievement of specific and measurable targets for infection and disease set by the World Health Organization for which continued actions are required to maintain elimination status. Surveillance will be required to ensure that the prevalence of infection remains below target thresholds and to verify interruption of transmission.

endemic area

Implementation unit where correct sampling of the population has a positivity rate for antigenaemia or microfilaraemia equal to or greater than 1%.

epidemiological coverage

Proportion of individuals who ingested the medicines during MDA among the total population in the implementation unit. The minimum epidemiological coverage considered effective for reducing LF transmission is 65% or greater.

filarial infection

Presence of adult filarial worms in human lymphatic vessels or of microfilariae in human blood.

geographical coverage

Proportion of administrative units that are implementing MDA of all those that require MDA.

hydrocele

Excess fluid inside the human scrotal sac that causes the scrotum to swell or enlarge.

IgG4 reduction*

Percentage reduction in IgG4 antibody to specific filarial antigens. Use of IgG4 in this document refers to antibody to BmR1 antigen of *Brugia malayi*.

Designated as an important outcome in the recommendation formulation process.

implementation unit (IU)

The smallest administrative unit in a country which is used as the basis for making decisions about implementing MDA. The IU must be defined before mapping takes place. For LF, the implementation unit is normally the district.

inactive adult worm nests*

Number of adult worm nests identified in human lymphatic vessels using ultrasonography that no longer exhibit the filarial dance sign.

Designated as an important outcome in the recommendation formulation process.

ineligible population

Group of individuals not qualified or entitled to receive anthelmintic treatment in MDA interventions. Ineligibility is usually determined by exclusion criteria based on drug safety.

interruption of transmission of lymphatic filariasis

Reduction in the prevalence of infection to a level where continued transmission and recrudescence are not expected.

lymphatic filariasis (LF)

A parasitic disease of humans caused by infection with nematodes (worms) of the Filarioidea family. *Wuchereria bancrofti* cause the majority (90%) of infections, which are mostly acquired in childhood; *Brugia malayi* and *Brugia timori* cause the remainder. *Anopheles*, *Aedes*, *Culex* and *Mansonia* mosquitoes are the main vectors responsible for transmission. Mosquitoes serve as biological hosts that both develop and transmit the parasite during blood-feeding and establish the infection in humans.

lymphatic system

The network of nodes and vessels that maintain the delicate fluid balance between the tissues and blood in humans. The lymphatic system is an essential component of the body's immune defence system.

lymphoedema

Swelling caused by the collection of fluid in tissue.

macrofilaricide (for LF)

A medicine that displays destructive properties against the adult worms in the body of people with LF.

mass drug administration (MDA)

A modality of preventive chemotherapy in which anthelmintic medicines are administered to the entire eligible population of an area (e.g. state, region, province, district, subdistrict, village) at regular intervals, irrespective of the individual infection status.

MDA round

Distribution of antifilarial medicines to the target population during a defined time period. Because MDA may not be conducted simultaneously throughout a country, an MDA round may take 1–2 weeks or longer before being completed at national level. An “effective MDA round” or reaching “effective coverage” during an MDA round is defined by epidemiological coverage of at least 65% in an implementation unit.

microfilaraemia

Presence of microfilariae in the blood.

microfilarial density (geometric mean)*

Estimated intensity of infection based on the number of microfilariae per millilitre of blood in an individual.

Designated as an important outcome in the recommendation formulation process.

microfilaraemia prevalence*

Proportion of persons with microfilariae in their blood. Microfilaraemia prevalence is expressed as a percentage.

Designated as an important outcome in the recommendation formulation process.

microfilaraemia prevalence reduction*

Percentage reduction in the prevalence of microfilaraemia.

Designated as an important outcome in the recommendation formulation process.

microfilariae

Microscopic larval stage of filarial parasites that circulate in the blood and are transmitted by mosquitoes.

microfilaricide (for LF)

A medicine that displays destructive properties against microfilariae in the blood of people infected with filarial parasites.

morbidity

Clinical consequences of infections and diseases that adversely affect the health of individuals. Lymphatic filariasis causes chronic morbidity through damage to the lymphatic system, kidneys, arms, legs or genitals (especially in men).

neglected tropical diseases

A group of primarily infectious diseases that thrive in impoverished settings, especially in the heat and humidity of tropical climates. These diseases have been largely eliminated elsewhere and thus are often forgotten. They include: Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis, echinococcosis, foodborne trematode infections, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, mycetoma, onchocerciasis, rabies, schistosomiasis, soil-transmitted helminth infections, taeniasis and cysticercosis, trachoma and yaws (endemic treponematoses).

pharmacovigilance

The science of and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible problems related to medicines. Pharmacovigilance is an aspect of patient care that aims to optimize the use of medicines in order to treat or prevent disease. Good pharmacovigilance identifies risks and risk factors in the shortest possible time to avoid or minimize harm.

pre-transmission assessment survey (pre-TAS)

Follow-up assessments of sentinel and spot-check sites after five effective MDA rounds. An IU passes pre-TAS when the prevalence of infection has been reduced to less than 1% microfilaraemia or less than 2% antigenaemia in sentinel and spot-check sites. If pre-TAS is passed, an IU may progress to the transmission assessment survey (TAS).

sentinel site

A geographical area, with a population of at least 500 people, selected in order to collect parasitological data to monitor the success of the programme. It should remain the same throughout the course of the programme. Sentinel site assessments are conducted (along with spot-check site assessments) at baseline, at the mid-term (optional) and during the pre-TAS survey.

serious adverse events (SAEs) following MDA*

Any untoward medical occurrence that at any dose results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, or is life-threatening. Cancers and congenital anomalies or birth defects should be regarded as serious; medical events that would be regarded as serious if they had not responded to acute treatment should also be considered serious. In the studies reviewed, any Grade 4 or 5 AE or any overnight admission to a health facility was considered an SAE.

Designated as a critical outcome in the recommendation formulation process.

spot-check site

A geographical area, with a population of at least 500 people, selected in order to collect parasitological data to complement data collected in sentinel sites. Spot-check sites should be chosen for each assessment and will change over the course of the programme. Spot-check sites (and sentinel sites) are assessed at baseline, at the mid-term and during the pre-TAS survey.

surveillance

The ongoing, systematic collection and evaluation of data describing the occurrence and spread of disease; also the part of the programme that aims to discover, investigate and eliminate continuing transmission, prevent and cure infections and, finally, substantiate the claimed absence of transmission.

target population (for LF the target population is the eligible population)

Population in an implementation unit that is targeted for treatment. In the context of lymphatic filariasis, the target population for MDA is the same as the population eligible to receive the medicines, according to the criteria for drug safety, which is usually 80–90% of the total population.

transmission assessment survey (TAS)

A survey designed to measure whether evaluation units have lowered the prevalence of infection to a level where recrudescence is unlikely to occur, even in the absence of MDA interventions. TAS is a decision-making tool to determine when MDA can stop.

validation (of the elimination of LF as a public health problem)

Validation is the process used to document the elimination of LF as a public health problem. A validation dossier is submitted to and approved by WHO. Validation is not a permanent state and does not represent an end to programme activities. While some activities, such as MDA, may no longer be required, programmes should continue to undertake post-validation surveillance and ensure the minimum package of care for patients remains available within the health care system.

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Guideline development group

The guideline development group was chaired by Margaret Gyapong, social scientist (Ghana Health Service, Ghana). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodologist and the meeting co-chair was Mohammed Toseef Ansari (University of Ottawa, Canada). Membership of the group comprised the following experts: Luccene Desir, epidemiologist and LF elimination programme specialist (The Carter Center, Haiti), Améyo Dorkenoo, national neglected tropical disease coordination and LF elimination programme management (Université de Lomé, Togo), Deirdre Hollingsworth, mathematical modeller (University of Warwick, United Kingdom), John Horton, scientist parasitology (Consultant, United Kingdom), Amy Klion, scientist immunology (National Institutes of Health, United States of America), Nilima Kshirsagar, clinical pharmacology (Indian Council of Medical Research, India), Deborah McFarland, health economist (Emory University, United States of America), Sammy Njenga, scientist parasitology (Kenya Medical Research Institute, Kenya), Rahmah Noordin, scientist immunology (Universiti Sains Malaysia, Malaysia), Melissa Parker, medical anthropologist (London School of Hygiene & Tropical Medicine, United Kingdom), Kapa Ramaiah, epidemiologist (Consultant, India), Reda Ramzy, scientist (National Nutrition Institute, Egypt) and Nupur Roy, scientist and LF elimination programme management (Ministry of Health and Family Welfare, India).

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Contributors to the systematic reviews

The following researchers contributed to the coordination of the systematic reviews and the development of the evidence profiles and GRADE tables: Xavier Bosch-Capblanch (Swiss Tropical and Public Health Institute, Switzerland) led the team and conducted the statistical analysis, Amanda Ross (Swiss Tropical and Public Health Institute, Switzerland) conducted the statistical analysis, Meike Zuske (Swiss Tropical and Public Health Institute, Switzerland) coordinated the review, Peter Steinmann (Swiss Tropical and Public Health Institute, Switzerland) and Jonathan King (WHO, Switzerland) were the experts on LF. The following researchers conducted the systematic review: Ekpereonne Esu (University of Calabar, Nigeria) conducted the effectiveness and safety review, Chioma Moses Oringanje (University of Calabar, Nigeria) conducted the effectiveness and safety review, and Heather Ames (Swiss Tropical and Public Health Institute, Switzerland) conducted the qualitative scoping synthesis. The search strategist was John Eyers (Swiss Tropical and Public Health Institute, Switzerland).

Coordination

Jonathan King (WHO, Switzerland) coordinated the guideline development process.

WHO steering committee

The WHO steering committee comprised the following staff: Jonathan King (Scientist and Focal Point, Lymphatic Filariasis Elimination, Preventive Chemotherapy and Transmission Control, Department of Control of Neglected Tropical Diseases, Switzerland), Piero Olliaro (Team Leader, Intervention and Implementation Research, Special Programme for Research and Training in Tropical Diseases, Switzerland), Shanthi Pal (Group Lead, Safety and Vigilance: Medicines, Essential Medicines and Health Products, Switzerland), Azadeh Baghaki (Technical Officer, Neglected Tropical Diseases Strategy Development and Implementation, Switzerland), Christopher Fitzpatrick (Health Economist, Department of Control of Neglected Tropical Diseases, Switzerland), Benido Impouma (Adviser, Neglected Tropical Diseases, WHO Regional Office for Africa), Santiago Nicholls (Regional Advisor, National Immunization Day, WHO Regional Office for the Americas), Albis Gabrielli (Regional Advisor, Neglected Tropical Diseases, WHO Regional Office for the Eastern Mediterranean), Mohamed Jamsheed (Regional Advisor, Neglected Tropical Diseases, WHO Regional Office for South-East Asia) and Rabindra Abeyasinghe (Coordinator, Malaria, Other Vectorborne and Parasitic Diseases, WHO Regional Office for the Western Pacific).

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Other contributors

Emily Toubali (Consultant, United States of America) and Jonathan King (WHO, Switzerland) wrote the guideline. Additional input was provided by Mohammed Toseef Ansari (University of Ottawa, Canada) and Gautam Biswas (WHO, Switzerland). Elie Akl (American University of Beirut, Lebanon) provided initial insight into the development of the research questions, evidence to decision tables and

organization of evidence to address all domains of the evidence to decision tables. Drafts were reviewed and additional contributions provided by the guideline development group, the external peer review group and the WHO steering committee. Susan Norris (WHO Guidelines Review Committee Secretariat) provided valuable guidance throughout the process. The Guidelines Review Committee contributed important feedback that was incorporated into the final version of the guideline.

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External partners

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GUIDELINE:¹

Alternative mass drug administration regimens to eliminate lymphatic filariasis

Executive summary

Lymphatic filariasis is a vector-borne neglected tropical disease that causes damage of the lymphatic system and can lead to lymphoedema (elephantiasis) and hydrocele in infected individuals. The global baseline estimate of persons affected by lymphatic filariasis is 25 million men with hydrocele and over 15 million people with lymphoedema. At least 36 million persons remain with these chronic disease manifestations. The disease is endemic in 72 countries. In 2016, an estimated total population of 856 million were living in areas with ongoing transmission of the causative filarial parasites and requiring mass drug administration (MDA).² Lymphatic filariasis disfigures and disables, and often leads to stigmatization and poverty. Hundreds of millions of dollars are lost annually due to reduced productivity of affected patients. WHO has ranked the disease as one of the world's leading causes of permanent and long-term disability.

In 1997, the Fiftieth World Health Assembly resolved to eliminate lymphatic filariasis as a public health problem. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched by WHO in 2000 with the goal to achieve global elimination of the disease as a public health problem by 2020. The comprehensive elimination strategy promoted by GPELF comprises annual MDA to achieve interruption of transmission, and morbidity management and disability prevention to prevent and alleviate the suffering of affected individuals.

Since 2000, annual coverage of MDA has expanded from 3 million people in 12 countries to 6.7 billion cumulative treatments delivered to over 850 million persons in 66 of the 72 countries where the disease is known to be endemic. At least 20 (28%) endemic countries are now under post-MDA surveillance to demonstrate that elimination has been achieved. Despite progress, 22 of 52 (42%) endemic countries requiring MDA have not started MDA in all of their endemic implementation units. Additionally, some countries that have completed five effective MDA rounds are now grappling with suboptimal assessment results. Clearly, global elimination by 2020 will not be achieved using the existing regimens. This guideline therefore serves as a response to countries that have requested WHO to devise alternative regimens to realign their national programmes towards elimination by 2020.

¹ This publication is a World Health Organization (WHO) guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A standard guideline is produced in response to a request for guidance in relation to a change in practice, or controversy in a single clinical or policy area; it is not expected to cover the full scope of the condition or public health problem. A recommendation provides information about what policy-makers, health-care providers or patients should do; it implies a choice between different interventions that have an impact on public health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

² Global programme to eliminate lymphatic filariasis: progress report, 2016. *Wkly Epidemiol Rec.* 2017;92:594–607.

The guideline was developed in accordance with the procedures established by the WHO Guidelines Review Committee and the WHO handbook for guideline development published in 2014. A WHO steering committee was formed to develop the PICO (population, intervention, comparator and outcome) questions and the scope of the guideline. A guideline development group reflecting diverse areas of expertise, multiple geographical regions and gender balance was formed and contributed to the refinement of the PICO questions. A systematic review team was externally commissioned to conduct a systematic review, meta-analysis and critical appraisal of the evidence.

At a meeting of the guideline development group (Geneva, May 2017) the available evidence was carefully reviewed and recommendations were formulated based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Two alternative regimens for MDA to eliminate lymphatic filariasis were considered: (i) a three-drug regimen (ivermectin, diethylcarbamazine and albendazole) instead of the current two-drug regimens (diethylcarbamazine and albendazole or ivermectin and albendazole); and (ii) biannual MDA with the current two-drug regimens, and albendazole instead of annual MDA with the same regimens. The assessment of the evidence included the priority of the problem, benefits and harms, certainty and quality of the evidence, resource implications, equity, acceptability and feasibility.¹ Based on the evidence appraised during the meeting, recommendations for alternative regimens were formulated for different epidemiological and technical situations (Table 1). The final guideline was reviewed by the WHO steering committee, the guideline methodologist, the guideline development group and the peer reviewers before submission to the WHO Guidelines Review Committee.

Chapters 1 and 2 provide the context for the justification of alternative regimens and the methodology and process for developing the guideline using the GRADE approach. Chapters 3 and 4 outline the recommendations of the guideline development group, the details of the GRADE approach and the evidence to decision process employed in the formulation of the recommendations. Chapter 5 details WHO's plan to disseminate, implement, and monitor and evaluate the guideline.

¹ The recommendations contained in this guideline were made independently of the donation potential of the various antifilarial medicines.

Table 1. WHO recommendations on alternative MDA regimens to eliminate lymphatic filariasis

In countries using DA to eliminate lymphatic filariasis (endemic for lymphatic filariasis but without either onchocerciasis or loiasis)		
Recommendation	Strength of recommendation	Quality of evidence
WHO recommends annual IDA rather than annual DA in the following special settings: <ul style="list-style-type: none"> • for IUs that have not started or have fewer than four effective rounds of DA; • for IUs that have not met the epidemiological thresholds in sentinel and spot-check site surveys or in transmission assessment surveys despite meeting drug coverage targets; and • for communities where post-MDA or post-validation surveillance identified infection suggesting local transmission. 	Conditional recommendation	Low
WHO recommends annual DA rather than biannual DA.	Conditional recommendation	Low
In countries using IA to eliminate lymphatic filariasis (endemic for lymphatic filariasis and either having onchocerciasis or being co-endemic for loiasis)		
Recommendation	Strength of recommendation	Quality of evidence
(Onchocerciasis endemic in any part of the country) WHO recommends annual IA rather than annual IDA.	Conditional recommendation	Low
(Onchocerciasis endemic in any part of the country) WHO recommends annual IA rather than biannual IA, except in areas where biannual distribution of ivermectin is already being delivered for onchocerciasis.	Conditional recommendation	Very low
WHO recommends biannual albendazole rather than annual albendazole in IUs where LF is co-endemic with loiasis and ivermectin has not already been distributed for either onchocerciasis or LF.	Conditional recommendation	Very low

DA, diethylcarbamazine + albendazole; IA, ivermectin + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IU, implementation unit; LF, lymphatic filariasis; MDA, mass drug administration

1. Background

Lymphatic filariasis (LF) is a vector-borne neglected tropical disease caused by infection with the filariae *Wuchereria bancrofti*, *Brugia malayi* and *Brugia timori* (*Brugia* spp.). The adult worms live in the lymphatic system of humans. After mating, the female worms produce several thousand larvae (microfilariae), which circulate in the peripheral blood at times that coincide with the biting activity of the mosquito vectors. The microfilariae are ingested by the mosquitoes during blood-feeding, develop inside the insects and are transmitted when the infected mosquito bites other human hosts (1). Filarial infection may be clinically asymptomatic or present as one or more acute manifestations, including fever, local swelling, tropical pulmonary eosinophilia syndrome and lymphangitis. Chronic complications include lymphoedema (elephantiasis) of the limbs, damage to the scrotum in men (hydrocele), damage to the kidney (including chyluria) and damage to the lymphatic system (1, 2).

An estimated 1 billion people in 72 countries live in areas where the disease is endemic, including at least 36 million people who are affected by the associated morbidity (3, 4). Reduced productivity experienced by patients results in hundreds of millions of dollars in economic losses each year (3, 5, 6). The disease is not fatal. However, WHO has ranked it as one of the world's leading causes of permanent and long-term disability (7, 8).

In 1997, the Fiftieth World Health Assembly resolved to eliminate LF as a public health problem, with resolution WHA50.29 urging WHO Member States "... to take advantage of recent advances in the understanding of lymphatic filariasis and the new opportunities for its elimination by developing national plans..." and "... to improve clinical, epidemiological and operational activities directed towards eliminating lymphatic filariasis as a public health problem" (9). In response, the Global Programme to Eliminate Lymphatic Filariasis (GPELF) was launched by WHO in 2000 with a comprehensive two-pronged strategy to achieve the elimination target by 2020: (i) interrupt transmission through annual mass drug administration (MDA) targeting the eligible population; and (ii) implement morbidity management and disability prevention to prevent and alleviate the suffering of affected individuals (8, 10–12).

Elimination of LF as a public health problem is operationally defined as reducing infection to levels at which transmission is no longer sustainable and ensuring the availability of a WHO-recommended basic package of care to manage lymphoedema and hydrocele. The following measurable elimination thresholds must be demonstrated before stopping MDA: (i) microfilaraemia prevalence of less than 1% or antigenaemia prevalence of less than 2% in sentinel and spot-check surveys; and (ii) incident infection below 1% or 2%¹ measured during the transmission assessment survey (TAS) (8). Documentation that these infection thresholds have been met for at least 4 consecutive years after MDA has been discontinued is required to validate the claim of elimination (13). Follow-up surveys in sentinel and spot-check sites, also known as pre-TAS, are recommended after five MDA rounds and the results used to determine eligibility for implementing TAS.

The regimens recommended by WHO for MDA to eliminate LF (LF MDA) using the antifilarial medicines listed below (Box 1) are administered annually for the duration of the reproductive lifespan of adult worms. Microfilaricides display destructive properties against the microfilariae, but some have a limited

¹ Incident infection of < 1% antigenaemia in areas where *Wuchereria bancrofti* is transmitted by *Aedes* spp.; < 2% antigenaemia for *W. bancrofti* and other vectors; and < 2% antibody prevalence for filariasis due to *Brugia* spp. (8).

effect on the adult parasite (14–16). All are designated antihelminthics in the *WHO model list of essential medicines* (17). MDA plays a role in primary prevention by decreasing and reducing transmission rates in populations at risk. Additionally, MDA can prevent progression from subclinical to clinical disease and worsening morbidity, thereby yielding economic savings at the community level and enhanced productivity from healthier individuals (2, 18). The effectiveness of the MDA strategy depends on epidemiological coverage, which is defined as the proportion of the total population ingesting the medicines during MDA. WHO considers at least 65% epidemiological coverage to be an effective MDA round. In programmes where drug coverage is poor or where transmission is particularly intense, more than five MDA rounds are needed to lower levels of infection below elimination thresholds (8).

Since the launch of GPELF in 2000, MDA has expanded globally, with 6.7 billion treatments delivered to more than 850 million people at least once. This achievement is the result of strong political will at the country level, unprecedented levels of donor support and coordinated partnership among stakeholders. Annual coverage of MDA using the existing regimens recommended by WHO has expanded from 3 million people in 12 countries to just under 700 million people in 63 countries, representing a greater than 200-fold increase in people treated and a more than 5-fold increase in countries treated in 15 years (3, 8). Of the 72 endemic countries, 20 (28%) have successfully implemented the recommended strategies, discontinued MDA and are under surveillance to demonstrate that elimination has been achieved (3). Programme interventions through 2015 are estimated to have prevented or cured more than 97 million cases of the disease and to have averted more than US\$ 100 billion in economic losses over the lifetime of those who have benefitted (4, 25).

Box 1. Existing WHO recommendations for MDA to eliminate lymphatic filariasis

1. Annual MDA of diethylcarbamazine (6 mg/kg) with albendazole (400 mg) in communities without onchocerciasis (19) – this regimen is denoted as DA
 - *Eligible population.* The entire population at risk of LF transmission; i.e. the entire population in an area where LF transmission occurs (implementation unit), except those excluded (see *ineligible population*).
 - *Ineligible population.* Pregnant women, children aged < 2 years and the severely ill (1, 20); diethylcarbamazine is contraindicated in areas co-endemic for onchocerciasis and loiasis (19).

2. Annual MDA of ivermectin (150–200 µg/kg) with albendazole (400 mg) in communities where LF and onchocerciasis are co-endemic – this regimen is denoted as IA
 - *Eligible population.* The entire population at risk of LF transmission; that is, the entire population in an area where LF transmission occurs (implementation unit), except those excluded (see *ineligible population*).
 - *Ineligible population.* Pregnant women, children < 90 cm in height (approximately equivalent to < 15 kg body weight) and the severely ill (1, 11, 20–22). Use of ivermectin for LF is contraindicated in areas co-endemic for loiasis and is used restrictively for onchocerciasis based on potential serious adverse events in loiasis patients (11, 23).

3. Annual but preferably biannual MDA of albendazole (400 mg) in communities where loiasis is co-endemic – this provisional regimen is denoted as albendazole (24)
 - *Eligible population.* The entire population at risk of LF transmission; i.e. the entire population in an area where LF transmission occurs (implementation unit), except those excluded (see *ineligible population*).
 - *Ineligible population.* Pregnant women in the first trimester of pregnancy, children aged < 2 years and individuals with a history of neurocysticercosis or seizures (1, 20).

Despite the dramatic expansion of LF MDA in endemic countries and the progress made under GPELF, 22 of 52 (42%) countries remain endemic and require MDA but have not started MDA in all of their endemic implementation units [IUs] (3). Because at least five effective MDA rounds are needed, achieving the elimination target in these countries by 2020 is unlikely. Additionally, countries with IUs that have already achieved five effective MDA rounds are grappling with assessment results that reveal suboptimal responses to current MDA regimens (3). Given the current status of GPELF countries, achieving global elimination of LF by 2020 is no longer technically feasible using the existing regimens. Countries have therefore requested guidance from WHO on how to realign their national programmes towards achieving the 2020 target. In response, WHO has evaluated the available evidence on alternative regimens and employed a rigorous guideline development process (Chapter 2) for recommending alternative LF MDA regimens to eliminate the disease (Chapters 3 and 4). With the global 2020 target on the horizon, this guideline is part of the intensified efforts required to realign countries endemic for LF on the path towards elimination.

1.1. Objective of the guideline

The consideration of alternative LF MDA regimens focused on a three-drug regimen of antifilarials comprising ivermectin, diethylcarbamazine and albendazole (IDA) compared to the current DA and IA regimens; and biannual MDA with DA, IA and albendazole compared to annual MDA with the same regimens. This document provides endemic countries with the option of using recommended alternative MDA regimens where warranted. Table 2 summarizes existing and alternative recommendations for national programmes that take into account specific epidemiological situations of co-endemicity with onchocerciasis and loiasis at both the country and IU levels.

While this guideline was written to be applicable in all LF epidemiological situations, it is specific in that it focuses only on LF MDA. It does not cover any of the other important public health interventions targeted for LF, including morbidity management and disability prevention, vector control, health education, and details on comprehensive monitoring and evaluation for the various LF interventions. Guidance qualifying these aspects of implementation for LF elimination has already been published by WHO.¹

¹ This guideline on alternative MDA regimens to eliminate LF was designed to complement the following published WHO guidelines and materials on (i) preparing and implementing a national plan to eliminate LF where onchocerciasis is and is not co-endemic (WHO, 2000), (ii) preparing and implementing a programme for integrated MDA for neglected tropical diseases (WHO, 2006), (iii) provisional guidance on LF treatment in implementation units co-endemic for loa loa from eighth meeting the Strategic Technical and Advisory Group for Neglected Tropical Diseases (WHO, 2015), (iv) monitoring and evaluation of LF across the lifespan of a programme (WHO, 2011), (v) management of serious adverse events in control of neglected tropical diseases (WHO, 2011), (vi) morbidity management and disability prevention strategies for LF (WHO, 2013), (vii) drug coverage evaluation surveys for MDA (WHO, 2016) and (viii) validation of the elimination of LF as a public health problem (WHO, 2017). These documents in their entirety are available at www.who.int.

Table 2. Recommended MDA regimen changes from existing WHO recommendations, by co-endemicity setting

Co-endemic anywhere in the country ^a	Co-endemic in the IU ^a		Existing recommendations (1, 8, 24)	MDA regimen changes under new recommendations
	onchocerciasis	loiasis		
–	–	–	Annual DA	Use annual IDA rather than DA in specified settings; use annual DA in all other settings
+	–	–	Annual IA	No changes to the recommended use of annual IA
+	+	–	Annual IA	Use annual IA; biannual IA may be used as an exception when ivermectin is already being delivered biannually to eliminate onchocerciasis.
+	+ or –	+	Annual, preferably biannual albendazole ^b (provisional recommendation)	Use biannual albendazole

DA, diethylcarbamazine + albendazole; IA, ivermectin + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IU, implementation unit; LF, lymphatic filariasis; MDA, mass drug administration

^a + refers to disease(s) co-endemic with LF; – refers to disease(s) not co-endemic with LF.

^b Recommended regimen for LF MDA in settings where ivermectin has not been distributed to eliminate either LF or onchocerciasis because loiasis is co-endemic (24).

1.2. Guiding principles

The goal of WHO is to ensure the highest attainable level of health for all people globally, while promoting the utmost level of respect for their dignity, worth, equality and diversity (26). This guideline has been developed with this principle in mind, as well as that of the United Nations *Universal Declaration of Human Rights* (27). Many people suffering from LF are socially marginalized and have inadequate access to health care. Those with visible hydrocele and lymphoedema (elephantiasis) in particular are often the victims of discrimination and stigmatization in their communities (28). Decision-makers in countries where the disease is endemic are therefore urged to ensure that this guideline and the policies derived from it incorporate basic human rights, and that the rights of individuals and patients to confidentiality of information and informed decision-making are upheld in accordance with prescribed national ethical guidelines (2).

1.3. Target audience

This guideline presents the summary of evidence that formed the basis of the WHO recommendations contained herein. It is intended to help key decision-makers in countries where LF is endemic determine if, when and how to use alternative MDA regimens. The guideline will be used to inform policy on MDA for LF endemic countries. The target audience includes coordinators of national programmes to control and eliminate neglected tropical diseases, managers of national programmes to eliminate LF, and national committees or technical groups that help programmes make critical programmatic decisions about policy. It is intended for use as a reference document for all stakeholders supporting GPELF, including but not limited to health ministries, WHO, the regional programme review groups, and other technical review bodies, pharmaceutical manufacturers of MDA medicines, bilateral donor organizations, nongovernmental organizations and academic institutions.

1.4. Guideline questions

The WHO steering committee tabled the provisional guideline questions and determined the scope of the guideline. The guideline development group confirmed the scope and further refined the questions. The guideline questions (Tables 3 and 4) were formulated as per the recommended approach with pre-specified PICO (population, intervention, comparator and outcomes) questions. These questions formed the basis for the protocol of the systematic review of the literature and the strategies for the literature searches.

Table 3. PICO questions used in the comparison of alternative versus existing MDA regimens in countries using DA to eliminate lymphatic filariasis

PICO Question 1. Should IDA versus DA be used for annual MDA to eliminate LF in IUs where onchocerciasis is NOT co-endemic?	
Population/setting: LF endemic communities (either <i>Wuchereria bancrofti</i> or <i>Brugia</i> spp.) in countries using DA for the elimination of LF	
Intervention: Annual treatment with IDA	
Comparator: Annual treatment with DA	
Outcomes: Community members with LF infection <ul style="list-style-type: none"> • Complete mf clearance • Microfilarial density (geometric mean) • CFA • AEs Grade 2 to 4 among mf positive persons • Any AEs among mf positive persons 	Outcomes: All community members <ul style="list-style-type: none"> • SAEs • AEs Grade 3 and 4 • AEs Grade 2 • AEs Grade 2 to 4 among communities with no prior MDA • Any AEs
PICO Question 2. Should biannual DA versus annual DA be used for MDA to eliminate LF in IUs where onchocerciasis is NOT co-endemic?	
Population/setting: LF endemic communities (either <i>Wuchereria bancrofti</i> or <i>Brugia</i> spp.) in countries using DA for the elimination of LF	
Intervention: Biannual treatment with DA	
Comparator: Annual treatment with DA	
Outcomes: Community members with LF infection <ul style="list-style-type: none"> • Complete mf clearance • Microfilarial density (geometric mean) • CFA • Inactive adult worm nests 	Outcomes: All community members <ul style="list-style-type: none"> • Mf prevalence reduction • CFA reduction (<i>W. bancrofti</i>) • IgG4 reduction (<i>Brugia</i> spp.)

AE, adverse event; CFA, circulating filarial antigen; DA, diethylcarbamazine + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IU, implementation unit; LF, lymphatic filariasis; MDA, mass drug administration; mf, microfilaraemia; PICO, population, intervention, comparator, outcome; SAE, serious adverse event

Table 4. PICO questions used in the comparison of alternative versus existing MDA regimens in countries co-endemic for onchocerciasis using IA to eliminate lymphatic filariasis

PICO Question 3. Should IDA versus IA be used for annual MDA to eliminate LF in IUs where onchocerciasis is NOT co-endemic?	
Population/setting: LF endemic communities (<i>Wuchereria bancrofti</i>) in countries co-endemic with onchocerciasis using IA for the elimination of LF	
Intervention: Annual treatment with IDA	
Comparator: Annual treatment with IA	
Outcomes: Community members with LF infection <ul style="list-style-type: none"> • Complete mf clearance • Microfilarial density (geometric mean) • CFA • Inactive adult worm nests 	Outcomes: All community members <ul style="list-style-type: none"> • SAEs • AEs Grade 2 • Any AE
PICO Question 4. Should biannual IA versus annual IA be used for MDA to eliminate LF in IUs where onchocerciasis is co-endemic?	
Population/setting: LF endemic communities (<i>Wuchereria bancrofti</i>) in countries co-endemic with onchocerciasis using IA for the elimination of LF	
Intervention: Biannual treatment with IA	
Comparator: Annual treatment with IA	
Outcomes: Community members with LF infection <ul style="list-style-type: none"> • Mf prevalence • CFA 	Outcomes: All community members <ul style="list-style-type: none"> • Mf prevalence reduction • CFA reduction
PICO Question 5. Should biannual albendazole versus annual albendazole be used for MDA to eliminate LF in IUs where loiasis is co-endemic?	
Population/setting: LF endemic communities (<i>Wuchereria bancrofti</i>) co-endemic with loiasis where ivermectin has not already been distributed	
Intervention: Biannual treatment with albendazole	
Comparator: Annual treatment with albendazole	
Outcomes: All community members <ul style="list-style-type: none"> • Mf prevalence reduction • CFA reduction 	

AE, adverse event; CFA, circulating filarial antigen; IA, ivermectin + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IU, implementation unit; LF, lymphatic filariasis; MDA, mass drug administration; mf, microfilaraemia; PICO, population, intervention, comparator and outcome; SAE, serious adverse event

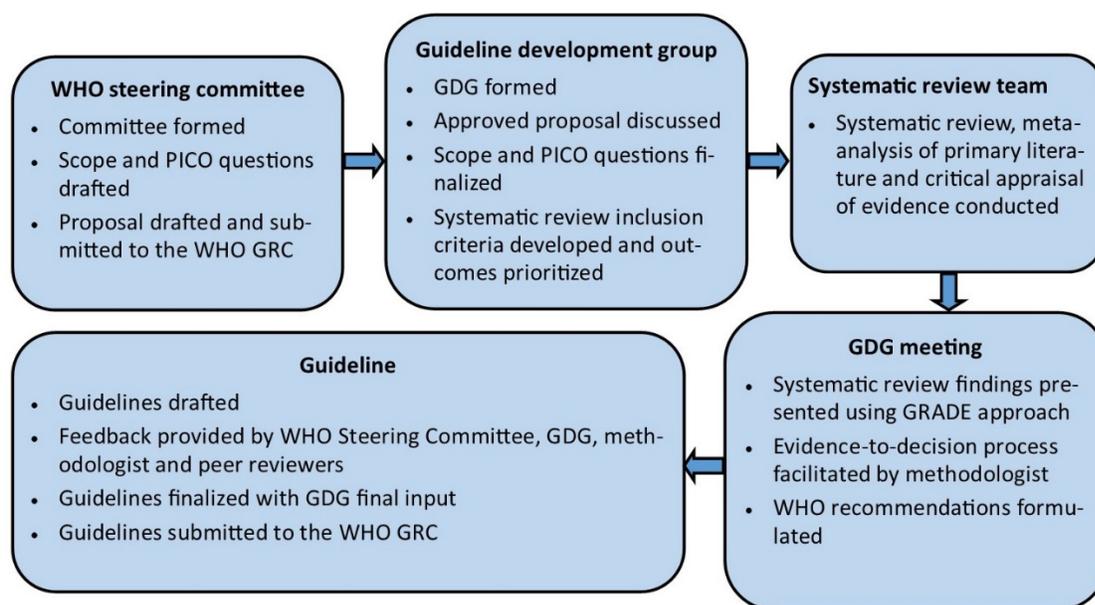
2. Methodology and process used to develop the guideline

2.1. WHO guideline development process

This WHO guideline was developed in accordance with the procedures outlined in the *WHO handbook for guideline development* published in 2014 (29). The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach was used to judge the quality of the evidence and to develop the recommendations (29).

The guideline development process included input from the WHO steering committee, the guideline development group, the systematic review methodologists and the guideline methodologists with expertise in the GRADE approach. As a measure of quality assurance, peer review of the guideline was also requested and addressed before submission to the WHO Guidelines Review Committee and its public release (Fig. 1).

Fig. 1. Flowchart depicting the guideline development process for alternative MDA regimens to eliminate lymphatic filariasis



GDG, guideline development group; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; GRC, guidelines review committee; LF, lymphatic filariasis; MDA, mass drug administration; PICO, Population, Intervention, Comparator and Outcome; WHO, World Health Organization

2.2. Systematic review

A systematic review of the primary literature following widely accepted methodological standards was commissioned externally to address the research (PICO) questions. Two types of study designs were considered for inclusion: randomized controlled trials (RCTs) with subject-level intervention allocation among people infected with *Wuchereria bancrofti* or *Brugia* spp., and RCTs with community-level allocation of interventions among communities as a whole, both infected and uninfected. The search strategy did not exclude studies on the grounds of year of publication, publication status, language or participants' characteristics, and therefore data from ongoing trials were included. Studies comparing the alternative regimens prioritized by the guideline development group were also included. Meta-analysis was carried out on the efficacy and safety outcomes listed in the PICO questions within comparisons of interest, and provided more than one point estimate to provide evidence of the relative efficacy and safety of the alternative regimens.

The quality of the evidence was assessed by the systematic review team and the methodologist. The initial rating for outcomes in RCTs was high and low for observational studies. The rating for each outcome was then adjusted based on (i) risk of bias (using the Cochrane Risk of Bias assessment tool), (ii) inconsistency, (iii) indirectness, (iv) imprecision or (v) publication bias. On the basis of the rating of the available evidence, the overall quality of the evidence was categorized as high, moderate, low, or very low. Summaries of the quality of the evidence used to address each outcome were entered in the GRADE profiler software (GRADEproGDT). The GRADE evidence profiles are included in Annex 1 and the full systematic review report including search strategies are reported in Annex 2.

A qualitative scoping synthesis was also conducted to identify, appraise and synthesize qualitative studies exploring perceptions and experiences of MDA from the perspective of the endemic communities and those delivering the MDA medicines. The qualitative scoping synthesis was conducted by one author using a developed search strategy, systematic data extraction methodology and a thematic analysis using the Supporting the Use of Research Evidence framework. This framework is designed to assist with evidence-informed policy-making in low- and middle-income settings. Categories and subcategories from the framework were used to construct the findings. Findings from the synthesis supported the evidence-to-decision framework (described in section 2.7), including considerations for programme implementation. An adaptation of the Critical Appraisal Skills Programme quality assessment tool for qualitative studies was used to assess the methodological quality of the included studies (30). The overall assessment of included studies was presented to the guideline development group and is reported in the systematic review report (Annex 2, Table 14).

2.3. Guideline development group

The guideline development group was formed in January 2017, with 18 members invited to participate from key LF MDA stakeholder groups, including researchers, clinicians, programme managers, an economist, a mathematical modeller, social scientists, a medical anthropologist and members of regional programme review groups. Geographical representation, diversity in skillset and gender balance were considered in selecting members. Their names and professional affiliations are listed in Annex 3.

2.4. Conflicts of interest

Evaluation and management of potential conflicts of interest was a priority activity of the WHO Department of Control of Neglected Tropical Diseases throughout the guideline development process in accordance with the Organization's guidelines for declaration of interests for WHO experts. Prior to assuming their roles in the guideline development group, all members were requested to complete declaration of interests statements. Upon receiving the declaration of interests, the curriculum vitae were reviewed, and PubMed and google search results were used to identify potential conflicts of interests not stated by the member. All statements were reviewed by WHO and a consensus decision was made to determine whether any statements from members would be considered a conflict of interest to participation in any part of the guideline development process. The biographies of the proposed members were announced publicly on the WHO website for 3 weeks to allow any public concerns of the nominations to be submitted and reviewed by the steering committee. No public comments were received.

Additionally, at the meeting of the guideline development group (Geneva, May 2017) the members verbally disclosed any interests at the beginning of the meeting. After analysing each declaration of interests statement, WHO concluded that no member had financial or commercial interests related to LF MDA, and that there were no significant intellectual conflicts of interests that would exclude any member from fully participating in the guideline development process. As a result, options for conditional participation, partial exclusion or total exclusion of any member were not discussed. Likewise, declaration of interests statements were received from the methodologists, key informants and peer reviewers, then reviewed to decide whether to restrict participation. All declaration of interests statements are summarized in Annex 4.

2.5. Roles

The WHO steering committee developed the guideline proposal including the scope and draft of the initial PICO questions. The guideline development group further refined the PICO questions, reviewed the evidence profiles, formulated and agreed upon the wording of the recommendations, and reviewed and approved the final guideline. The systematic review team ensured that all relevant evidence was sought and presented a critical appraisal of included studies for quality, as well as a systematic presentation and synthesis of the characteristics and findings of the included studies. The guideline methodologist led the guideline development group through the evidence-to-decision process to ensure that the GRADE approach was appropriately applied. The methodologist also helped to formulate the wording and strength of the recommendations. After examining the document, peer reviewers provided comments and suggestions to improve clarity and understanding from the perspective of the end user.

2.6. Development of the guideline

After approval of the guideline proposal by the WHO Guidelines Review Committee, the guideline development group was engaged first by sharing the proposal via email as background and to request input into the intended scope and the PICO questions. At the same time, the draft protocol for the systematic review and qualitative scoping synthesis was circulated to members with expertise in the respective areas. No changes were suggested to the proposed scope of the guideline by the guideline development group, which determined and prioritized the outcomes as critical, important and not important based on their technical relevance from the public health programme perspective. Members also pre-specified subgroups of interest for stratified comparisons of outcomes. The specific wording

and numbers of PICO questions were changed based on the prioritization of the outcomes and the MDA regimens to compare.

The guideline development group held a face-to-face meeting (Geneva, 17–19 May 2017) to review the evidence and formulate the recommendations. The guideline was drafted following the meeting after the final wording and the justification of recommendations had been agreed. The draft guideline was circulated to peer reviewers. Before submission to the WHO Guidelines Review Committee, comments from peer reviewers and proposed revisions to the guideline were circulated to the guideline development group for additional input and final approval. These suggestions were kept in a separate file with a point by point response indicating how and where the guideline was revised in order to address each point. There were no discrepancies of suggestions among peer reviewers or between peer reviewers and members of the guideline development group. External partners did not contribute to the development of the guideline at any point in the process.

2.7. Formulation of recommendations

During the face-to-face meeting (Geneva, 17–19 May 2017), the results of the systematic reviews and the evidence profiles for each of the PICO questions were presented, reviewed and deliberated to ensure that there was understanding and agreement on the scoring criteria. The GRADE evidence-to-decision framework was followed in formulating the recommendations using the online [Guideline Development Tool](#). Details of the framework have been published previously (31). The framework for Health System and Public Health Recommendations was selected, which comprises the following key decision-making criteria for recommending between two or more management options:

- How substantial desirable and undesirable anticipated effects are
- Outcome importance
- Balance of desirable and undesirable outcomes
- Certainty of the evidence of desirable and undesirable effects
- Resource requirements and cost–effectiveness
- Certainty of resource requirements
- Impact on health equity
- Acceptability of intervention
- Feasibility of intervention

The guideline development group examined the evidence presented by the systematic review team, including the GRADE evidence profile and the summary of findings tables, and considered the aforementioned criteria in formulating recommendations. The GRADE system classifies the strength of a recommendation in two ways: “strong” and “conditional” (32). The strength of each recommendation is informed by the quality of evidence. A strong recommendation is limited to when the quality of evidence rating is “high” and the group is confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects across all settings. The reasons for making a conditional recommendation include the absence of high-quality evidence and when the group considers that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the confidence about these trade-offs varies by setting. A conditional recommendation means that a national programme should consider the setting-specific situation before adopting an alternative MDA regimen.

Consensus of the guideline development group was developed using an informal approach that stipulated a priori that judgements for each of the evidence-to-decision criteria would be made with complete consensus achieved through group discussions. Should complete consensus fail to be reached, judgements made with more than 50% of votes would be considered final. For strong recommendations, however, judgements for these criteria should have been made with more than two-thirds votes. The chair and co-chair of the meeting ensured that member participation was not tokenistic. Members were actively asked for dissenting views. During actual deliberations, group discussions helped to reach full consensus for all criteria for all questions. Members drafted and reviewed the final recommendations for editorial changes on the final day of the meeting. A draft of the recommendations was circulated again to the group for any final editorial changes before submission to the WHO Guidelines Review Committee.

2.8. Target population preferences and views

No evidence was found addressing how patients and other healthy members of the community would differentially value the outcomes and variability in outcome values across the two subgroups. As such, the perspective of IUs was taken and the guideline development group was used as their proxy in determining and prioritizing outcomes. The indicators of LF infection (microfilaraemia, antigenaemia and antibody prevalence) used to define elimination as a public health problem were prioritized. It was noted that microfilaraemia prevalence reduction, microfilarial density, circulating filarial antigen (CFA) reduction, IgG4 reduction, inactive adult worm nests and any adverse events (AEs) were not as critical outcomes as complete microfilaraemia clearance and adverse events above Grade 2 (that is, AEs interfering with activities of daily living for ≥ 1 day). A priori, the group considered that AE outcomes in comparison of biannual versus annual MDA with existing regimens were not as critical as AE outcomes in comparison of the new triple-drug versus existing two-drug regimens. The relative importance of outcomes was factored in judging the balance of desirable and undesirable outcomes.

3. Recommendations for countries using DA MDA to eliminate lymphatic filariasis

Countries endemic for lymphatic filariasis but without either onchocerciasis or loiasis

3.1. Comparison of annual IDA versus annual DA

Background

The DA regimen is a safe and effective microfilaricidal combination used for MDA in IUs where onchocerciasis is not co-endemic. It displays destructive properties against the thousands of microfilariae circulating in the blood of people infected with LF. The medicines, used alone and in combination, have also shown macrofilaricidal effects against the adult worms (18, 33–36). Because adult worms do not always die after treatment, MDA must be maintained for the duration of time the adult worms retain fecundity, which is an average of 5–7 years although not definitively known (37). The development of a more efficacious, field-ready and safe macrofilaricide for LF has been sought, and research has been ongoing for several decades.

In 2016, an innovative study focused on the IDA combination dose. The results indicated superior parasite killing effects, including clearance of microfilaraemia for 24 months with a single treatment, suggesting permanent sterilization or destruction of adult worms, and no increased SAEs among persons with heavy parasite loads (38). The study results prompted immediate expansion of RCTs to replicate the findings of the original study, as well as to collect data on efficacy and safety.

Comparative evidence between IDA and DA was sought because the use of IDA is anticipated to heighten the effectiveness of MDA on interrupting transmission, shorten the number of rounds needed to reach the criteria for stopping MDA and conserve scarce healthcare resources. The guideline development group considered annual IDA to be an alternative regimen for countries using DA to employ in their approach to eliminating LF as a public health problem and to address pre-specified technical situations. Given the risk of SAEs, diethylcarbamazine is contraindicated in persons infected with *Onchocerca volvulus*; therefore, this alternative regimen would be an option only for IUs endemic for LF that are NOT co-endemic with onchocerciasis.

In countries using DA to eliminate lymphatic filariasis

Recommendation: [PICO 1]

WHO recommends annual IDA rather than annual DA in the following special settings:

- for IUs that have not started or have fewer than four effective rounds of DA;
- for IUs that have not met the appropriate epidemiological targets in sentinel and spot-check site surveys or in TAS despite meeting drug coverage targets; and
- for communities where post-MDA or post-validation surveillance identified infection suggesting local transmission.

This is a conditional recommendation based on overall low quality of evidence until new data supporting more broad use of IDA MDA in DA countries become available and WHO updates guidelines.

Justification for the recommendation

Evidence available from comparative studies shows a large effect in efficacy favouring IDA over DA (low quality of evidence). Large randomized community studies in four countries found no increased risk of SAEs or AEs interfering with activities of daily living in IDA MDA compared to DA MDA (moderate quality of evidence). Although the magnitude is uncertain, confidence was expressed in a reduced duration (number of rounds) of IDA required compared to DA, which may lead to moderate resource savings.

A majority of key stakeholders considered that IDA was as acceptable as the current two-drug regimen. A mixed methods survey conducted among beneficiaries of LF MDA identified factors influencing acceptability of IDA and concluded that IDA was as acceptable as DA. While most stakeholders considered IDA would be as feasible as the current regimen, concerns were noted with the availability of ivermectin and initial programme adjustments associated with transitioning from two to three medicines. There were no concerns about health equity of MDA with IDA compared to DA.

Subgroup considerations

According to the existing WHO guidance referenced in Chapter 1 in the discussion on eligible and ineligible populations: (i) pregnant women would be excluded from MDA, (ii) the severely ill would be excluded from MDA, and (iii) children aged 2–4 years would be given DA; persons taller than 90 cm (approximately equivalent to ≥ 15 kg body weight) would be given IDA.

Implementation considerations

The guideline development group emphasized that IDA is not a regimen to be used to address poor MDA coverage. Effective drug coverage of the at-risk population, defined as epidemiological coverage of at least 65% for each MDA round, is a critical component of each country's LF MDA strategy. As such, the administration of IDA will not solve the issues of suboptimal responses to MDA that result from inadequate drug coverage, even though the popularity of ivermectin because of its collateral medical benefits is likely to enhance population compliance with the IDA regimen.

Additionally, the guideline development group encourages the following actions during implementation:

- Raise awareness of decision-makers and communities about the new MDA regimen and expected AEs.
- Engage communities to develop an acceptable administration strategy to maximize coverage.
- Understand and address concerns expressed at a local level that impact coverage (for example, concerns that “MDA regimens are ineffective”).
- Ensure that the connection of the drug distributor and the health authorities is known by the community.
- Understand and address community perceptions about infection, disease and MDA regimens, including side-effects.
- Enhance administration strategies to ensure treatment is directly observed.
- Target 100% of the eligible population.
- Enhance training of drug administrators to ensure capacity to understand and explain aims, benefits and how to manage AEs.
- Improve and strengthen capacity for reporting and managing SAEs and mitigating social implications of false information.
- Coordinate with national pharmacovigilance agencies to ensure appropriate and timely reporting of and response to SAEs.
- Follow standard national procedures for ensuring quality of the medicines used in MDA.
- Promote the health benefits populations receive from the IDA regimen.

Note: Conducting an effective round of LF MDA is a large-scale public health undertaking that must be well planned, coordinated, executed, monitored and evaluated. Social mobilization is an important component of implementation that affects coverage. Country-level implementation considerations for these critical components of MDA will be discussed in depth in a forthcoming WHO field guide for programme managers on implementation of alternative LF MDA regimens, which is a derivative product of this guideline designed to support programmes at various stages of national and subnational implementation of LF MDA.

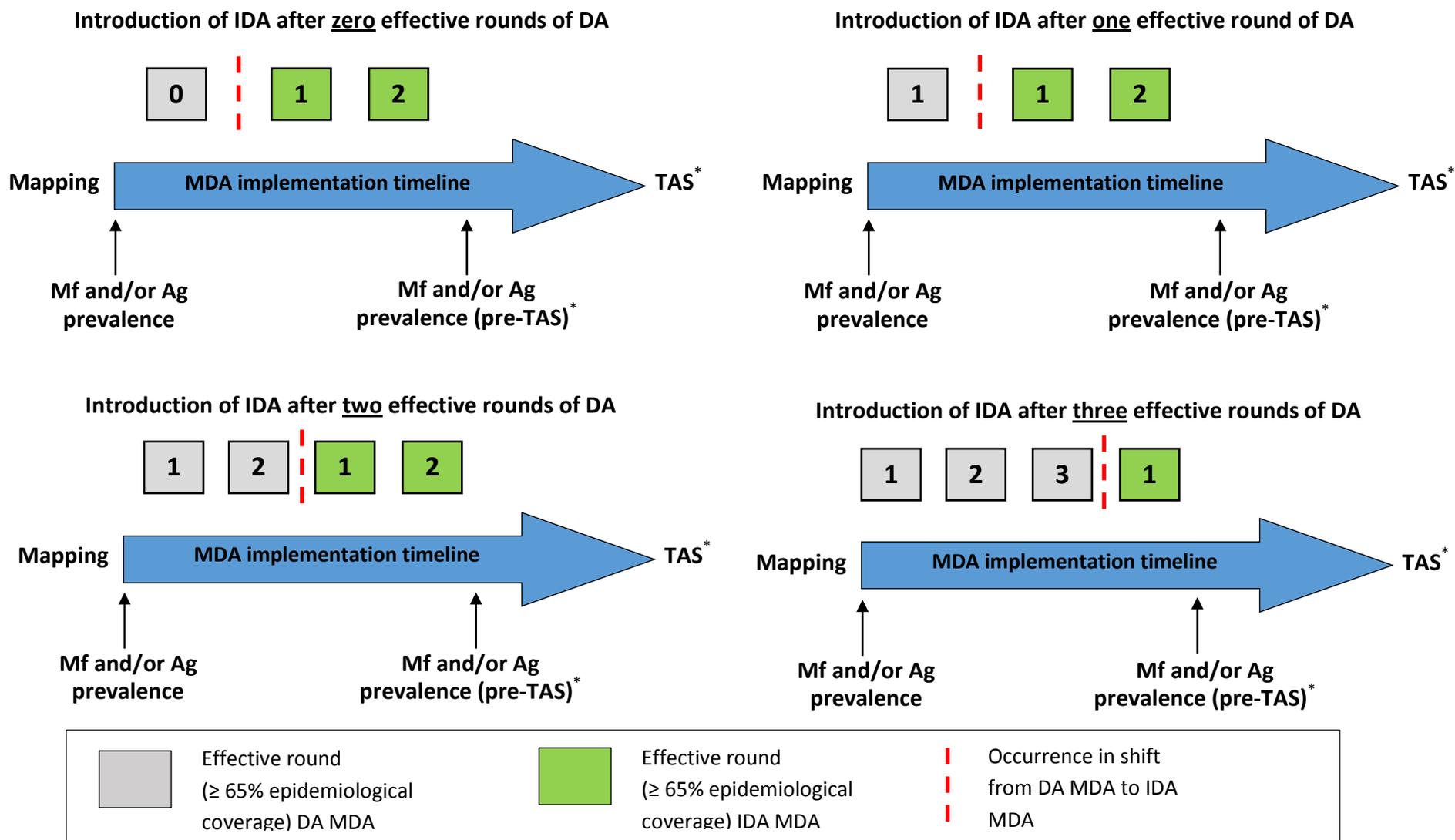
Monitoring and evaluation

In IUs with no previous MDA, endemicity at baseline should be established according to the current GPELF framework before starting IDA, either through data collected from mapping surveys or from baseline sentinel site surveys. To monitor uptake of IDA, programmes are encouraged to implement a drug coverage evaluation survey after the first round of IDA. To evaluate the impact of IDA, programmes should conduct assessments of sentinel and spot-check sites at the following times during the MDA life cycle (Figs. 2 and 3):

- at least 6 months after the second effective IDA round in treatment naive IUs, or in those which have previously undergone one or two effective rounds of DA;
- at least 6 months after the first effective IDA round in IUs which have previously undergone three effective rounds of DA; and
- at least 6 months after the second effective IDA round in IUs which have previously undergone at least five effective rounds of DA yet failed pre-TAS or TAS.

When epidemiological criteria (< 1% microfilaraemia or < 2% antigenaemia) are achieved in sentinel and spot-check site assessment results, the IU can progress to TAS. When these epidemiological criteria are NOT achieved in sentinel and spot-check sites or in TAS results following IDA, the IU must undergo two additional rounds of IDA before spot-check site assessments are repeated.

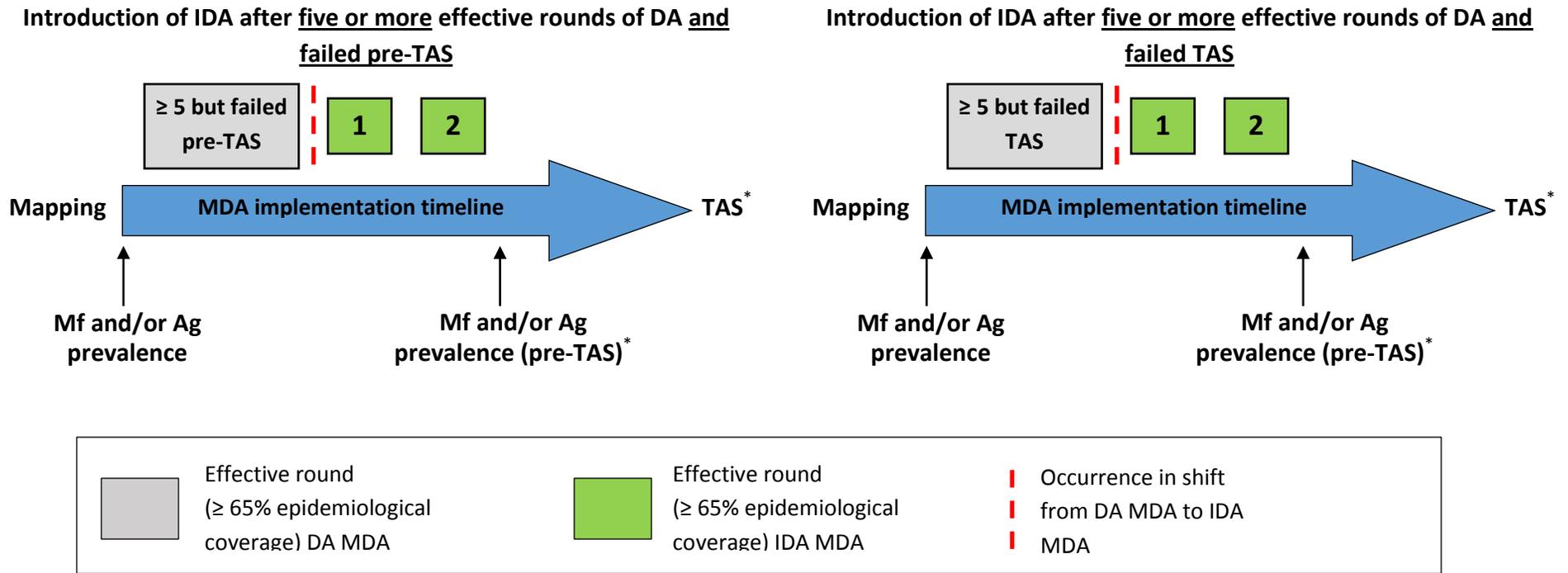
Fig. 2. Evaluating the impact of IDA: timing of pre-TAS and TAS in implementation units that have not yet undergone follow-up assessments



* Pre-TAS and TAS take place 6 months after MDA completion. When epidemiological targets are NOT achieved in sentinel and spot check sites (pre-TAS) or TAS following IDA MDA, the IU should undergo two additional effective rounds of IDA MDA before spot-check site assessments are repeated.

Ag, antigenaemia; DA, diethylcarbamazine + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IA, ivermectin + albendazole; MDA, mass drug administration; Mf, microfilaraemia; PICO, population, intervention, comparator, outcome; pre-TAS, pre-transmission assessment survey; SAE, serious adverse event; TAS, transmission assessment survey

Fig. 3. Evaluating the impact of IDA: timing of pre-TAS and TAS in implementation units with prior failed follow-up assessments



* Pre-TAS and TAS take place 6 months after MDA completion. When epidemiological targets are NOT achieved in sentinel and spot-check sites (pre-TAS) or TAS following IDA, the implementation unit should undergo two additional effective rounds of IDA before spot-check site assessments are repeated.

Ag, antigenaemia; DA: diethylcarbamazine + albendazole; IDA, ivermectin + diethylcarbamazine + albendazole; IA, ivermectin + albendazole; MDA, mass drug administration; Mf, microfilaraemia; PICO, population, intervention, comparator, outcome; pre-TAS, pre-transmission assessment survey; SAE, serious adverse event; TAS, transmission assessment survey

Summary of the GRADE evidence: effectiveness

Two RCTs conducted among individuals infected with *W. bancrofti* (Population) examined complete microfilaraemia clearance at 24 months (Outcome) after a single treatment with IDA (Intervention) compared to single and annual treatment with DA (Comparison) (38, 39). These studies, which are included in GRADE Table 1 (Annex 1), compared outcome data available at 24 months from 60 and 61 people, respectively. Pooled analysis from the two RCTs showed a significant increase in complete microfilaraemia clearance at 24 months post-treatment in the intervention group compared to the control group (relative risk [RR]: 1.75; 95% confidence interval [CI]: 1.39–2.20; low quality of evidence). The absolute risk estimate indicates that 406 more (95% CI: 211 to 649 more) persons per 1000 would have microfilaraemia clearance at 24 months after a single treatment with IDA. Pooled analysis from the two RCTs showed that the mean microfilarial density at 24 months (Outcome) after IDA (Intervention) was 10 times lower (ratio of geometric means 0.10; 95% CI: 0.07–0.14; low quality of evidence) compared to single treatment of DA (Comparison). Analysis from one RCT showed that among 116 persons (58 in the IDA group, 58 in the DA once group) tested with the Alere Filariasis Test Strip (FTS) at 24 months, there was no difference in CFA prevalence between IDA and DA groups (RR: 1.0; 95% CI: 0.95–1.04; low quality of evidence).

Summary of the GRADE evidence: safety

Data on AEs from four large community RCTs conducted in four LF endemic countries where onchocerciasis is not co-endemic were analysed to compare undesirable effects between IDA and DA (40–43). In each study community (Population), both infected and uninfected individuals received MDA with IDA (Intervention) or DA (Comparison) according to the community-level random allocation of the MDA regimen. The WHO-recommended strategy for monitoring the safety of medicines in public health interventions (cohort event monitoring) was implemented as part of the study protocol to monitor AEs at baseline and for 7 days post-treatment (10). Across the four sites combined, data from 10 519 people treated with IDA and 10 677 people treated with DA were analysed. The following priority outcomes were compared: SAEs (Grade 4 or 5); Grade 3 and Grade 4 AEs; AEs that interfered with daily activities for at least 1 day (Grade 2–4); AEs among microfilariae-positive persons (Grade 2 and above); and Grade 2 and above AEs from study sites where no previous MDA had been implemented. Grade 1 AEs were considered not important by the guideline development group; however, they are reported in the outcome any AE (Grade 1–4). These studies, which are included in GRADE Table 1 (Annex 1), yielded the following outcomes:

- *Serious adverse events.* There were no deaths (Grade 5) in any of the four RCTs. Three persons with AEs in one study site were monitored overnight in a health facility after treatment with DA and thus categorized as Grade 4. Pooled analysis showed that there was no significant difference in the occurrence of AEs (Grade 4) post-MDA between the IDA and DA communities (crude RR: 0.48; 95% CI: 0.08–2.90; moderate quality of evidence) of more than 20 000 persons (10 486 in IDA communities and 10 329 in DA). The absolute risk estimate indicates 15 fewer people per 100 000 population (95% CI: 27 fewer to 57 more) might experience a Grade 4 SAE after IDA compared to DA.
- *Grade 3 and 4 adverse events post-MDA.* Pooled analysis from the four RCTs showed that there was no significant difference in the occurrence of Grade 3 and Grade 4 AEs post-MDA between the IDA and DA communities (RR: 0.57; 95% CI: 0.22–1.45; moderate quality of evidence) of more than 20 000 persons (10 486 in IDA group and 10 329 in DA). The absolute risk estimate

indicates 50 fewer people per 100 000 population (95% CI: 91 fewer to 52 more) might experience a Grade 3 or 4 AE after IDA compared to DA.

- *Grade 2 to 4 adverse events in communities with no prior MDA.* Pooled analysis from the two RCTs among study sites where MDA had not previously been delivered (3430 people in IDA communities, 3180 people in DA communities) found a higher frequency of Grade 2 to 4 AEs in communities receiving IDA compared to DA, but the difference was not statistically significant (RR: 1.51; 95% CI: 0.96–2.39; moderate quality of evidence). The absolute risk estimate indicates 5 more (95% CI: 0 fewer to 14 more) persons per 1000 in communities with no prior MDA would experience a Grade 2 to 4 AE after IDA compared to DA.
- *Grade 2 to 4 adverse events among persons infected with microfilariae.* Pooled analysis from the four RCTs showed that there was no significant difference in the occurrence of Grade 2 to 4 AEs post-MDA between the IDA and DA groups (RR: 3.47; 95% CI: 0.68–17.73; low quality of evidence) among persons infected with microfilariae (447 people in IDA group, 415 people in DA group). The absolute risk indicates that 36 more (95% CI: 5 fewer to 242 more) persons per 1000 microfilaraemic persons would experience a Grade 2 to 4 AE after IDA compared to DA.
- *Any adverse events among persons infected with microfilariae.* Pooled analysis from the four RCTs showed that among persons infected with microfilariae (447 people in IDA group, 414 people in DA group), those treated with IDA compared to DA were more likely to experience any AE, but the difference was not statistically significant (RR: 1.50; 95% CI: 0.99–2.27; low quality of evidence). The absolute risk indicates that 120 more (95% CI: 2 fewer to 304 more) persons per 1000 microfilaraemic persons would experience an AE after IDA compared to DA.
- *Grade 2 adverse events post-MDA.* Pooled analysis from the four RCTs showed that there was no significant difference in the occurrence of Grade 2 AEs post-MDA between IDA (10 486 people) and DA (10 329 people) communities (RR: 1.27; 95% CI: 0.26–6.19; low quality of evidence). The absolute risk estimate indicates that seven more persons per 1000 people (95% CI: 20 fewer to 142 more) might experience a Grade 2 AE after IDA compared to DA.
- *Any adverse events.* Pooled analysis from the four RCTs showed that there was no significant difference in the occurrence of AEs among community members post-MDA between the IDA and DA communities (RR: 1.10; 95% CI: 0.67–1.78; low quality of evidence) among persons infected with microfilariae (10 519 people in IDA communities, 10 617 people in DA communities). The absolute risk indicates that 11 more (95% CI: 35 fewer to 83 more) persons per 1000 persons would experience an AE after IDA compared to DA.

Summary of evidence discussed in other domains

- *Balance between desirable and undesirable effects.* The guideline development group's judgement on this criterion was that the balance of trade-offs probably favoured IDA (see *Justification*). While not statistically significant, pooled estimates among MDA naive communities and microfilaraemic persons indicated higher frequency of lower-grade AEs post-MDA with IDA compared to DA. It was noted that under current regimens, AEs are more common among persons infected with microfilariae and after the first treatment. AEs in such

persons are associated with dying microfilariae and a more efficacious regimen might lead to more frequent AEs.

- *Quality of evidence.* The overall quality of evidence was low based on the lowest quality of evidence across critical outcomes.
- *Resource requirements.* No published studies exist that assess the impact of IDA on resource use and cost–effectiveness. A specific modelling study commissioned by WHO for the meeting of the guideline development group was presented for discussion and aimed to forecast resource requirements. The resource needs were estimated based on a Markov model developed by WHO to forecast the number of MDA rounds and medicines anticipated to reach elimination targets in each LF endemic country based on current MDA strategies (DA, IA and albendazole). The model estimates the probability of progression of a single IU through MDA to the probability of meeting pre-TAS and TAS criteria. Epidemiological data reported from countries were used to set parameters for passing pre-TAS and TAS criteria (King J, WHO, unpublished data, 17 May 2017). The following assumptions about the number of annual IDA rounds required to meet elimination targets derived from Irvine et al 2017 (44) were applied to the model: three IDA rounds in IUs with no prior DA rounds; two IDA rounds in IUs with up to two prior DA rounds with effective coverage; a single IDA round in IUs with three prior effective DA rounds; and a single IDA round in IUs that did not meet epidemiological criteria in pre-TAS or TAS evaluations. Implementation costs were derived from country-specific benchmarks for the cost per person treated (45). Under IDA, all 18 IDA-eligible countries were forecast to have undergone 219 million fewer treatments in total and stopped MDA in more than 90% of LF-endemic IUs by 2020, compared to 2027 under DA. Cost savings were estimated at US\$ 227 million (23%) in undiscounted economic costs if ivermectin is purchased (Fitzpatrick C, WHO, unpublished data, 17 May 2017). The costs compared were from the perspective of the implementing programme and did not take into account benefits (if any) related to IDA in preventing or reversing pathology in patients and preventing new infections. If the model included costs saved from more effective infection clearance, taking into account new cases and infections averted, then additional cost savings would be possible. It was agreed that IDA may reduce costs related to the delivery of medicines compared to DA based on the assumption that fewer MDA rounds would be required. However, the group was uncertain on the amount of cost savings with IDA compared to DA because of the low certainty in the efficacy assumptions of IDA derived from Irvine et al (44) and the cost of additional ivermectin. Assuming that the outcomes of IDA are no worse than for DA, it was agreed that the evidence on cost savings implies that IDA is probably more cost–effective than DA.
- *Health equity.* No published studies exist that assess the impact of IDA on health equity. A study was conducted by WHO in 2015 to assess the availability of gender disaggregated treatment data and gender equity in current MDA implementation (Mbabazi P, WHO, unpublished data, 17 May 2017). Gender disaggregated treatment data from MDA in 11 countries were reported by implementing partners and national programmes. The study did not find that neglected tropical disease control or elimination programmes systematically reach men with higher drug coverage during MDA than women. However, in MDA for LF and onchocerciasis programmes, drug coverage differed significantly between genders with slightly higher coverage in females relative to males. Study limitations included varied quality of reported treatment data, variable format of denominator data and inability to stratify data by socioeconomic status. As MDA platforms are based at the community level and reach the most underserved, it was agreed that there is

probably no difference in health equity between IDA and DA. It was noted, however, that national programmes are not currently systematically monitoring equity (e.g. gender, mobile populations) in drug coverage data and should consider doing so to ensure MDA is equally accessible to the entire eligible population. The group was concerned by not being able to give ivermectin to children below 90 cm in height due to existing WHO drug exclusion criteria perhaps preventing children aged 2–4 years from any additional benefit of ivermectin.

- *Acceptability among key stakeholders.* No published studies exist that assess the impact of IDA on acceptability among key stakeholders. Based on the evidence summarized below, it was agreed that IDA was probably acceptable to key stakeholders (i.e. MDA beneficiaries, community drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors).
 - Unpublished data from an ongoing mixed methods assessment of IDA acceptability following the implementation of IDA community studies in Haiti, India and Indonesia were presented (Krentel A, Bruyère Research Institute, unpublished data, 17 May 2017). Quality of data collection was ensured through a multi-stage translation process using three translators for all research tools to ensure consistency of the tools across all countries, field testing of tools in each country prior to data collection to ensure plain language, enumerator training and supervised data collection. Limitations of the research included: purposive selection of the participants in the qualitative methods and homogenous selection of research sites within each country. Through post-treatment questionnaires, focus groups and in-depth interviews, community members reported their feelings about the treatment received; these varied between sites but were similar among IDA and DA communities. An overall score was developed based on nine indicators of acceptability. A mean score above the value 18 indicated acceptability among the community. The mean acceptability score combined for Haiti, India and Indonesia for DA was 28.6 (standard deviation [SD]: 3.42) and 29.1 (SD: 3.2) for IDA. Regardless of treatment, 95% of persons with a clinically assessed AE said they would agree or strongly agree to take the treatment again. Acceptability as measured across the methods was similarly high for IDA and DA.
 - The WHO Department of Control of Neglected Tropical Diseases disseminated an online self-administered questionnaire through 42 international organizations and five regional offices of WHO to assess perceptions of acceptability and feasibility of alternative MDA regimens compared to current MDA regimens among stakeholders of LF MDA above the community level (e.g. drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors) (Blundell H, WHO, unpublished data, 17 May 2017). The survey methodology followed the strategy used previously for WHO guidelines on rehabilitation services (46). Likert scale responses were dichotomized as follows: responses 1–6 were coded “not as acceptable or feasible” and 7–9 “as acceptable or feasible”. Some 153 key stakeholders from 40 different countries covering all five LF endemic WHO regions responded to the survey. Participants from the South-East Asia and African regions represented 39.9% and 34.6% of respondents respectively. Most participants were from India (34.6%). The majority had a national level of responsibility (34.5%), followed by an international level of responsibility (20.9%). Most had an education level of doctoral degree (60.1%) or master’s degree (34.0%). A triple-therapy regimen of IDA was reported as acceptable as the current two-drug MDA regimens by 52.6% of survey respondents. The majority of respondents

reported that distributing three medicines during MDA would be as acceptable to drug distributors as distributing two medicines. Half of the respondents (49.6%) indicated that three-drug MDA would be as acceptable as current MDA by community members receiving the medications. Efficacy was a factor reported by the most number of respondents (87.1%) to be extremely influential in determining acceptability. Certain perspectives may have been underrepresented (pharmaceutical company representatives $n = 4$, donors $n = 5$, drug distributors $n = 6$, members of communities receiving MDA $n = 8$).

- Key themes were extracted from 14 studies that met inclusion criteria of the qualitative scoping synthesis concerning current MDA strategies: three qualitative studies, two studies reporting qualitative data collection with frequency analysis, four studies reporting qualitative findings only from a larger mixed-method study, and five mixed methods studies reporting qualitative and quantitative findings in the same article (Ames H, Swiss Tropical and Public Health Institute, unpublished data, 17 May 2017; see Annex 2). The synthesis highlighted several gaps with implementation of current MDA strategies including: lack of knowledge in the endemic communities about the disease and its transmission as well as the link with clinical manifestations and the purpose of MDA; lack of trust in the programme and community distributors; and negative impact of rumours and fear of side-effects. If not appropriately addressed, these problems are assumed to reduce acceptability of IDA. When communities understood the aims and benefits of current MDA regimens and the potential side-effects of the medicines, they were more open to and accepting of the MDA campaigns. Participation in MDA tended to be higher when communities were involved in planning and implementation, when the disease and the programme were considered a priority and when the drug distributors were trusted. Access to and provision of treatment for side-effects during MDA campaigns could help increase compliance. It was important for the drug distributor to be known in the community, and some community members preferred health workers with medical training to distribute the medicines. Taking into consideration local events, timing, context and location of where the medicines are distributed was found to be important to beneficiaries. Studies highlighted the need for improved training of distributors and more frequent information about MDA through a variety of preferred communication channels.
- *Feasibility*. No published studies exist that assess the feasibility of implementing IDA versus DA. Based on discussion of the evidence presented below, the guideline development group concluded that the feasibility of implementing IDA was varied.
 - In the online self-administered questionnaire described above, 55.0% of respondents perceived that implementation of IDA would be as feasible as DA. Additionally, more than 50% of respondents reported that the triple-therapy regimen of IDA would be as feasible as two-drug MDA for all implementation components of MDA: supply chain management (52.5%), directly observed therapy (53.3%), achieving effective coverage within communities (54.5%), availability of the three medications (54.8%), cost of distribution (64.5%), ability of community volunteers to distribute medications (65.6%), training of drug distributors (66.1%), and monitoring and supervision (67.7%) (Blundell H, WHO, unpublished data, 17 May 2017).
 - The qualitative scoping synthesis (see Annex 2) identified key health system factors that were considered to influence the feasibility of current MDA regimens, which would also

apply to any alternative MDA regimen. Financial resources must be available at the right time to enable programmes to plan with communities, enlist sufficient distributors and meet target delivery dates in order to maximize coverage. Involvement of and support from all levels of health-care services in MDA was important for success.

Research priorities

- Monitor in the first few countries that adopt IDA the impact of the regimen after each annual IDA round in at least one IU to provide further understanding on the number of rounds required to meet elimination thresholds, by measuring treatment coverage and changes in the following indicators: microfilaraemia, antigenaemia, and antibody serology and infection in mosquitoes (where feasible).
- Confirm whether children aged 6–7 years are appropriate age groups for measuring the impact during TAS following IDA.
- Assess whether ivermectin could be administered to children below 90 cm in height:
 - Would exclusion of this group be a deterrent to social mobilization in countries that are ivermectin naive for LF MDA (e.g. historically DA countries)?
 - Are additional data needed to support this group as an ineligible population?
- Understand how local social contexts shape community acceptance of new MDA regimens:
 - Under what social contexts are drug coverage rates at or above target levels, and under what circumstances are drug coverage rates below the required target levels?
 - How and why do these rates vary within countries?
- As programmes uptake the new regimen and roll out IDA MDA strategies, capturing cost needs to be included as part of the process. Additionally, for any research involving IDA, methods to capture costing data and cost–effectiveness need to be included in the study design from the beginning.
- Assess IUs with multiple rounds of MDA with low coverage:
 - Would raising coverage of DA through enhanced MDA have the same public health impact as introducing IDA?

3.2. Comparison of biannual DA versus annual DA

Background

In addition to its use in LF MDA in IUs co-endemic for LF and loiasis (47), twice-yearly or more MDA has been successfully implemented to eliminate or control neglected tropical diseases other than LF. Foci of onchocerciasis have been eliminated in both the Americas and African regions with biannual or more frequent MDA with ivermectin. Biannual MDA is also currently implemented in certain countries to control schistosomiasis (praziquantel) and soil-transmitted helminth infections (albendazole, mebendazole) where the prevalence and intensity of these infections are high.

The impact of more frequent than annual MDA on LF is not well documented. Published mathematical models of the impact of biannual treatment agree that the number of years required to interrupt transmission is reduced when compared to annual treatment, although the quantitative predictions differ (48).

Comparative evidence between biannual DA and annual DA was sought because the use of biannual DA is anticipated to decrease the time needed to eliminate LF as a public health problem. The guideline development group considered the use of biannual DA as an alternative MDA regimen for countries using DA to employ in their approach to eliminating LF as a public health problem and to address pre-specified technical situations. Given the risk of SAEs, diethylcarbamazine is contraindicated in persons infected with *O. volvulus*, and therefore this alternative biannual MDA would be an option for LF endemic IUs NOT co-endemic with onchocerciasis.

In countries using DA to eliminate lymphatic filariasis

Recommendation: [PICO 2]

WHO recommends annual DA rather than biannual DA.

This is a conditional recommendation based on overall very low quality of evidence until new data supporting improved efficacy of biannual DA MDA become available and WHO updates guidelines.

Justification for the recommendation

Critical yet limited evidence from comparative studies does not demonstrate improved efficacy of biannual DA over current annual DA (low quality of evidence). Evidence from the available clinical trials (low quality of evidence) and from the expert opinion did not elicit concern for any more AEs associated with DA MDA taking place every 6 months, compared to a single annual DA MDA. Economic and financial modelling yielded negligible cost savings. There were no concerns about health equity of biannual DA compared to annual DA, and it was noted that biannual treatment may increase overall annual coverage, as collectively the campaigns may reach populations unable to participate in a single annual round. The majority of stakeholders considered that more frequent than annual MDA was not as acceptable or feasible as annual MDA.

Subgroup considerations

There are no new subgroup considerations. Refer to existing WHO guidance concerning populations eligible and ineligible for treatment with DA (Chapter 1, refer to diethylcarbamazine and albendazole).

Implementation considerations

There are no new implementation considerations. Refer to existing WHO guidance concerning implementation of annual DA (1, 8).

Monitoring and evaluation

There are no new monitoring and evaluation considerations. Refer to existing WHO guidance concerning monitoring and evaluation of annual DA (8).

Summary of the GRADE evidence: effectiveness

Two RCTs conducted among individuals infected with *W. bancrofti* (Population) examined complete microfilaraemia clearance and inactive adult worm nests at 24 months post-MDA (Outcomes), and one observational study examined microfilaraemia prevalence reduction, CFA reduction and IgG4 reduction at 36 months post-MDA (Outcomes) following treatment with biannual DA (Intervention) compared to annual DA (Comparison) (18, 34, 49). These studies, which are described in GRADE Table 2 (Annex 1), yielded the following outcomes:

- *Complete microfilaraemia clearance.* Pooled analysis across the two RCTs did not show a significant difference in complete microfilaraemia clearance at 24 months post-biannual DA treatment (77 people) groups, compared to post-annual DA treatment (76 people) groups (RR: 0.98; 95% CI: 0.92–1.05; low quality of evidence). The absolute risk estimate indicates that 17 fewer persons per 1000 would experience complete microfilaraemia clearance at 24 months post-biannual DA treatment compared to post-annual DA treatment, but the true microfilaraemia clearance could be 69 fewer to 43 more persons per 1000 infected (95% CI).
- *Microfilarial density at 24 months.* Pooled analysis from the two RCTs showed that there was no statistically significant difference between biannual DA (75 people) groups and annual DA (76 people) groups in the observed change in geometric mean microfilarial density (ratio of means 1.23; CI: 0.95–1.59; low quality of evidence).
- *Inactive adult worm nests.* Analysis from one RCT did not show a significant difference in inactive adult worm nests at 24 months post-biannual DA treatment (19 people) groups compared to post-annual DA treatment (18 people) groups (RR: 1.15; 95% CI: 0.89–1.48; low quality of evidence). The absolute risk estimate indicates that 117 more persons (95% CI: 86 fewer to 373 more) per 1000 infected persons would experience inactive adult worm nests at 24 months post-biannual DA treatment compared to post-annual DA treatment.
- *Microfilaraemia prevalence reduction.* Analysis from one observational study did not show a significant difference in the observed microfilaraemia prevalence reduction at 36 months between biannual DA (1027 people) and annual DA (1776 people) communities (RR: 1.69; 95% CI: 0.53–5.37; very low quality of evidence).
- *CFA reduction (assessed with BinaxNow Filariasis ICT).* CFA data as assessed with the ICT or the FTS were not available from the two RCTs reviewed. Analysis from one observational study showed a significant increase in observed CFA reduction at 36 months in the biannual DA communities (1027 people) compared to the annual DA communities (1985 people); (RR: 2.33; 95% CI: 1.12–4.82; very low quality of evidence).
- *IgG4 antibody reduction (assessed with Brugia Rapid Test).* Analysis from one observational study did not show a significant difference in the IgG4 reduction observed at 36 months between biannual DA (1027 people) communities and annual DA (1776 people) communities (RR: 0.94; 95% CI: 0.61–1.44; very low quality of evidence).

Summary of evidence discussed in other domains

- *Safety (non-GRADE evidence).* No direct or indirect evidence of comparative safety was identified. As such, the WHO Programme for International Drug Monitoring database (VigiBase) was screened for reports of suspected adverse drug reactions reported with diethylcarbamazine and albendazole, individually and combined, to determine the frequency of reports and identify any unknown adverse drug reactions (50); Ilesanmi N, WHO, unpublished data, 19 May 2017).¹ Reports submitted to VigiBase generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. Some national centres that contribute information to VigiBase assess the likelihood that a medicinal product caused the suspected reaction, while others do not. Information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. As of November 2016, 149 individual case safety reports including on diethylcarbamazine have been reported in 12 countries (six LF endemic) since the inception of the programme. The highest number of reports across years originated from countries that integrate pharmacovigilance into their public health programmes. The most frequent adverse drug reactions reported included nausea (23), headache (18), vertigo (16), vomiting (15), asthenia (14), pruritus (13) and dizziness (12). No signals for unknown adverse drug reactions were detected among the individual case safety reports reported. Seven individual case safety reports were reported in two LF endemic countries for DA where 372.2 million MDA treatments were reported.
- *Balance between desirable and undesirable effects.* The guideline development group's judgement on this criterion was that the balance probably favours annual DA over biannual DA (see *Justification*).
- *Quality of evidence.* The overall quality of evidence was very low based on the lowest quality of evidence across critical outcomes.
- *Resource requirements.* No published studies exist that assess the impact of biannual DA on resource use and cost-effectiveness. The modelling study described above (in section 3.1) using a Markov model based on probabilities of achieving five effective MDA rounds and passing pre-TAS and TAS evaluations was used to estimate treatments and rounds of MDA required under biannual DA compared to annual DA. Each biannual MDA round was assumed as effective as an annual MDA round based on previous mathematical model simulations (47). Implementation costs were derived from country-specific benchmarks for the cost per person treated (45). All 18 DA-eligible countries were forecast to have undergone 28 million more treatments and the same number of rounds under biannual DA compared to annual DA, and to have stopped MDA in more than 90% of endemic IUs by 2024 under biannual DA compared to 2027 under annual DA. Based on a scenario that biannual DA is introduced to every district where eligible (areas currently receiving DA), biannual DA was projected to save US\$ 102 million (13%) of undiscounted economic cost in DA-eligible countries (Fitzpatrick C, WHO, unpublished data, 18 May 2017). The costs compared were from the perspective of the implementing programme, and did not take into account benefits (if any) related to biannual DA in reversing pathology in

¹ Data come from the WHO global database of reports of adverse drug reaction, otherwise known as individual case safety reports. Currently (June 2017) there are over 15 million individual case safety reports in VigiBase originating from 127 countries. Data from VigiBase are from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases.

patients and preventing new infections. It was uncertain whether biannual DA reduces costs associated with delivery compared to annual DA because of the low certainty in the efficacy assumptions for biannual DA that were applied to the costing model. It was agreed that the cost-effectiveness of biannual DA was unknown as no studies were available.

- *Health equity.* No published studies exist that assess the impact of biannual DA on health equity. Based on the evidence described above (section 3.1), the guideline development group agreed that there is probably no impact on health equity between biannual DA and annual DA (Mbabazi P, WHO, unpublished data, 17 May 2017). It was noted that delivering more than one MDA round per year might increase the likelihood that an individual would be treated at least once annually.
- *Acceptability among stakeholders.* No published studies exist that assess the acceptability of biannual DA among key stakeholders. It was concluded that biannual DA was probably not as acceptable as annual DA based on discussion of the available evidence.
 - In the WHO administered online stakeholders' questionnaire described above (section 3.1), increasing the yearly frequency of the current MDA regimen was found not as acceptable as annual MDA by 53.5% of survey respondents. Over 50% of respondents felt that delivering MDA more than once yearly would not be as acceptable as annual MDA to both drug distributors (52.7%) and community members (51.8%) receiving the medications. The factor reported by the most number of respondents to be extremely influential in determining acceptability was efficacy (87.1%) (Blundell H, WHO, unpublished data, 18 May 2017).
 - Results from the qualitative scoping synthesis (Annex 2) were also considered (Ames H, Swiss Tropical and Public Health Institute, unpublished data, 17 May 2017). Specific challenges identified concerning the acceptability of the current annual MDA (see 3.1 *Acceptability*) could be compounded by the implementation of biannual MDA, particularly lack of motivation of both communities and distributors.
- *Feasibility.* No published studies exist that assess the feasibility of biannual DA versus annual DA. The guideline development group noted that on the basis of MDA for both LF and other neglected tropical diseases, national programmes are capable of delivering biannual MDA (e.g. for onchocerciasis, schistosomiasis and soil-transmitted helminthiasis). In the WHO-administered online stakeholders' questionnaire described above (section 3.1), the alternative MDA strategy of increasing the yearly frequency of the current MDA regimen was found not to be as feasible as annual MDA by 57.7% of survey respondents. Over 60% of respondents reported the following components of delivering more than annual MDA not as feasible: cost of distribution (69.5%), supply chain management (62.2%) and the availability of drugs (61.2%). Achieving effective coverage in the community was felt not as feasible as annual MDA by 52.1% of respondents (Blundell H, WHO, unpublished data, 18 May 2017). Health system factors identified in the qualitative scoping synthesis such as lack or delay of available resources such as medicines, funds and personnel for delivery at the times preferred by the community might only be amplified with biannual MDA. The group concluded that biannual DA and its feasibility to implement was varied.

Research priorities

There are no research priorities identified by the guideline development group for biannual DA at this time. The value of determining whether biannual DA is more effective than annual DA is low, given the stakeholders' perspectives of acceptability and feasibility as well as the stronger efficacy demonstrated by IDA, which in certain settings is the preferred alternative MDA regimen in IUs implementing DA (see section 3.1). If, however, individual countries choose to use biannual DA regimens to address specific issues (e.g. hot spots) instead of introducing IDA into their programmes, the outcomes should be captured to increase the evidence base for the effectiveness of the biannual DA.

4. Recommendations for countries co-endemic for onchocerciasis using IA MDA to eliminate lymphatic filariasis

Countries endemic for lymphatic filariasis and either having onchocerciasis in any implementation unit or being co-endemic with loiasis

4.1. Comparison of annual IDA versus annual IA (*onchocerciasis endemic in any part of the country*)

Background

Similarly to DA (described above), the IA regimen is a safe and effective microfilaricidal combination used for LF MDA in onchocerciasis co-endemic countries. It displays limited macrofilaricidal effects, requiring an average of 5–7 years for successful LF MDA programmes. Comparative evidence between IDA and IA effectiveness was sought because the use of IDA might be anticipated to heighten the effectiveness of MDA on interruption of transmission, shorten the number of rounds needed to reach the criteria for stopping MDA and conserve scarce health-care resources. The guideline development group considered annual IDA as an alternative MDA regimen for countries using IA to employ in their approach to eliminating LF as a public health problem, according to pre-specified technical situations.

In IUs where onchocerciasis is co-endemic with LF, diethylcarbamazine is not used due to SAEs that might occur in persons infected with *O. volvulus*; thus IA is used. The distribution of *O. volvulus* endemicity in some LF-endemic countries is limited to only certain areas not covering all subnational IUs. This alternative annual MDA regimen was considered as an option in LF-endemic countries where onchocerciasis is endemic in any part of the country but only in IUs where onchocerciasis is NOT co-endemic with LF.

**In countries using IA to eliminate lymphatic filariasis
(onchocerciasis endemic in any part of the country)**

Recommendation: [PICO 3]

WHO recommends annual IA rather than annual IDA.

This is a conditional recommendation based on overall low quality evidence until new data supporting safety and detailing delineation of IDA MDA in onchocerciasis-endemic countries become available and WHO updates guidelines.

Justification for the recommendation

The limited evidence available from comparative studies shows a large effect favouring IDA over current annual IA (low quality of evidence). Although the magnitude is uncertain, confidence was expressed in a reduced number of rounds of IDA compared to IA, which may lead to moderate resource savings.

In a single RCT, the relative risk of Grade 2 AEs in the IDA versus IA study was increased nine-fold, and the study was not powered to detect a rarer occurrence of Grade 3 and 4 AEs (categorized as SAEs); thus the undesirable effects were noted as moderate (low quality of evidence). However, the influencing concern for undesirable effects was the risk of accidental administration of diethylcarbamazine to someone with onchocerciasis even in an IU considered non-endemic for onchocerciasis. There was also a general concern about the addition of diethylcarbamazine to diethylcarbamazine naive populations in Africa. The community RCTs reviewed in the comparison of IDA to DA (see section 3.1) included treatment naive settings (Indonesia and Papua New Guinea) and found no statistically significant difference in occurrence of Grade 2 and above AEs between IDA and DA communities.

A majority of key stakeholders considered that IDA MDA was as acceptable as the current two-drug regimen and that IDA would be as feasible as IA. However, concerns were noted with initial programme adjustments associated with transitioning from two to three medicines. There were no concerns about health equity of IDA compared to IA, and it was expected that IDA would broaden the age group receiving LF MDA (compared to the IA regimen), to extend DA to children below 90 cm in height.

However, based on expert opinion, IDA is not recommended in countries using IA because of onchocerciasis co-endemicity. Given the frequent mobility of populations and the uncertain delineation of onchocerciasis, the guideline development group perceived a significant risk of SAEs that could occur from accidental administration of diethylcarbamazine to a person with onchocerciasis. As no evidence was presented to support or refute this perception, the recommendation was made at the level of the country.

Subgroup considerations

There are no new subgroup considerations. Refer to existing WHO guidance concerning populations eligible and ineligible for treatment with IA (Chapter 1, refer to ivermectin and albendazole).

Implementation considerations

There are no new implementation considerations. Refer to existing WHO guidance concerning implementation of annual IA (1, 8).

Monitoring and evaluation

There are no new monitoring and evaluation considerations. Refer to existing WHO guidance concerning monitoring and evaluation of annual IA (8).

Summary of the GRADE evidence: effectiveness

One RCT among individuals infected with *W. bancrofti* (Population) examined complete microfilaraemia clearance, CFA prevalence and inactive adult worm nests, both at 12 months post-treatment (Outcomes), after treatment with IDA (Intervention) compared to IA (Comparison) (51). This study, which is described in GRADE Table 3 (Annex 1), yielded the following outcomes:

- *Complete microfilariae clearance at 12 months post-MDA.* The study compared outcome data from 38 people in the IDA group and 43 people in the IA group. Data analysis showed a

significant increase in complete clearance of microfilariae from the blood at 12 months post-IDA treatment compared to post-IA treatment (RR: 2.98; 95% CI: 1.74–5.12; low quality of evidence). The absolute risk estimate indicates that 507 more persons (189 more to 1000 more) per 1000 microfilaraemic persons would experience microfilaraemia clearance at 12 months post-IDA treatment, compared to post-IA treatment.

- *Microfilarial density at 12 months.* The study found that microfilarial density was lower (ratio of means 0.16, 0.12–0.22; low quality of evidence) in the IDA treatment group (38 people) than in the IA treatment group (43 people).
- *Inactive adult worm nests at 12 months post-MDA.* The study compared outcome data from 20 people in the IDA group and 27 people in the IA group. Data analysis showed a significant increase in *inactive* adult worm nests at 12 months post-IDA treatment, compared to post-IA treatment (RR: 3.28; 95% CI: 1.69–6.37; low quality of evidence). The absolute risk estimate indicates that 591 more persons (179 more to 1000 more) per 1000 infected persons would clear adult worm nests at 12 months post-IDA treatment, compared to post-IA treatment.
- *CFA prevalence.* The study found that among 81 persons (38 in the IDA group and 43 in the IA group) tested with the Alere FTS at 12 months, there was no significant difference in CFA prevalence between IDA and IA groups (RR: 0.92; CI: 0.83–1.02; very low quality of evidence). The absolute risk estimate indicates that 80 fewer persons (170 fewer to 20 more) per 1000 infected persons would be CFA positive 12 months post-IDA treatment, compared to post-IA treatment.

Summary of the GRADE evidence: safety

No data were available for this comparison among all community members, infected as well as uninfected. However, the safety data for IDA in communities with no prior MDA included in the IDA versus DA community safety studies were discussed (refer to Annex 1 GRADE, Table 1, outcome AEs Grade 2–4 in communities with no prior MDA) (52).

One RCT among persons infected with *W. bancrofti* examined three different adverse event outcomes: SAEs 1–7 days post-MDA; Grade 2 AEs days 1–7 post-treatment; and any AE 1–7 days post-treatment (Outcomes) (51). The study was conducted on the community (Population) and included both infected and uninfected individuals treated with IDA (Intervention) compared to IA (Control). The study, which is described in GRADE Table 2 (Annex 1), yielded the following outcomes:

- *Serious adverse events 1–7 days post-MDA.* There were no deaths (Grade 5) in the study. In both groups (42 people IDA, 49 people IA), 0 people reported SAEs during the follow-up period; however, the RR was not estimable with both the intervention and control outcomes being 0 (0%; very low quality of evidence).
- *Grade 2 adverse events 1–7 days post-MDA.* Across the two groups in the study (42 people IDA, 49 people IA), data analysis showed a significant increase in the occurrence of Grade 2 AEs 1–7 days post-IDA treatment, compared to post-IA treatment (RR: 9.33; 95% CI: 1.22–71.61; very low quality of evidence). The absolute risk estimate indicates that 170 more persons (95% CI: 4 to 1000 more) per 1000 infected persons would experience Grade 2 AEs from 1–7 days post-IDA treatment, compared to post-IA treatment.

- *Any adverse event 1–7 days post-MDA.* Across the two groups in the study (42 people IDA, 49 people IA), data analysis did not show a significant difference in the occurrence of any AE 1–7 days post-IDA treatment, compared to post-IA treatment (RR: 0.98; 95% CI: 0.58–1.66; low quality of evidence). The absolute risk estimate indicates that 8 fewer persons (95% CI: 163 fewer to 256 more) per 1000 infected persons would experience any AE from 1 to 7 days post-IDA treatment, compared to post-IA treatment.

Summary of evidence discussed in other domains

- *Balance between desirable and undesirable effects.* The guideline development group’s judgement on this criterion was that the balance probably favoured IDA (see *Justification*).
- *Quality of evidence.* The overall quality of evidence was low based on the lowest quality of evidence across critical outcomes.
- *Resource requirements.* No published studies exist that assess the impact of IDA on resource use and cost effectiveness. The modelling study described above (section 3.1) using a Markov model based on probabilities of achieving five effective rounds, and passing pre-TAS and TAS evaluations was used to estimate treatments and rounds of MDA required under IDA, compared to IA. The number of IDA rounds required for each IU to meet elimination thresholds was derived from a separate modelling study (42). Implementation costs were derived from country-specific benchmarks for the cost per person treated (45). For the purposes of the analysis, only Sudan was considered for the comparison of IDA versus IA due to the limited foci of onchocerciasis in the country where use of diethylcarbamazine is contraindicated. Sudan was projected to stop MDA in more than 90% of endemic IUs by 2023 under IDA compared to 2027 under IA. An estimated 24 million fewer treatments would be required under IDA compared to the current IA regimen to reach elimination thresholds in all IUs. Cost savings were estimated at US\$ 29 million (35%) in undiscounted economic costs if diethylcarbamazine is purchased (Fitzpatrick C, WHO, unpublished data, 17 May 2017). The costs compared were from the perspective of the implementing programme. If the model included costs saved from more effective infection clearance, taking into account new cases and infections averted, then additional cost savings would be possible. The guideline development group was uncertain about the amount of cost savings related to the delivery of IDA compared to IA due to the low certainty of the evidence for the actual number of MDA rounds required. Assuming that the outcomes of IDA are no worse than IA, it was agreed that the evidence on cost savings implies that IDA is probably more cost-effective than IA.
- *Health equity.* No published studies exist that assess the impact of IDA on health equity. Based on the evidence described above (sections 3.1, 3.2) for health equity comparisons, it was agreed that there is probably no impact on health equity between annual IDA and annual IA (Mbabazi P, WHO, unpublished data, 17 May 2017). It was noted that there is increased inclusion of the 2–4 years age group if IDA is introduced in programmes currently using IA: where children below 90 cm in height are not included in IA MDA, introducing IDA in these settings would extend DA to younger children.

- *Acceptability among key stakeholders.* No published studies exist that compare acceptability of IDA versus IA specifically. The mixed methods assessment described above (section 3.1) only compared IDA to DA. Direct evidence was not available on how these findings would vary for a setting where MDA with IA is delivered. The same evidence described above (section 3.1) for both the self-administered online questionnaire and the qualitative scoping synthesis was considered in judging the acceptability of annual IDA compared to annual IA. Most respondents (54.3%) of the online questionnaire were working in areas co-endemic for onchocerciasis (Blundell H, WHO, unpublished data, 17 May 2017). The same problems with implementation of the current MDA regimens identified in the scoping synthesis would need to be addressed before introducing IDA (Ames H, Swiss Tropical and Public Health Institute, unpublished data, 17 May 2017). Based on this evidence, it was agreed that IDA was probably acceptable to key stakeholders (i.e. community drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors).
- *Feasibility.* No published studies exist that assess the feasibility of implementing IDA versus IA. The same evidence described above (section 3.1) for the online questionnaire was considered in determining the feasibility of annual IDA versus annual IA because the questionnaire specified only triple therapy versus two-drug regimens (Blundell H, WHO, unpublished data, 17 May 2017). It was agreed that the feasibility of implementing IDA was varied among key stakeholders.

Research priorities

- Some countries currently using IA have very limited foci of onchocerciasis endemicity. Programmatic studies to delineate the absence of onchocerciasis and loiasis that demonstrate safe introduction of diethylcarbamazine into such countries are therefore needed.
- Because one of the most serious potential consequences of using diethylcarbamazine to treat individuals with onchocerciasis is posterior-segment eye damage, limited in-hospital clinical studies are warranted to compare the potential ocular effects of IA and IDA before IDA is considered for MDA in any area potentially endemic for onchocerciasis.

4.2. Comparison of biannual IA versus annual IA (onchocerciasis endemic in any part of the country)

Background

As described above (section 3.2), twice-yearly or more MDA has been successfully implemented for other neglected tropical diseases. Comparative evidence between biannual IA and annual IA was sought as an alternative MDA regimen to reduce the time required to eliminate LF as a public health problem and address pre-specified technical situations. This alternative biannual MDA regimen was considered in LF-endemic countries where onchocerciasis is endemic in any part of the country as an option for LF-endemic IUs that are co-endemic with onchocerciasis.

**In countries using IA to eliminate lymphatic filariasis
(onchocerciasis endemic in any part of the country)**

Recommendation: [PICO 4]

WHO recommends annual IA rather than biannual IA, except in areas where biannual distribution of ivermectin is already being delivered for onchocerciasis.

This is a conditional recommendation based on overall very low quality of evidence until new data supporting improved efficacy of biannual IA MDA become available and WHO updates guidelines.

Justification for the recommendation

Important yet limited evidence from comparative studies does not indicate a difference in efficacy between biannual IA over annual IA (very low quality of evidence). Although no evidence existed on safety, the expert opinion did not elicit concern for more AEs associated with an additional IA MDA round 6 months after a first round compared to a single annual IA MDA. Economic and financial modelling yielded negligible cost savings, and the expert opinion noted potential increased costs due to an anticipated small increase in the number of treatments required in biannual IA versus annual IA if programmes were required to purchase the additional ivermectin. There were no concerns about equity of biannual IA compared to annual IA, and it was noted that biannual treatment may increase overall annual coverage, as each campaign may reach populations unable to participate in an annual MDA. The majority of stakeholders considered that more frequent than annual MDA was not as acceptable or feasible as annual MDA.

In IUs that are co-endemic for LF and onchocerciasis and already undergoing biannual treatment for onchocerciasis, the addition of albendazole to ivermectin in another round would be reasonable in order to align with onchocerciasis elimination activities and potentially improve annual coverage and impact.

Subgroup considerations

According to existing WHO guidance referenced in Chapter 1 in the discussion on eligible and ineligible populations, three groups are to be excluded from IA MDA: (i) pregnant women, (ii) the severely ill and (iii) children below 90 cm in height (approximately equivalent to < 15 kg body weight).

Implementation considerations

- Enhance administration strategies to ensure treatment is directly observed.
- Coordinate with national pharmacovigilance agencies to ensure appropriate reporting of and response to SAEs.

Monitoring and evaluation

IUs starting biannual IA would follow the same monitoring and evaluation framework conducting pre-TAS and TAS in the same number of years as with annual MDA. In IUs undergoing biannual

onchocerciasis MDA with ivermectin and a shift to biannual LF MDA with IA, monitoring and evaluation can be implemented according to existing¹ WHO guidance for IA:

- Establish baseline endemicity either through data from mapping survey or baseline sentinel site survey before beginning MDA.
- Implement a coverage evaluation after the first few rounds of MDA.
- At least 6 months after the fifth effective MDA round, monitor mid-term impact in sentinel and spot-check sites.
- At least 6 months after the tenth effective MDA round, monitor impact in sentinel and spot-check sites through a pre-TAS.
- When epidemiological thresholds (< 1% microfilaraemia or < 2% antigenaemia) are achieved in sentinel and spot-check site results, the IU can progress to TAS.
- When these epidemiological targets are NOT achieved in sentinel and spot-check sites or TAS results following MDA, the IU must undergo two additional effective MDA rounds before spot-check site assessments are repeated.

Summary of the GRADE evidence: effectiveness

One RCT among individuals infected with *W. bancrofti* (Population) examined microfilaraemia prevalence at 24 months post-MDA (Outcome), and two observational studies examined microfilaraemia prevalence reduction and CFA reduction at 24 months post-MDA (Outcomes), after treatment with biannual IA (Intervention) compared to annual IA (Comparison) (53–55). These studies, which are described in GRADE Table 4 (Annex 1), yielded the following outcomes:

- *Microfilaraemia prevalence.* In one RCT, data analysis across both groups (18 people biannual IA, 18 people annual IA) did not show a significant difference in microfilaraemia prevalence at 24 months post-biannual IA treatment compared to post-annual IA treatment (RR: 0.87; 95% CI: 0.61–1.23; very low quality of evidence). The absolute risk estimate indicates that 108 fewer persons per 1000 infected would have microfilaraemia prevalence 24 months post-biannual IA treatment, compared to post-annual IA treatment (95% CI: 325 fewer to 192 more).
- *Microfilaraemia prevalence reduction.* A pooled analysis from two observational studies did not show a significant difference in microfilaraemia prevalence reduction observed at 24 months between biannual IA (5675 people) communities and annual IA (6064 people) communities (RR: 0.83; 95% CI: 0.54–1.28; very low quality of evidence).
- *Circulating adult worm antigen reduction.* CFA data were not available from the included RCT of infected individuals. A pooled analysis from two observational studies did not show a significant difference in the circulating adult worm antigen reduction observed at 24 months between communities receiving biannual IA MDA (5675 people) and communities receiving annual IA MDA (6064); (RR: 0.55; 95% CI: 0.17–1.82; very low quality of evidence).

Summary of evidence discussed in other domains

- *Safety (non-GRADE evidence).* No direct or indirect evidence of comparative safety was identified. The WHO Programme for International Drug Monitoring's database (VigiBase) was screened for reports of suspected adverse drug reactions reported with ivermectin and

¹ Fig. 2 (8).

albendazole, individually and combined, to determine the frequency of reports and identify any unknown adverse drug reactions (50). As of November 2016, 1652 individual case safety reports had been reported in 39 countries for ivermectin alone and 13 countries (seven LF endemic) for ivermectin and albendazole since the inception of the programme (Iessa N, WHO, unpublished data, 19 May 2017). Of the total 692 different types of adverse drug reactions for ivermectin reported, the most frequently documented were pruritus (417), headache (230), dizziness (123), drug ineffective (114), vomiting (104), rash (88) and oedema (88). No unknown adverse drug reactions were detected among the individual case safety reports reported. In 2015, a total of 221 individual case safety reports were reported from 14 countries (6 LF endemic). In the 5 LF endemic countries using IA, 39.6 million persons received ivermectin and albendazole during MDA for LF and 28.5 million persons received ivermectin alone during MDA for onchocerciasis. The highest number of reports across years originated from countries that integrate pharmacovigilance into their public health programmes.

- *Balance between desirable and undesirable effects.* The guideline development group's judgement on this criterion was that the balance probably favoured annual IA (see *Justification*).
- *Quality of evidence.* The overall quality of evidence was very low based on the lowest quality of evidence across critical outcomes.
- *Resource requirements.* A study comparing the impact on resource requirements of biannual ivermectin and annual ivermectin distribution for onchocerciasis elimination resulted in higher costs per person treated (56). Similar studies that assess the impact of biannual IA for LF elimination on resource use and cost-effectiveness do not exist. The modelling study described above (section 3.1) using a Markov model based on probabilities of achieving five effective rounds and passing pre-TAS and TAS evaluations was used to estimate treatments and number of rounds of MDA required under biannual IA, compared to annual IA. Each biannual MDA round was assumed as effective as an annual MDA round based on previous mathematical model simulations (47). The model estimates 15 million more treatments and the same number of rounds would be required under biannual IA compared to annual IA. Some 23 countries were projected to stop MDA in more than 90% of endemic IUs by 2024 under biannual MDA compared to 2027 under annual IA. Based on a scenario that biannual IA is introduced to every district where eligible (areas currently receiving IA), biannual IA saves US\$ 161 million (13%) of undiscounted economic cost in IA countries (Fitzpatrick C, WHO, unpublished data, 18 May 2017). The costs compared were from the perspective of the implementing programme. It was noted that from the perspective of the health system, the savings in onchocerciasis co-endemic districts would be negligible, and possibly negative (more costly), if the yearly increase in ivermectin treatments due to the additional round would need to be purchased. It was uncertain whether biannual IA reduces costs associated with delivery compared to annual IA, because of the low certainty in the efficacy assumptions for biannual IA that were applied to the costing model. It was agreed that the cost-effectiveness of biannual IA was unknown as no studies were available.
- *Health equity.* No published studies exist that assess the impact of biannual IA on health equity. Based on the evidence described above (sections 3.1, 3.2, 4.1), the guideline development group agreed that there is probably no impact on health equity between biannual IA and annual IA (Mbabazi P, WHO, unpublished data, 17 May 2017). It was noted that delivering more than one

MDA round per year might increase the chance that an individual would be treated at least once.

- *Acceptability among stakeholders.* No published studies exist that assess the impact of biannual IA on acceptability among key stakeholders. Based on the evidence described above for biannual MDA versus annual MDA stakeholder acceptability comparisons (section 3.2), it was agreed that biannual IA was probably not as acceptable as annual IA to key LF stakeholders (i.e. community drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors).
- *Feasibility.* No published studies exist that specifically assess feasibility of biannual IA versus annual IA for LF. Ivermectin is distributed for onchocerciasis elimination more frequently than annually within some countries, demonstrating feasibility of this strategy. However, the majority of stakeholders considered that more frequent than annual MDA was not as feasible as the current annual MDA regimen (Blundell H, WHO, unpublished data, 18 May 2017). Given the discrepancy, it was agreed that the feasibility of implementing biannual IA was varied among key stakeholders.

Research priorities

There is moderate value in conducting additional studies to determine whether biannual IA is more effective than annual IA. Studies to determine whether two MDA rounds per year increases annual coverage of the population are warranted. Additionally, economic evaluations are needed to determine the cost–benefit ratio of any increased annual coverage with additional resource requirements due to delivery of two versus one round in a year.

4.3. Comparison of biannual albendazole versus annual albendazole (loiasis co-endemic)

Background

The standard treatment strategy of IA MDA for LF in onchocerciasis endemic countries is not recommended in areas of West and Central Africa where loiasis is co-endemic due to the risk of SAEs after treatment with ivermectin in individuals with high *Loa loa* microfilaraemia. In response to the need for an alternative regimen in IUs co-endemic for LF and loiasis, a provisional recommendation was developed after a technical consultation (57), which was then endorsed by the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases during their 8th meeting (Geneva, 21–22 April 2015) on once, preferably twice, yearly albendazole MDA with coordinated vector control where there is:

- any evidence of *L. loa*; and
- ivermectin treatment has not already been introduced either in LF-only or in LF districts with co-endemic or uncertain onchocerciasis (24).

As described above (sections 3.3, 3.4), twice-yearly or more frequent MDA with ivermectin has been successfully implemented for LF and other neglected tropical diseases. To address LF in loiasis co-endemic IUs, the provisional albendazole MDA strategy is currently being implemented biannually in at least one country. Vector control is still recommended with MDA for LF elimination in this setting and programmes are encouraged to coordinate vector control activities with malaria elimination efforts. The

guideline development group considered biannual albendazole as an alternative MDA regimen for loiasis and LF co-endemic countries to employ, along with vector control for malaria, to eliminate LF as a public health problem, and to address pre-specified technical situations.

Albendazole monotherapy MDA for LF elimination applies when ivermectin has never been introduced to loiasis co-endemic areas with or without onchocerciasis (53). Where ivermectin MDA has occurred for either LF or onchocerciasis elimination, IA regimen can continue under current guidance on use of ivermectin for onchocerciasis in areas co-endemic for loiasis (23, 58).

**In countries using IA to eliminate lymphatic filariasis
(lymphatic filariasis co-endemic with loiasis)**

Recommendation: [PICO 5]

WHO recommends biannual albendazole rather than annual albendazole in IUs where LF is co-endemic with loiasis and ivermectin has not already been distributed for either onchocerciasis or LF.

This is a conditional recommendation based on overall very low quality of evidence until new data on albendazole alone MDA become available and WHO updates guidelines.

Justification for the recommendation

No direct comparative studies investigate biannual versus annual albendazole MDA. Efficacy studies of annual albendazole administration alone were inconsistent. Important yet limited evidence from observational studies suggest that biannual albendazole MDA is safe and effective (very low quality). There were no concerns about health equity of biannual albendazole MDA compared to annual albendazole MDA, and it was noted that biannual treatment may reach populations unable to or unavailable to participate in a single yearly round. Biannual albendazole is being implemented currently in some LF and loiasis co-endemic countries, demonstrating acceptability and feasibility across key stakeholders. No costing study was available but resources associated with delivery are expected to increase in the short term with two MDA rounds versus one per year.

Subgroup considerations

According to existing WHO guidance referenced in Chapter 1 in the discussion on eligible and ineligible populations, three groups are to be excluded from biannual albendazole MDA: (i) pregnant women in the first trimester, (ii) individuals with history of neurocysticercosis or seizures and (iii) children aged under 2 years.

Implementation considerations

- Coordinate MDA with vector control activities of the malaria elimination programmes.
- Enhance administration strategies to ensure treatment is directly observed.
- Coordinate with national pharmacovigilance agencies to ensure appropriate reporting of and response to SAEs.

Monitoring and evaluation

According to existing¹ WHO guidance for IA and DA:

- Establish baseline endemicity either through data from mapping survey or baseline sentinel site survey before beginning MDA.
- Implement a coverage evaluation after the first few rounds of MDA.
- At least 6 months after the fifth effective MDA round, monitor mid-term impact in sentinel and spot-check sites (optional).
- At least 6 months after the tenth effective MDA round, monitor impact in sentinel and spot-check sites.
- When epidemiological thresholds (< 1% microfilaraemia or < 2% antigenaemia) are achieved in sentinel and spot-check site results, the IU can progress to TAS.

When these epidemiological thresholds are NOT achieved in sentinel and spot-check sites or TAS results following MDA, the IU must undergo two additional effective rounds of MDA before spot-check site assessments are repeated.

Summary of the GRADE evidence: effectiveness

No direct evidence of comparative effectiveness was available. One single-arm before–after observational study among individuals infected with *W. bancrofti* (Population) examined microfilaraemia prevalence reduction and circulating filarial antigen, both at 36 months post-MDA (Outcomes) following treatment with biannual albendazole (Intervention) (47). This study, which is described in GRADE Table 5 (Annex 1), yielded the following outcomes:

- *Microfilaraemia prevalence reduction.* 36 months post-MDA with biannual albendazole showed a 94.3% reduction in microfilaraemia prevalence (very low quality of evidence). This was a single-arm community cohort study. These findings were indirectly compared with another single-arm study investigating the effectiveness of annual albendazole (600 mg). After 15 months, 1/12 patients (< 10%) were cleared of microfilariae (59).
- *Circulating filarial antigen:* 36 months post-MDA with biannual albendazole showed a 72.8% reduction in circulating filarial antigen prevalence (very low quality of evidence). This was a single-arm community cohort study. These findings were indirectly compared with another single-arm observational study investigating the effectiveness of annual albendazole (600 mg). After 15 months, 0/12 patients were cleared of antigen (59).

Summary of the evidence in other domains

- *Safety (non-GRADE evidence).* No direct or indirect evidence of comparative safety was available. The WHO Programme for International Drug Monitoring database (VigiBase) was screened for reports of suspected adverse drug reactions reported with albendazole to determine the frequency of reports and identify any unknown adverse drug reactions (50). As of November 2016, a total of 2140 cumulative individual case safety reports (89 to 345 per year) originating from 67 countries had been submitted to VigiBase. Of the 563 different types of adverse drug reactions for albendazole reported, the most frequently documented were

¹ Fig. 2 (8).

vomiting (278), headache (275), abdominal pain (268), pruritus (262), nausea (184), diarrhoea (167) and rash (165). No signals for unknown adverse drug reactions were detected among the individual case safety reports reported. In 2015, 304 individual case safety reports were reported from 32 countries (12 LF endemic). In the 12 LF endemic countries, 335.1 million persons received albendazole during MDA for LF and 199.8 million persons received albendazole alone during targeted treatment for control of soil-transmitted helminth infections.

- *Balance between desirable and undesirable effects.* The guideline development group's judgement on this criterion was that the balance probably favoured biannual albendazole (see *Justification*).
- *Quality of evidence.* The overall quality of evidence was very low based on the lowest quality of evidence across critical outcomes.
- *Resource requirements.* No published studies exist that assess the impact of biannual albendazole on resource use and cost-effectiveness. Comparison of biannual albendazole versus annual albendazole was not conducted using the above-mentioned Markov model (sections 3.1, 3.2, 4.1, 4.2). The model only assumed biannual albendazole and that each two MDA rounds were equivalent in efficacy to a single MDA round with a two-drug regimen. Therefore, IUs starting biannual albendazole would be eligible to conduct pre-TAS and TAS in the same number of years as MDA with IA. All eight LF-loiasis co-endemic countries were projected to stop MDA in more than 90% of endemic IUs by 2027 under biannual albendazole. It was agreed that the cost-effectiveness of biannual albendazole was unknown as no studies were available.
- *Health equity.* No published studies exist that assess the impact of biannual albendazole on health equity. Based on the evidence described above (sections 3.1, 3.2, 4.1, 4.2), it was agreed that there is probably no impact on health equity between biannual albendazole and annual albendazole (Mbabazi P, WHO, unpublished data, 17 May 2017). It was also noted that delivering more than one MDA round per year might increase the chance that an individual would be treated at least once.
- *Acceptability among key stakeholders.* No published studies exist that assess the acceptability of biannual albendazole versus annual albendazole. It was agreed that biannual albendazole was probably acceptable to key stakeholders (i.e. community drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors). It was also noted that at least one country is currently implementing biannual albendazole for LF in loiasis co-endemic IUs, demonstrating stakeholder acceptability.
- *Feasibility.* No published studies exist that assess the feasibility of biannual albendazole versus annual albendazole. It was also noted that at least one country is currently implementing biannual albendazole for LF in loiasis co-endemic IUs, demonstrating feasibility. Albendazole is routinely administered biannually to school-aged children for the control of soil transmitted helminth infections in several countries. It was agreed that biannual albendazole is probably feasible to key stakeholders (i.e. MDA beneficiaries, community drug distributors, health workers, Ministry of Health staff, academic researchers, nongovernmental organization staff, pharmaceutical representatives and donors).

Research priorities

Future social and biological evidence comparing the impact of biannual and annual albendazole MDA would be required to consider a revision of the current recommendation.

5. Dissemination, implementation, and monitoring and evaluation of the guideline

5.1. Dissemination

The guideline will be disseminated on the WHO website and shared through the mailing lists of the WHO Department of Control of Neglected Tropical Diseases. Staff of the WHO secretariat will work at the international level to ensure broad dissemination across WHO regional and country offices, health ministries in countries endemic for LF, Regional Programme Review Groups, pharmaceutical manufacturers of MDA medicines, bilateral donor organizations, nongovernmental organizations, academic institutions and other key partners and stakeholders working to overcome neglected tropical diseases. The points of contact in the WHO regional offices will disseminate the guideline to WHO country offices, health ministries and key partners and stakeholders at the regional and country levels. The guideline and associated annexes will be accessible on the WHO website (in English and eventually in French).

The guideline will be complemented by a field guide for programme managers on implementation of alternative LF MDA regimens, a derivative product intended to aid in-country and subnational decision-making, planning, implementation, and monitoring and evaluation. This field guide will focus on improving access to the guideline and on related implementation considerations for stakeholders who play a crucial role in LF MDA at the national and subnational levels, including those who have historically faced barriers in accessing information (e.g. district-level public health officers responsible for MDA management and health worker supervisors of MDA).

5.2. Implementation

This guideline will be implemented by health ministries at the country level, and the strategies for implementing alternative MDA regimens should be adapted to the context of each Member State. WHO will technically support the efforts of stakeholders to adopt and adapt the guideline, and develop implementation plans tailored to the local context that are appropriate to the specific needs of country health systems. Building upon the preliminary work of the various stakeholders' surveys, the WHO secretariat will continue to work with all stakeholders and implementers to identify barriers and facilitators to guideline implementation.

Attaining consistent, effective rounds of LF MDA through the alternative regimens recommended herein will require integration of these new regimens into national guidelines on LF and neglected tropical diseases, and strong coordination and advanced planning of MDA with national health system implementation agendas. To aid countries in their implementation efforts, the WHO field guide for programme managers on implementation of alternative LF MDA regimens will contain planning and implementation tools for use at the national and subnational levels of endemic countries, with dedicated sections on leadership, advocacy and communication; staffing and human resources; medicines, supplies and supply chain; system organization and strategic planning; community-level implementation; and financial implications.

In accordance with existing WHO guidance on LF, this guideline follows the GPELF strategic framework, which is based on a public health approach to eliminate LF as a public health problem (9, 60). This approach seeks to ensure that consistent, effective rounds of MDA are provided at the population level

to interrupt transmission of LF in the community. Implementation strategies are therefore based on simplified and standardized approaches in MDA that have already proven technically feasible on a large scale through the health systems of countries endemic for LF with limited resources, including health system organization and capacity, human resources and staffing, medicines and availability of supplies, monetary resources, feasibility and community-level acceptability. Implementation of this guideline as part of the GPELF framework will help countries in their efforts to address the United Nations Sustainable Development Goals by 2030 and promote poverty reduction (SDG 1), health (SDG 3), quality education (SDG 4), gender equality (SDG 5), good jobs and economic growth (SDG 8) and reduced inequalities (SDG 10) (61).

5.3. Monitoring and evaluation

WHO will monitor the impact of the implementation of this guideline by collecting data on the number of countries and the number of IUs within countries that choose to use alternative LF MDA regimens according to WHO recommendations. The impact of the guideline will be evaluated by ascertaining progress towards meeting LF elimination criteria for interruption of transmission while using the alternative LF MDA regimens. Progress made at the IU and country level will be routinely monitored by WHO regional offices and discussed among the Regional Programme Review Groups as epidemiological data are closely reviewed on an ongoing basis. Data will be collected in each country's annual reporting to WHO through the Joint Application Package as well as documented in Regional Programme Review Group meeting reports and in the country validation of elimination dossiers. Annual data reported from LF endemic countries are housed in the WHO preventive chemotherapy databank. Annual progress updates on global LF elimination will be shared in the WHO *Weekly Epidemiological Record*.

The WHO Department of Control of Neglected Tropical Diseases will utilize reported data to monitor the coverage of the current and alternative MDA regimens using the following indicators:

- *Geographical coverage.* The proportion of LF endemic IUs that have started MDA.
- *Epidemiological coverage.* The proportion of the total population who ingested the medicine or combination of medicines during MDA.
- *Effective coverage.* The proportion of IUs implementing MDA that directly observed at least 65% of the total population ingesting the medicines.

Reported data will be utilized to monitor the impact associated with current and alternative MDA regimens by assessing the proportion of IUs successfully meeting the elimination targets including:

- the proportion of sentinel and spot-check surveys meeting epidemiological criteria of success (< 1% microfilaraemia or < 2% antigenaemia); and
- the proportion of IUs that pass TAS (number of infected children is below the critical cut-off threshold).

The following tracer indicator for the success of programmes towards meeting SDG 3 target 3.3 to “end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases” will be monitored specifically at the global level:

- The reduction in the population requiring interventions for neglected tropical diseases. For LF the target goal is an 80% reduction in the total population requiring MDA by 2020 compared to 1.4 billion persons estimated to have required MDA in 2010 (62, 63).

The WHO International Drug Monitoring Programme will continue to monitor and evaluate individual case safety reports submitted by WHO Member States related to the administration of ivermectin, diethylcarbamazine and/or albendazole. These data will be stored in the WHO Vigibase and will be available through VigiAccess™. Monitoring reports will be generated and reviewed annually through an interdepartmental collaboration between the WHO Department of Control of Neglected Tropical Diseases and the WHO Department of Essential Medicines and Health Products.

To aid countries in their comprehensive monitoring and evaluation efforts during and after implementation, a WHO field guide for programme managers on implementation of alternative LF MDA regimens will contain detailed guidance on epidemiological monitoring and evaluation, adverse event monitoring and national pharmacovigilance integration with MDA.

5.4. Guideline updates

Research trials are under way that aim to generate additional evidence related to efficacy and safety of the current and new MDA regimens for LF. As such, amendments to this guideline may be issued in accordance with the WHO handbook on guideline development. The WHO Department of Control of Neglected Tropical Diseases will review any additional evidence after 2 years from the release of this guideline and reassess the need to prepare updates. The guideline development group and their decision-making will remain guided by the need for effective, safe and accelerated strategies to enable countries to interrupt transmission of LF, and to attain elimination of the disease as a public health problem by 2020.

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