Malaria Policy Advisory Committee Meeting

14–16 September 2016, Geneva, Switzerland
Background document for Session 9

Ivermectin for malaria transmission control

Technical consultation meeting report
WHO Headquarters, Geneva 30 March–1 April 2016

Summary

Ivermectin is an antihelminthic drug used to control several neglected tropical diseases (NTDs). It has also been found to kill *Anopheles* mosquitoes that ingest it in a blood meal. As a result, the community administration of ivermectin may have the potential to reduce malaria transmission by acting as an *Anopheles* adulticide. This approach could be used to complement other measures used for vector control, targeting outdoor biting and crepuscular vectors that are less affected by LLINs and IRS. In view of this potential, and in light of the persistent gaps in evidence, clear guidance for the research and development of this tool is needed. This document summarizes the outcomes of a WHO technical consultation meeting on ivermectin for malaria transmission control, in which the current understanding of these issues was reviewed and a cohesive strategy for the next steps laid out.

The target product profile developed at this WHO technical consultation is presented for consideration by the WHO Malaria Policy Advisory Committee.

1. Background

One of the key supporting elements of the *Global Technical Strategy for Malaria 2016–2030* is to harness innovation and expand research *(1)*. To accelerate progress towards elimination and to counteract the emerging threats posed by drug and insecticide resistance, efforts should be centered on fostering innovation and developing new tools and actions to facilitate the introduction of new products and strategies.

Ivermectin is a broad-spectrum antihelminthic medicine that is used extensively for the control of onchocerciasis and lymphatic filariasis (LF). It is a core component of current mass drug administration (MDA) efforts in the elimination of both onchocerciasis and LF; it is administered as a single dose one to four times per year. This MDA, however, excludes children under 15 kg, pregnant women, lactating women in the first week postpartum, and those who are severely ill.

In vitro studies have shown that ivermectin also acts as an endectocide, causing the death of *Anopheles* mosquitoes that ingest sufficient doses in a blood meal *(2-6)*. These results have also been confirmed in clinical studies using membrane *(7)* and direct-feeding *(8)* methodologies. Modelling based on these studies indicates that MDA with ivermectin has the potential to reduce malaria transmission *(9, 10)*, mainly by negatively impacting mosquito survival, fitness, and fertility, and potentially inhibiting sporogony.

Although there has been a marked increase in the research on this topic in recent years, the different methods used and heterogeneity of study outcomes have limited comparability and precluded a systematic analysis of the evidence. The table in Annex 1 summarizes the available published studies assessing the effect of ivermectin on malaria vectors.

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Despite this increased attention, many unanswered questions remain, particularly with regard to a clear definition of effect, understanding the ideal dose, the duration of therapy, frequency of administration, and the percentage of the population that would need to be treated in order to see a meaningful effect on transmission. Furthermore, there is no clear understanding of how endemicity affects the impact of ivermectin, and there is a lack of clinical safety data on infants and pregnant women.

Given ivermectin's potential public health role at the intersection of control measures targeting malaria and NTDs, the WHO Global Malaria Programme and the Department for Control of Neglected Tropical Diseases jointly organized this technical consultation meeting. The objective was to develop a target product profile (TPP) that would define the key questions that an ivermectin research agenda should address in order to generate the appropriate evidence to ultimately define a WHO policy position on the role of ivermectin in the reduction of malaria transmission. It is hoped that this will help to better focus the efforts of multiple research initiatives on these policy and programme goals.

2. Overview

2.1 Rationale

The rationale for this meeting was to further explore the potential of ivermectin in malaria control and elimination, as summarized below.

Directly targeting the mosquito through the community-wide use of ivermectin as a complement to current control tools (e.g., good case management and vector control *(11, 12)*) has the potential to further reduce malaria transmission, particularly in the following situations:

a. Residual transmission resulting mainly from exophagic and exophilic vectors that escape vector control by long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), respectively *(13)*.

b. Insecticide resistance; this is because ivermectin´s mechanism of action differs from that of other current public health insecticides. Pilot studies have shown that pyrethroid-resistant *Anopheles* remain susceptible to ivermectin *(14)*. Although Drosophila can be selected for ivermectin resistance in the lab *(15, 16)*, the low fertility observed in mosquitoes after ivermectin exposure has so far precluded the selection of ivermectin-resistant mosquitoes (see below).

c. Settings where transmission persists despite implementation of all effective vector control interventions *(17)*.

Abbreviations

ACT	artemisinin combination therapies
DEC	diethylcarbamazine
DHA	dihydroartemisinin
EIR prequalification	entomological inoculation rate
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
IRS	indoor residual spraying
LC50	lethal concentration 50
LF	lymphatic filariasis
LLINs	long-lasting insecticidal nets
MDA	mass drug administration
MMV	Medicines for Malaria Venture
NTDs	Neglected Tropical Diseases
PK	pharmacokinetics
TPP	target product profile
WHO	World Health Organization
WHO-PQ	WHO prequalification

2.2 Objectives

General objective:

- To define the key missing data in order to make a policy recommendation on the use of ivermectin in the reduction of malaria transmission. The development of a target product profile (TPP) for ivermectin as a tool to reduce malaria transmission would help to achieve this objective.

Specific objectives:

- To define the experimental data needed to establish a regimen of ivermectin that can be used to reduce transmission. This needs to take in account the known safety data and data gaps on ivermectin, which necessarily place constraints on dose, dose frequency and the number of cycles of therapy;
- To set a threshold for the minimum desired efficacy for transmission reduction, and determine how this should be measured; to map a process for linking this back to public health impact or insect feeding assays;
- To define relevant delivery strategies for deployment in order to achieve the desired impact;
- To identify any additional gaps in the knowledge needed to support the implementation of ivermectin in resource-poor settings;
- To evaluate the clinical development and regulatory pathways for ivermectin as a tool for reducing malaria transmission.

2.3 Process

During the meeting, the following topics were presented and/or discussed:

1. Review of the mosquitocidal efficacy of ivermectin and its relationship with the pharmacokinetic properties of the drug;
2. Overview of ongoing clinical trials and potential designs for new trials;
3. Potential entomological endpoints for assessing the efficacy of ivermectin;
4. Potential markers of the effect of ivermectin on malaria transmission;
5. Modelling of the potential impact of ivermectin on malaria transmission;
6. Standardized, replicable assays to assess the efficacy of ivermectin with respect to malaria transmission;
7. Considerations regarding the safety of using ivermectin for malaria control, given the current approved doses and usage;
8. Ivermectin resistance: evidence from onchocerciasis elimination programmes and potential mechanisms in mosquitoes;
9. Progress and challenges of large-scale ivermectin use for the elimination of onchocerciasis and LF, and implications for malaria vector control;
10. Potential risks and benefits of ivermectin use for malaria control in the light of for its current use for NTDs;
11. Possible regulatory pathways for supporting the deployment of ivermectin as a vector control tool;
12. Considerations regarding supply and an appropriate business model;
13. Considerations for a TPP for ivermectin as a vector control tool.

3. Topics presented and discussed

3.1 Review of the mosquitocidal efficacy of ivermectin and its pharmacokinetic properties

Data from 26 studies evaluating the effect of ivermectin on the mortality of *Anopheles* mosquitoes were reviewed *(2-8, 14, 18-35)* (See table in annex 1). The multiplicity of methods and endpoints used has resulted in 137 different experiments generating data that cannot be easily pooled. The effect on mosquito mortality is nonetheless clear.

Two key factors influence the efficacy of ivermectin for reducing malaria transmission. The first is the plasma levels reached after a given dose. Mosquito mortality is related to ivermectin blood concentration in a dose-dependent manner. This relationship can be numerically expressed as the concentration that kills 50% of the mosquitoes within a certain time period after the blood meal – the lethal concentration 50 (LC50). The second factor is the length of time that the plasma concentration is sustained above this level. The net endectocidal effect is driven by the length of time above the LC50, rather than the peak ivermectin concentration *(10)*. Importantly, the LC50 is likely to vary depending on the mosquito species *(6)*.

Additionally, mosquitoes that consume a blood meal when ivermectin is present but below lethal concentration will experience sublethal effects, which include reduced fitness and fertility *(5)*. At these lower concentrations, partial sporogony inhibition may also be observed *(26, 32)*.

Several pharmacological strategies can increase the length of time above the LC50 and thus ivermectin's efficacy in killing mosquitoes:

a. Increasing the dose of ivermectin. This will increase the length of time above the LC50, but at the expense of higher peak concentrations; this may cause adverse events. It is worth noting that ivermectin has been approved for use at 200 mcg/kg *(36)*, but the doses currently being evaluated for malaria range from 150 mcg/kg *(37)* to 600 mcg/kg in various regimens *(38)*.
b. Repeated dosing regimens. Such regimens increase the length of time above the LC50 without a major effect on the Cmax, and are more attractive. However, they make field deployment more complicated. Ivermectin has been approved for up to two doses of 200 mcg/kg within 2 weeks for scabies; in severe cases of crusted scabies, however, more than three doses may be used *(39)*.
c. Long-lasting formulation suitable for administration in a single encounter. In the long term this type of formulation is more attractive, but requires new product development and registration.
d. Increasing population exposure to or blood sources with ivermectin, i.e., alternate sources of blood meal containing ivermectin for mosquitoes, for example, targeting cattle in areas where there are zoophilic vectors.

Although research programmes are currently assessing the potential of new long-lasting ivermectin formulations, these lay outside the scope of this meeting. Also, while some compounds currently in use in veterinary medicine have shown potential as adulticides with a longer half-life than ivermectin, developing these compounds for use in humans would involve an extensive developmental pathway; therefore, such compounds were not considered in this meeting.

Key conclusions

- Ivermectin increases the mortality of *Anopheles* mosquitoes that ingest it in a blood meal;

- Mosquito mortality is directly related to (a) the concentration of ivermectin in the blood (i.e., dose-response gradient) being above a known threshold that is lethal to the mosquito *and* (b) the duration of such concentration levels and percentage of blood sources treated with the medicine;
- The endectocidal effect is driven by the length of time above the LC50, rather than the maximum concentration of ivermectin;
- Pharmacological strategies to increase the efficacy of ivermectin include:
    a. The use of doses higher than the ones approved for onchocerciasis and LF;
    b. Periodic re-dosing schemes;
    c. Slow-release formulations suitable for administration in a single encounter;
    d. Increase of blood sources for mosquito ingestion containing ivermectin at concentrations above the threshold that is lethal to the mosquito.

3.2 Potential entomological endpoints for assessing the efficacy of ivermectin

The lethal concentration, expressed as the concentration that kills 50% of the mosquitoes within a certain time period after a blood meal (LC50), is an entomological parameter that is used to assess the susceptibility of any given mosquito species to the lethal effect of a chemical agent. The ivermectin-LC50 can be used to parameterize the susceptibility of each mosquito species to the mosquitocidal effect of the drug.

An increase in mosquito mortality following ivermectin MDA is expected to result in a decrease in malaria transmission. For the purposes of ivermectin evaluation, parasitological and entomological endpoints can be used to assess the drug's impact on transmission and to guide progress; yet, epidemiological outcome measures are needed to prove the drug's impact on human health and are proposed as the primary study endpoints.

Once an epidemiological impact is proven, it can be used to validate the best predictive entomological measure.

During the meeting, a reduction of at least 20% in clinical malaria incidence lasting for at least 1 month after a single round of ivermectin MDA was considered to be a target of public health relevance over the long term.

Key conclusions

- Any proposed entomological outcome measures of ivermectin efficacy should be validated against a proven human epidemiological impact;
- A reduction of at least 20% in clinical malaria incidence lasting for at least 1 month after a single round of ivermectin MDA was considered to be a target of public health relevance over the long term.

3.3 Potential surrogate markers of the effect of ivermectin on malaria transmission

Ivermectin affects nearly all aspects of vectorial capacity (i.e., survivorship, re-feeding frequency *(5)*, vector competence for *Plasmodium*) (26, 32) (See table in annex 1). The drug does not act by cuticular exposure like insecticides; it is absorbed via the mosquito gut. It then binds to the glutamate-gated chlorine channels, causing paralysis and death *(36)*. This mechanism differs from that of other public health insecticides used today. New data on ivermectin's sublethal effects suggest that it also disrupts sterol homeostasis, perturbs the peritrophic membrane and midgut structure and/or function, and interacts with the midgut microbiota *(35)*. Hence, an

insectary-based entomological surrogate alone is likely to fail to encompass the full effects on malaria transmission.

A number of measures for the broad effects of ivermectin have been proposed; these can be divided into five categories:

1. Basic entomological
    - Mosquito mortality (measured by the LC50 as indicated above) *(5, 6)*
    - Reduced mosquito fitness and fertility *(5, 24)*
2. Expanded entomological
    - Mosquito population age structure as measured by parity rates *(12, 22, 30)*
    - Mosquito density
    - Mosquito biting rate, measured directly or by human antibody response *(40)*
3. Entomological-parasitological
    - Sporozoite index, as markers of sporogony inhibition by ivermectin in the blood meal *(23, 26, 32)*
    - Variations in the entomological inoculation rate (EIR), resulting from direct and indirect mosquito killing and the effect of ivermectin on the completion of the sporogonic cycle
4. Epidemiological-parasitological
    - Prevalence of parasitaemia measured directly in humans
    - Incidence of parasitaemia measured indirectly in humans (i.e., through molecular force of infection, complexity of infection or serological markers of recent infection)
5. Incidence of malaria infections and clinical malaria cases

Key conclusions

- Ivermectin affects many biological functions, impacting the capacity of the *Anopheles* mosquitoes to transmit malaria;
- An insectary-based surrogate might fail to encompass the full effect of the drug on malaria transmission;
- The LC50 of ivermectin could be useful in guiding further epidemiological studies;
- Ivermectin's impact on mosquito longevity and mosquito population age structure may be the main mechanism affecting malaria transmission. The impact of ivermectin on the age structure of wild mosquito populations needs to be better elucidated;
- The sublethal effects of the drug on mosquito fertility, flying capacity and sporogony may also increase the impact on public health.

3.4 Modelling the potential impact of ivermectin on malaria transmission

A mathematical model of the impact of ivermectin on malaria transmission has been developed based on the pharmacokinetics of the drug after oral administration and the expected increase in mosquito mortality after ingesting blood at different concentrations of ivermectin *(10)*. This model has been found to correlate well with empirical findings for a wide range of scenarios *(9)*. It can also be used to inform trial design.

The model suggests that (a) the increase in the mortality risk to mosquitoes is exposure-dependent, (b) the effect begins rapidly with maximum vector mortality occurring within 24 hours after blood-feeding, (c) the mosquito mortality rate remains above baseline for

approximately 6 days after a single round of MDA, and (d) the duration of the mosquitocidal effect of the drug (i.e., the length of time above mosquito-killing levels) is the main parameter that drives impact.

The FDA-approved ivermectin regimen for onchocerciasis – a single yearly dose of 150 mcg/kg – would achieve a plasma concentration above the LC50 for *Anopheles* mosquitoes for approximately 6 days. Such an effect would have a very limited impact on the local mosquito population, explaining the lack of a measurable effect on malaria transmission in areas receiving ivermectin MDA for NTDs.

The main modelled findings suggest that (a) ivermectin can increase the impact of MDA with an ACT on malaria prevalence and incidence, i.e., with fewer MDA rounds, (b) adding ivermectin can sustain impact if ACT coverage is reduced, and (c) formulations or dosage schemes that can deliver longer plasma residence times would more effectively suppress vector populations. See Annex 2 for an example of the modelled impact of theoretical treatment schemes capable of sustaining mosquito-killing concentrations for a duration of at least 2 weeks.

Key conclusions

- The model can simulate a wide range of scenarios, including transmission intensity, different formulations and combination with other interventions;
- Modelling can be used to assist with trial design.
- The main findings are that:
    a. Ivermectin can increase the impact of MDA with an ACT on malaria transmission;
    b. Adding ivermectin could help to sustain impact on malaria prevalence and incidence if MDA ACT coverage is reduced;
    c. Extending ivermectin exposure with re-dosing or longer-lasting formulations or dosing schemes could suppress vector populations for prolonged periods.

3.5 Standardizing assays to assess the impact of ivermectin on malaria transmissibility and mosquito mortality

There has been considerable progress in harmonizing the protocols for membrane-feeding assays in several expert centres, and in increasing the capacity to replicate these in the field. These methods can be used to identify (Bousema, personal communication) or profile systemic insecticides (24, 26) and measure the LC50. These evaluations can assess the magnitude and duration of effect, and the potential transmission-blocking properties of ivermectin *(26, 32)*. Coupling these assay results with pharmacokinetic (PK) analysis and modelling may help to predict a community effect (9, 10); however, this approach requires validation in field studies.

Some studies have suggested that a concentration of 6 ng/ml of ivermectin in the blood meal would be enough to kill 50% of the *Anopheles gambiae* that take a blood meal, within 10 days *(7)*.

Conflicting evidence has been generated with regard to the differences in mosquito mortality observed following direct skin and membrane feeding at the same ivermectin concentration (Ter Kuile and Monteiro, personal communication).

Key conclusions

- Membrane feeding can be used to identify, characterize and compare systemic insecticides in a controlled environment;
- Membrane feeding can also be used to assess the potential transmission-blocking capacity of some systemic insecticides, including ivermectin;

- Membrane feeding assays, coupled with PK analysis and modelling, could help to predict a community effect of ivermectin MDA; although this approach has not yet been validated, evidence has been accumulating;
- The association between ivermectin efficacy by membrane-feeding assays and by skin-feeding assays needs to be parameterized.

3.6 Pharmacokinetic considerations regarding the safety of the use of ivermectin for malaria

When used at the dose currently approved for onchocerciasis or lymphatic filariasis (150–400 mcg/kg one to four times a year) or *Strongyloides stercoralis* (200 mcg/kg in a single dose), ivermectin is remarkably safe for humans weighing more than 15 kg *(36)*. More frequent administration has been recommended for use against scabies in Australia *(39)*. If the dose or frequency required to reduce malaria transmission is higher, it will be important to establish the safety of the new treatment schemes.

Based on pharmacokinetic modelling, a regime consisting of a daily dose of 600 mcg/kg for 3 days has the potential to sustain ivermectin concentrations lethal to *Anopheles* mosquitoes for at least 1 week *(41)*.

The extensive data available in the context of the Mectizan® donation programme suggest that the current dose approved for onchocerciasis or lymphatic filariasis is extremely safe. By inference, prudent exploration of the safety of higher doses is warranted. In fact, single doses as high as 2000 mcg/kg (10-fold the dose currently used for onchocerciasis) and cumulative doses of up to 3200 mcg/kg in 1 week have been well tolerated by healthy volunteers *(42)*.

Drug–drug interactions with concomitant therapy, such as artemisinin combination therapies (ACTs), have not been well explored. In a small study in Burkina Faso, coadministration with artemeter-lumefantrine was well tolerated [7]; preliminary data from Kenya have suggested that coadministration with DHA-piperaquine could also be safe (Ter Kuile, personal communication).

There are extremely limited safety data on children under 15 kg, who are not currently covered under the US FDA or Australian TGA approval for ivermectin (39, 43). Use during pregnancy has not been studied extensively, presenting a potential risk if the mass administration includes women of childbearing age. In effect, if the population coverage needs to be increased to include these special populations, additional data will be needed.

Ivermectin MDA for malaria would yield an indirect personal benefit if it could be demonstrated that it reduces local malaria transmission. Transmission (defined as infection incidence) should be the primary endpoint of any pivotal study. The precise measure of transmission would need to be tailored according to the endemicity of the study site.

If ivermectin is administered to individuals with a high burden of the filarial nematode *Loa loa* (particularly above 30 000 mf/ml), there is risk of a severe adverse event (SEA) in the form of encephalopathy syndrome that might cause death *(44)*. The mechanism of this complication is unclear (45, 46), which means that ivermectin MDA for blocking malaria transmission would be precluded from large areas of Central Africa. Therefore, more research on this mechanism is urgently needed. Current management strategies include enhanced community and health worker awareness, as well as case management guidelines *(44)*. The Rapid Assessment Procedure for Loiasis (RAPLOA) *(47)* can help predict the *Loa loa* community prevalence based on common manifestations of the disease.

Key conclusions

- At the doses recommended for MDA and the treatment of onchocerciasis, LF or strongyloides, ivermectin has a remarkable safety profile. Limited data suggest that higher doses are also safe;
- Preliminary evidence suggests that ivermectin can be given safely in conjunction with antimalarials;
- Operational research on the impact of ivermectin MDA will address the need to include children under 15 kg and pregnant women currently excluded from ivermectin MDA for NTDs;
- The *Loa loa*-associated encephalopathy induced by ivermectin is a serious problem that precludes large populations from receiving ivermectin and requires additional research to identify appropriate risk-mitigation strategies.

3.7 Ivermectin resistance: evidence from onchocerciasis elimination programmes and potential mechanisms for mosquito resistance

Regarding helminths: Suboptimal response to ivermectin in onchocerciasis patients, defined as persistent, significant microfilaridemia, has been reported in West Africa *(48-50)*. Yet, these sites show persistent impact on infection prevalence *(51)*. This finding could be related to lower coverage due to problems with delivery/uptake *(52-55)*. Increasing the frequency of rounds of ivermectin MDA has been proposed as a strategy to reduce the impact of suboptimal-responding parasites as part of onchocerciasis-elimination strategies.

There is currently no evidence to suggest that MDA with ivermectin for malaria control would negatively impact NTD control (Kuesel, personal communication).

Regarding mosquitoes: Ivermectin binds to glutamate and GABA-gated chlorine channels, causing hyperpolarization and paralysis. The results of in vitro experiments showed a natural variant isoform of these channels in *Anopheles gambiae* to be insensitive to the drug; however, the implications of the expression of this isoform in wild mosquitoes for the lethal effect of ivermectin remain unclear *(56)*. So far, no ivermectin-resistant mosquitoes have been identified. Although *Drosophila* can be selected for ivermectin resistance (15, 16), mosquitoes feeding on sublethal concentrations of ivermectin have shown reduced fertility, impeding the selection of ivermectin-resistant mosquitoes in the lab (B. Foy, personal communication).

A study done with *Anopheles coluzzi* carrying the *kdr* mutation associated with pyrethroid resistance showed that the mosquitoes remained susceptible to ivermectin *(14)*.

Key conclusions

- There is currently no evidence to suggest that ivermectin MDA for malaria would negatively impact onchocerciasis control. Increasing treatment frequency is one strategy to manage suboptimal ivermectin response with onchocerciasis;
- Ivermectin's mechanism of action on *Anopheles* mosquitoes differs from that of public health insecticides used for malaria vector control;
- A potential ivermectin-resistance mechanism could be the selective expression of glutamate-gated channels insensitive to the medicine; yet, the antifertility effect of the drug has hampered the lab-based selection of ivermectin-resistant mosquitoes;
- There has been no evidence of cross-resistance to ivermectin in *kdr*-carrying mosquitoes.

3.8 3.8 Safety of ivermectin in MDA campaigns

Given its mechanism of action, the central nervous system (CNS) is the primary target of ivermectin toxicity in all species examined.

Preclinical safety studies to support deployment against nematodes have included 14 weeks of daily repeated administration in rats and dogs *(57)*, establishing a "no observed adverse event level" (NOAEL) of 400 and 500 mcg/kg/day, respectively. This duration is considerably longer than that of the scheme expected to reduce malaria vector survival. Additionally, a 2-week study in immature *Rhesus* monkeys with daily doses of up to 1200 mcg/kg found no treatment-related adverse events *(57)*.

In another study using ascending doses in Rhesus monkeys, emesis was first observed at the 2000 mcg/kg dose *(57)* – a level that is significantly higher than the exposure required to kill feeding mosquitoes.

Phase I trials in healthy volunteers in the US have suggested that a single dose of up to 2000 mcg/kg is well tolerated *(42)*. Multiple-dose studies in human volunteers have shown that cumulative doses of up to 3200 mcg/kg in a week *(42)* or quarterly doses of up to 800 mcg/kg *(58)* are well tolerated. The adult dose approved by the US FDA for onchocerciasis and LF is 150–200 mcg/kg; multiple-dose regimens at this dose have been approved in Australia for scabies *(39)*.

Until March 2015, the cumulative number of ivermectin tablets used worldwide was 2.7 billion, accounting for more than 928 million patient-years of treatment (Hetty Waskin MD, Merck, personal communication). Most of these tablets have been used in the context of MDA programmes for onchocerciasis or LF.

With the standard dose of 150–200 mcg/kg, the most common, direct adverse events seen in disease programmes or field studies have been hypersensitivity and inflammatory/allergic reactions (arthralgia 9.3%, lymphadenopathy 1.2–12.6%, rash/pruritus 22.7% and fever 22.6%) *(36)*. Patients with existing hyperreactive onchodermatitis may be more likely to experience severe adverse reactions. There are no published reports of life threatening immune reactions such as Stevens Johnson Syndrome, despite the fact that this possibility is noted on the label *(36)*.

Ivermectin MDAs at higher concentrations have been performed for NTDs. Ivermectin (400 mcg/kg) MDAs have been administered safely to thousands of people in India *(59)*, Cameroon *(60)*, Papua New Guinea *(61)* and French Polynesia *(62)* with minimal adverse events reported. Ramaiah et al. *(59)* have conducted the largest human study to date of ivermectin MDA at 400 mcg/kg; in the study, five entire villages, roughly 10 000 people, were treated by MDA nine times over an 11-year period. French regulatory authorities have recommended ivermectin (400 mcg/kg) MDA in selected areas *(62)*.

The primary safety concern is *Loa loa*-associated encephalopathy, which places a geographical restriction on the deployment of ivermectin. However, the mechanism is not well understood.

The clinical safety of ivermectin during pregnancy has not been appropriately studied. Preclinical studies in pregnant mice, rats and rabbits have shown teratogenicity at doses toxic to the mother (400 mcg/kg, 5000 mcg/kg and 3000 mcg/kg during pregnancy days 6–18, respectively) *(36, 57)*. Ivermectin has been shown to produce delayed development and increase pup mortality in rats at maternal doses of 1600 mcg/kg *(57)*. To track exposure in pregnancy, 1276 reports of inadvertent exposure in pregnant women have been filed, of which 442 were in the first trimester *(63-66)*.

Toxicology studies in neonatal *Rhesus* monkeys have shown no adverse reactions after 2 weeks of daily 100 mcg/kg doses *(57)*. Safety in paediatric patients weighing less than 15 kg has not been evaluated, and this population is currently not included on the US FDA-approved label *(36)*.

Key conclusions

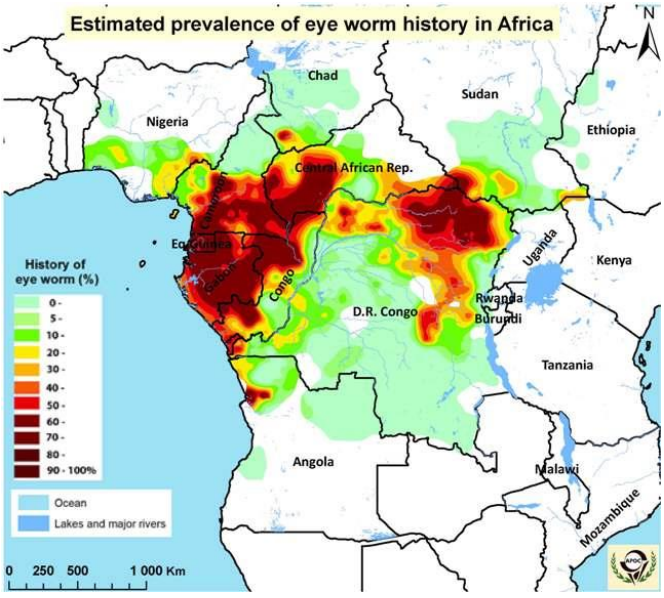
- The central nervous system is the primary target of ivermectin toxicity in mammals;
- In animal studies, ivermectin has been found to be teratogenic at or near maternotoxic doses;
- Safety in paediatric patients weighing less than 15 kg has not been established;
- Additional data may be needed to support the use of higher dose/repeated dosing regimens.

3.9 Progress and challenges of large-scale ivermectin for onchocerciasis and LF elimination: implications for malaria vector control

In 2014 alone, more than 260 million people were treated with ivermectin for onchocerciasis/LF. Due to its success, the LF programme has been downscaled in 11 countries; by contrast, 18 African countries are in need of urgent upscaling. The global demand for ivermectin is expected to grow due to additional indication for scabies and new evidence that a single dose of ivermectin-diethylcarbamazine (DEC)-albendazole can accelerate LF elimination *(67)*.

Ivermectin is currently donated to countries' NTD programmes through the Mectizan® donation programme. The main delivery strategy is through community volunteers annually, semi-annually or quarterly.

Coendemicity with *Loa loa* and the adverse events seen with ivermectin treatment will limit ivermectin's usage for malaria in the areas of Africa where this parasitic disease is prevalent, namely Angola, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Nigeria and South Sudan *(68)* (see map). Additionally, population movement from *Loa loa*-endemic areas must be taken into account.



Map taken from Zoure et al. (68)

Key conclusions

- Ivermectin demand will remain high for nematode and scabies control over the next decade. Currently, ivermectin is donated by the manufacturer for use in onchocerciasis/LF elimination, with no commitment to expand donation to other indications;
- To reduce the risk to the supply chain, it will be important to encourage the prequalification of additional manufacturers and to establish a public health price for the product. Ivermectin is on the list of essential medicines that can be submitted for prequalification;
- There is an extensive network of trained community-based voluntary distributors.

3.10 Potential risks and benefits for NTDs from ivermectin distribution for the reduction of malaria transmission

The impact of ivermectin distribution for malaria on NTD programmes will depend on the extent, frequency and timing of the distribution. Coordination mechanisms between both programmes will need to be in place in order to maximize synergistic potential.

Apart from the direct effect on nematodes and ectoparasites, an additional beneficial effect can be expected in areas where the LF vector is *Anopheles*, as increased mosquito mortality will further reduce transmission *(69)*.

Ivermectin MDA for malaria could improve coverage rates and decrease the implementation burden for NTDs.

Key conclusions

- It is possible to optimize ivermectin use for NTD and malaria programmes, but the dose, frequency and timing of ivermectin MDA will require coordination between programmes;
- Joint distribution efforts and cost-sharing between NTD and malaria programmes and other synergies can increase impact;
- The business model and cost for the malaria indication need to be determined.

3.11 Overview of ongoing or planned clinical trials on the impact of ivermectin on malaria transmission

A number of studies are ongoing *(70)*, generating preliminary data.

The repeated ivermectin MDA trial for control of malaria (RIMDAMAL) began in Burkina Faso in 2015. Preliminary data from this cluster randomized trial have shown a 20% reduction (OR 1.3 [1.13-1.42]) in the clinical incidence of malaria in children under 5 by active case detection with rapid diagnostic tests when administering ivermectin alone at 150 mcg/kg once every 3 weeks (six times), with an average of 72% coverage (total population 2662). Approximately 156 cases have been averted in a cohort of 295 children by treating 1407 people in the intervention villages.

The IVERMAL study of the efficacy and safety of high-dose ivermectin for reducing malaria transmission recently completed recruitment in Kenya. This double-blind, placebo-controlled trial assesses mosquito mortality after feeding on blood from patients with uncomplicated falciparum malaria treated with dihydroartemisinin (DHA)-piperaquine and ivermectin at doses of 0, 300, 600 mcg/kg/day for 3 days. Ivermectin doses were chosen using PK modelling. The code has not yet been broken. Preliminary, fully blinded and pooled data (i.e., all three arms

pooled, averaging 300 mcg/kg/day) show a difference in mosquito mortality in the mosquitoes that fed on blood taken from patients who started ivermectin up to 14 days earlier. Preliminary analysis suggests a good safety profile and no difference in mortality between direct-skin and membrane feeding at the same ivermectin concentration.

The Ivermectin for Malaria in Southeast Asia (IMSEA) study is an open-label study to evaluate the safety, tolerability, potential pharmacokinetic interaction and mosquito-lethal effects of orally coadministered ivermectin, primaquine and DHA-piperaquine in healthy adult subjects in Thailand. A single ivermectin dose of 400 mcg/kg, given in combination with primaquine and DHA-piperaquine, was well tolerated by 16 local volunteers and lethal to local vectors for up to 10 days after a single dose.

A planned field trial will assess the impact of ivermectin MDA in rubber plantations in southern Thailand (Kobylinski, presentation during the meeting).

Key conclusions

- Preliminary data suggest that ivermectin MDA at a dose of 150 mcg/kg every 3 weeks can have a measurable impact on malaria incidence in high transmission areas;
- Preliminary data suggest that ivermectin doses up to 600 mcg/kg/day for 3 days, combined with DHA-piperaquine, are well tolerated by patients with uncomplicated *falciparum* malaria. Fully blinded and pooled data across three arms show a difference in mosquito mortality in mosquitoes that fed on blood taken from patients who took the first dose of ivermectin up to 14 days earlier;
- Preliminary data suggest that a single 400 mcg/kg dose of ivermectin can increase the mortality of *Anopheles dirus* and *Anopheles minimus* for up to 10 days after treatment.

3.12 The possible regulatory pathway for ivermectin as a vector control tool

For NTDs, ivermectin MDA provides individuals with a direct benefit by reducing disease. It also gives the community the indirect benefit of reducing NTD transmission. For malaria, ivermectin MDA at the appropriate dose and regimen would provide an indirect benefit to the community in terms of reducing malaria transmission.

The reduction of malaria transmission clearly requires a different dose and dose schedule compared to those used in MDA against helminths or for treating scabies. One approach would be for a current manufacturer to apply to a stringent regulatory authority to add a new indication for malaria transmission reduction to the intended use on the label. To do so, additional data on safety, dose schedule and epidemiological endpoints would be needed. Neither modelling nor parasitological endpoints are sufficient for registration and/or policy recommendation.

The WHO prequalification (WHO-PQ) scheme already includes ivermectin in its list of medicines that can be evaluated *(71)*; it has also specified that additional dose strengths can be approved. One question that needs further clarification is whether including ivermectin in the WHO standard malaria treatment guidelines or a WHO policy recommendation, following a full review of the published data, would be sufficient to extend the prequalification of a medicine to this new treatment paradigm.

If the label from the stringent regulatory authority needs to be changed for a WHO policy recommendation, then the choice of registration entity is important for determining the specific regulatory requirements for the new malaria indication. This choice also has an impact on the expected timelines for approval and roll out. Currently, the main manufacturer is a US-based company, and the primary entity responsible for approval is the US FDA. Merck has filed the endectocide approval for scabies with the Australian TGA *(39)*. The US FDA's 505(b)*(2)* pathway

or EMA's positive scientific opinion under Article 058 may offer advantages in terms of the speed of approval.

Finally, there remains the question of whether FDA/EMA registration is needed if the product is manufactured and used outside of the US or Europe. Nevertheless, the product would still need to be registered in both the country of manufacture and country of use. Two artemisinin combination therapies have followed such a path (amodiaquine-artesunate and artesunate-mefloquine). In both cases, WHO-PQ was a key part of the strategy, as it presumably would be in the case of ivermectin for malaria.

The uptake by national malaria control programmes (NMCP) will ultimately depend on whether the research agenda addresses their specific questions. Early consultation with the countries will be critical.

Key conclusions

- The reduction of malaria transmission represents a new indication, and the dose and dosing regimen will need to be defined accordingly;
- Epidemiological impact and safety data from trials will be needed. Mosquito mortality and modelling are unlikely to be enough for registration;
- Given that a WHO policy recommendation is the primary goal, it is critical that early discussion of the product development plan for this indication take place in order to ensure that it can potentially result in a recommendation;
- Stringent regulatory authority approval followed by WHO-PQ is the most commonly taken regulatory pathway. Yet, the extent to which WHO-PQ can approve a medicine for use beyond its approved label remains to be seen;
- More than one manufacturer of ivermectin is needed, and WHO-PQ would be the simplest mechanism to ensure high-quality generic medicines;
- Repurposing pathways, such as the FDA´s 505(b)*(2)*, may be appropriate for extending the indication of ivermectin with stringent authorities.

3.13 Possible target product profile components for ivermectin as a vector control tool

New tools are needed to reduce malaria transmission. Ivermectin MDA has the potential to become one such tool. The most straightforward regulatory pathway for ivermectin administration is likely to be as a stand-alone endectocide. However, different strategies should be evaluated. For example, coadministration with an ACT in MDA could help to accelerate elimination. However, if this path is followed, safety and impact data with respect to the particular combination will be needed.

The key step in achieving the efficacy target will be to define the target impact on malaria transmission and the safety requirements to support a WHO policy recommendation and inclusion in the WHO malaria treatment guidelines.

One first step is that the regimen of the current drug that will achieve the desired epidemiological endpoint must be systematically defined. This will include determining the dose and duration of therapy, using either the tablets currently available or the new tablet strengths already suggested by WHO-PQ. Once the target regimens have been defined, it will then be possible to develop new formulations or delivery methodologies to make implementation more efficient.

The safety of the new regimen must be established and population coverage identified for the malaria impact endpoints. If the proposal includes coadministration with a second drug, then the drug–drug interactions must be assessed.

If ivermectin is coadministered with an ACT, the ACT–ivermectin combination will be the target evaluated by regulatory authorities, and data on safety and efficacy of the combination will be required. There are recommended ACT schemes being used for seasonal malaria chemoprevention.

Key conclusions

- Given the current need for new tools to reduce malaria transmission, the shortest regulatory path should be identified;
- Defining the desired epidemiological impact for a policy recommendation is a critical step. Target reduction of incidence of infection or clinical malaria needs to relate to specific levels of transmission;
- Evaluating the impact may be easier in high-transmission settings;
- Entomological endpoints based on mosquito survival are less likely to lead to registration or WHO policy recommendation;
- Once the safety and effectiveness of a defined ivermectin regimen is available, then consideration can be given to an ACT–ivermectin combination as the target product. In this case, evidence of the efficacy of ivermectin on its own will be needed.

3.14 Possible trial design to assess the impact of ivermectin on malaria transmission

Study designs discussed included: (a) observational studies in areas where MDA with ivermectin is already being conducted against LF and onchocerciasis, (b) cluster randomized controlled trials evaluating the incremental benefits of ivermectin on top of core vector control interventions and case management, and (c) before and after studies of ivermectin MDA, with control and intervention sites.

Assumptions for a clinical trial include that (a) the dose and frequency of ivermectin treatment are defined, (b) using ivermectin for malaria control will complement, rather than compromise, the benefits against LF and onchocerciasis, and (c) ivermectin will be used in addition to, rather than in place of, existing malaria prevention LLINs/IRS, case management and perhaps ACT MDA.

Sufficient knowledge of the baseline vector behaviour is important for evaluating this intervention, particularly in terms of the proportion of blood meals taken from humans as opposed to animals. The potential of ivermectin MDA to affect insecticide-resistant mosquitoes must be evaluated as a potential lateral benefit.

Preliminary estimates of the sample size required to evaluate ivermectin's impact on malaria transmission suggest that studies would be most efficient in areas of high transmission. This does not negate ivermectin's potential for impact towards elimination in low-transmission settings.

A clinical trial should demonstrate that orally administered ivermectin can provide a significant incremental reduction in malaria transmission, measured as incidence of clinical malaria, beyond levels achievable with recommended vector control interventions.

Ultimately, deployment options for ivermectin MDA could include combinations with other vector control tools, antimalarials and antihelminthics.

Key conclusions

- Trials should aim at proving an incremental reduction in incidence of infection or clinical malaria episodes beyond the levels achievable with recommended vector control interventions, such as LLINs, at scale;
- Impact on residual transmission and insecticide-resistant mosquitoes should be reflected as secondary outcomes in trial design;
- Thorough knowledge of the local main vectors and their behaviour is essential for study design and site selection.

3.15 Considerations regarding supply and business model

It is critical that multiple suppliers of ivermectin become available in order to mitigate the supply risk to the deployment of the medicine. This applies to medicine not only for malaria transmission, but also for treatment of helminths. WHO-PQ offers an easier approach to bringing in new manufacturers. The prequalification process can evaluate the quality and safety of the ivermectin product/dose intended for use against malaria, but "not the new indication per se" (WHO-PQ statement during the meeting).

Cost of goods needs further clarification. Currently, most of the ivermectin used in nematode control programmes is donated by the US licence holder, Merck & Co. Merck has made no commitment to expand this donation to other indications. Therefore, it will be important to have a variety of suppliers that can deliver products to UN agencies and other procurers at affordable prices. Prequalifying several suppliers of ivermectin tablets is one approach to resolving this issue.

Key conclusions

- Having more ivermectin suppliers available would help to reduce supply risk. WHO-PQ is the easier way to involve new manufacturers;
- Ivermectin is currently donated for its use in NTD elimination programmes. If the indication expands to malaria transmission reduction, however, it will be important to have a variety of suppliers that can deliver product to UN agencies and other procurers at affordable prices.

4. Conclusions and recommendations

4.1 General considerations

Ivermectin MDA could reduce vectorial capacity primarily by reducing vector survival and fitness, and, to a lesser extent, by partially inhibiting sporogony and negatively affecting vector fertility.

This potential new application of ivermectin warrants full understanding, particularly in terms of its role in: (a) reducing the residual transmission of malaria, (b) curbing insecticide resistance, and (c) accelerating progress towards elimination.

Research should be guided by the target product profile (TPP) developed on the basis of ivermectin's expected public health role in malaria control. The critical components of the TPP will be efficacy, safety and regulatory/policy requirements.

4.1.1 Efficacy

- There is robust evidence that *Anopheles* mosquitoes that ingest ivermectin in a blood meal are killed in a dose-dependent manner.
- The efficacy of ivermectin MDA in reducing malaria transmission will be directly related to the levels of the drug in the blood, the duration of these levels and the population coverage.
- The FDA has approved an ivermectin regimen for onchocerciasis comprised of a single yearly dose of 150 mcg/kg. This regimen achieves a plasma concentration above the LC50 for *Anopheles* mosquitoes for less than 5 days, which would not be sufficient to have a significant impact on transmission.
- The impact of ivermectin on malaria transmission could be increased through pharmacological strategies, such as using higher single doses, repeated dosing, or new formulations allowing longer term plasma exposure.
- Ivermectin will be deployed with other forms of vector control and could be deployed in combination with a parasite-focused MDA. Such combinations could facilitate efficiency of delivery, but involve a more complex regulatory pathway.
- The primary data required for a decision on ivermectin will be: (a) safety and (b) reduction of infection or clinical malaria with gametocyte carriage, entomological outcomes, and morbidity measures such as anaemia as secondary endpoints.
- Mathematical models can simulate a wide range of deployment scenarios. One model has been used effectively to assist with trial design *(9, 10)*. This model, coupled with membrane-feeding assays and PK analysis, can help to estimate the impact of ivermectin on malaria transmission; however, these estimates require validation through trials.
- Modelling has suggested that adding ivermectin to ACT MDA could increase the drug's impact on malaria transmission by reducing the number of MDA rounds and supporting elimination in areas with higher endemicity, where ACT-MDA alone is not sufficient (9). If ivermectin is to be deployed with an ACT as a partner-drug candidate, empirical evidence of ivermectin´s efficacy on its own will be needed.
- A specific workstream is needed to better define the required doses for malaria transmission reduction in different settings.

4.1.2 Safety

- Preclinical safety studies have shown a wide safety margin for use in nematode control. This safety margin is lower for malaria transmission reduction, since this outcome would require a higher sustained plasma exposure.
- Preclinical studies in pregnant mice, rats and rabbits have shown teratogenicity at doses toxic to the mother (400 mcg/kg, 5000 mcg/kg and 3000 mcg/kg during pregnancy days 6–18, respectively) *(57)*. Neonatal toxicology studies in Rhesus monkeys have shown no adverse reaction after 2 weeks of daily low doses of 100 mcg/kg.
- Ivermectin has been deployed at 150 mcg/kg in millions of individuals as part of onchocerciasis/LF control programmes. Data from very small trials with healthy volunteers suggest that higher single doses (up to 2000 mcg/kg) are also safe *(42)*.
- There is no systematic database recording inadvertent exposure in pregnancy.
- Since the modelling suggests that effective population coverage needs to be above 50%, it will be important to establish the safety of ivermectin in children and infants under 15 kg. Unless pregnancy registers for inadvertent exposure can be set up rapidly, ivermectin use will be restricted to exclude women of childbearing potential.

- Loa loa-associated encephalopathy is the most serious clinical adverse event. This can be initially managed through geographic restrictions on the deployment of ivermectin in the control of malaria transmission.
- There is no evidence that the deployment of ivermectin for malaria transmission control would raise any additional safety issues due to interactions with nematodes.

4.1.3 Regulatory and policy pathways

- The primary policy question is to clearly define what safety and efficacy data are required to support a WHO policy recommendation for ivermectin as a tool for the reduction of malaria transmission. An important next step would be consultation with relevant regulatory agencies and policy makers from countries to determine what additional data they would need to deploy the regimen.
- Prior to deployment, it will be important to have approval for use from a stringent regulatory authority or WHO-PQ. Approval of the product in the country of manufacture will also be critical.
- The most effective regimen for malaria transmission reduction will most likely involve an increase in the dose and frequency of administration above that currently approved by the US FDA and recommended by WHO for onchocerciasis and LF.
- Repurposing pathways, such as the FDA´s 505(b)(2) or equivalent in other agencies, could be appropriate, although an in-depth review of the clinical safety data would be required.
- Currently, ivermectin is donated by one supplier. Prequalification of multiple suppliers will be critical for maintaining the stability of supply and for achieving an appropriate price for procurement through United Nations agencies or the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). It should not be assumed that the current donation programme will or even can be extended to cover malaria transmission reduction.

4.1.4 Market/supply

- In order to reduce supply risks, it is critical that several ivermectin suppliers be available. One approach to resolving this issue is WHO-PQ of several suppliers of ivermectin tablets.
- The business model of ivermectin to reduce malaria transmission is likely to differ from that of ivermectin MDA for NTDs wherein the drug is donated by the manufacturer.

4.1.5 Key knowledge gaps

- Efficacy
    - Determine the exposure response for insect lethality via direct skin-feeding on humans; develop an understanding of the LC50 for all key insect vector species;
    - Conduct studies on children and those with coinfections in order to understand the factors that might impact plasma exposure;
    - Evaluate the potential for *Anopheles* mosquitoes to develop resistance to ivermectin, and if proven, develop laboratory-based resistance markers before wide-scale deployment;
    - Validate lab-based entomological endpoints for assessing ivermectin's efficacy and investigate their correlation with epidemiological impact.
- Safety

- Develop an acceptable safety profile of ivermectin when used at the higher doses or longer regimens required to achieve LC50 levels for the main vectors;
- Analyse whether the current safety windows in preclinical safety studies for normal animals and juveniles and in EFT studies support more frequent or increased dosing;
- Analyse the current safety data with respect to children under 15 kg;
- Establish pregnancy registries to investigate the safety of inadvertent exposure in pregnancy, especially during the early first trimester;
- Develop new diagnostics and strategies to prevent *Loa loa*-related adverse effects in the long term.

- Regulatory and policy pathways
  - Elicit clear guidance from WHO MPAC as to the evidence that would best inform a policy recommendation on the use of ivermectin for the reduction of malaria transmission;
  - Gather operational data on cost–effectiveness and delivery mechanisms, and initiate discussions with disease-endemic countries as to the thresholds required for introduction into health policy;
  - Consult with WHO-PQ as to the data requirements for using an already prequalified medicine in a new indication;
  - Identify other ICH-approved manufacturers able to produce alternative supplies of ivermectin in order to reduce the risk of dependence on a single supplier.

4.2 Proposed target product profile

Efficacy	Desired	Minimally acceptable
In combination with an ACT and core vector control interventions *(Target product antimalarial + ivermectin)*	A significant reduction in incidence of clinical malaria 12 months after a single intervention in combination with ACT MDA and core vector control measures	A significant reduction in infection incidence 12 months after three interventions given at monthly intervals in combination with an ACT MDA and core vector control measures
Stand-alone insecticide *(ivermectin as a target candidate)*	At least 20% reduction in the incidence of clinical malaria, lasting for at least 1 month after a single round of MDA irrespective of baseline transmission levels	*In areas of moderate to high transmission:* At least 20% reduction in the infection incidence in children under 5, lasting for at least 1 month following a single regimen *In areas of low transmission:* A significant reduction in infection incidence, lasting for at least 1 month following a single regimen

Efficacy-related concepts				
Parameter	**Desired**		**Minimally acceptable**	
	Target	**Rationale**	**Target**	**Rationale**
Target population	Acceptable in children 5–15 kg (children < 90 cm as proxy) Acceptable in women of reproductive age without a pregnancy test Acceptable in pregnant women Acceptable in lactating women	An increase in coverage is expected to be directly related to greater efficacy. This will, however, depend on the exposure of children and pregnant women to malaria transmission.	All populations in the target areas, with the exception of: - Pregnant women - Lactating women in the first week postpartum - Children < 15 kg (< 90 cm as proxy) - The severely ill	The minimally acceptable exclusion criteria proposed are the current WHO recommendations for onchocerciasis *(72).* Coverage with this limitation in the RIMDAMAL study *(37)* was 72%. At population level, efficacy will be directly related to coverage.
Dosage & schedule	Single-dose administration of a slow-release formulation The cumulative dose (mcg/kg/day) best matched to the area under the curve (AUC) needed for the efficacy target Cmax below the theoretical mosquito LC_{100} Timed to malaria transmission season	Administration in a single encounter will facilitate compliance and enable directly observed therapy. High adherence will be directly related to effectiveness and, together with therapeutic efficacy, contribute to effective coverage. 2000 mcg/kg is the highest single dose that has been administered safely to healthy volunteers. The maximum cumulative dose that has been tested and published is 3200 mcg/kg in 1 week *(42).* A challenge with this approach is the significant R&D investments that would be needed to develop a new formulation.	Single-encounter, manageable multiple-dose scheme (once a day for up to 3 days, with or without an ACT) Based on PK modelling *(41)*, a starting dose of 400–600 mcg/kg /day for 3 consecutive days is proposed. -and/or- Repeated MDA (single encounter at each MDA, with or without an ACT) at 2–8 weekly intervals in areas with limited transmission seasons Studies with a wide range of doses desired in order to select the most cost–effective and safe	The use of the current dosage and existing formulation. Up to 1400 mcg/kg within 1 month is the dose recommended by the CDC for crusted scabies *(73).* Challenges include: adherence, the safety of higher Cmax, and a theoretical limit to efficacy once the mosquito LC_{100} is reached.
Formulation	Slow-release (non-injectable)	This approach could allow for administration in a single encounter and the maximization of the AUC:efficacy ratio.	Current oral formulation (3 or 6 mg tablets) used in multiple doses	

Safety & related concepts				
Parameter	Desired		Minimally acceptable	
	Target	Rationale	Target	Rationale
Safety profile	Incidence of adverse events of total dose/body weight/timeframe less than 1:10 000 New strategy available for risk minimization in *Loa loa*-endemic areas	This is the current threshold proposed by MMV for the development of novel malaria drugs (74).	No severe adverse drug reactions AND frequency of moderate adverse events ≤ 1.3 % Defined strategy for risk minimization in *Loa loa*-endemic areas or exclusion	This is the frequency of the moderate adverse events observed in onchocerciasis control campaigns (75). New research is needed to develop strategies for ivermectin distribution in *Loa loa*-endemic areas.
Drug–drug interactions	No significant interaction with antimalarials, ARV, TB drugs and antihelminthics If longer-lasting formulations or schemes are proposed, the safety of coadministration with common over-the-counter drugs should also be evaluated.	Coendemicity of NTDs and malaria; longer-lasting formulations would have a larger cumulative dose and greater likelihood of coadministration. Ivermectin is metabolized by the cytochrome p4503A4 (76) and a substrate of the p-glycoprotein *(77)*.	No significant interactions with ACTs, primaquine, or transmission-blocking vaccine candidates	These interventions are likely to be used together in elimination settings.

Feasibility & related concepts				
Parameter	Desired		Minimally acceptable	
	Target	Rationale	Target	Rationale
Manufactura-bility			Production process fully scalable to meet the requirements for NTDs and malaria Commitment of multiple potential suppliers with prequalified products or approval from stringent regulatory authorities	There is no current pharmaceutical alternative to ivermectin for the control of onchocerciasis. Procurement of ivermectin for malaria should not affect the global production and supply for the control and elimination of NTDs.
Packaging & presentation			Adequate programmatic suitability for MDA campaigns	Cost-reduction strategies need to be considered early in the development of new dosage regimens and formulations.
Shelf life & storage	Stable for at least 60 months at 37 ºC and 75% humidity	Target based on MMV´s TPPs (74)	Stable for at least 24 months at 37 ºC and 75% humidity	The current label recommends storage below 30 ºC (36). This is the minimum acceptable target based on MMV´s TPPs (74).

Costs				
Parameter	Desired		Minimally acceptable	
	Target	Rationale	Target	Rationale
Cost of goods	< 0.2 US$	Based on costs of the active pharmaceutical ingredient (API)	1.5–6 US$/person/day	The estimated donated value in the Mectizan donation programme (78)
Cost–effectiveness	US$ 2.20 (0.88–9.54) for 1 year of protection/person	The estimated cost/person/year of protection of LLINs (79) Cost per case averted is likely to be a better parameter for ivermectin.	US$ 6.70 (2.22–12.85) for 1 year of protection/person	The estimated cost/person/year of protection of IRS (79) Cost per case averted is likely to be a better parameter for ivermectin.

Registration				
Parameter	Desired		Minimally acceptable	
	Target	Rationale	Target	Rationale
Registration and WHO-PQ	Use products approved or licensed by a stringent regulatory agency. More than one supplier with approval from a stringent regulatory authority or prequalified by WHO		One supplier with product approved by stringent regulatory agency or prequalified by WHO Country registration	Approval by a stringent regulatory agency or WHO-PQ is the requirement for procurement by the Global Fund and many agencies.

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Annex 1. Studies assessing the lethal effect of ivermectin on Anopheles mosquitoes

Reference	Method (1)	Method (2)	Species	Dose	Timespan dose to feeding	Most relevant results	Additional observations
Pampiglione 1985 *(18)*	treated subjects	mice	*An. stephensi*	140 to 28 000 µg/kg (once, subcutaneously)	12 hours	3-day mortality: 60% in the 280 µg/kg group Controls 20% (significance not reported)	
Iakubovich 1989 *(2)*	membrane	in vitro mixture (blood + ivermectin)	*An. stephensi* *An. sacharovi*	1 to 50 ppm	N/A	[time of mortality assessment not stated] *An. stephensi* LC100 1ppm *An. sacharovi* LC100 50 ppm	
Iakubovich 1989 *(2)*	treated subjects	rabbits	*An. stephensi* *An. sacharovi* *An. atroparvus*	340 mcg/Kg (once, subcutaneously)	not available	***An. stephensi*** 4-day mortality: 93% (significant) ***An. sacharovi*** No difference from control ***An. atroparvus*** No difference from control	
Jones 1992 *(3)*	membrane	blood from treated dogs	*An. quadrimaculatus*	10 to 2500 mcg/Kg (once, orally)	4 hours	2-day mortality: 92% in the 500 µg/kg group Controls 3.4% (significant)	
Jones 1992 *(3)*	treated subjects	dogs	*An. quadrimaculatus*	10 to 2500 mcg/Kg (once, orally)	4 hours	2-day mortality: 98.6% in the 10 µg/kg group Controls 4.3%	
Gardner 1993 *(19)*	treated subjects	dogs	*An. quadrimaculatus*	6 to 24 mcg/Kg (once, orally)	4 hours	24-hour mortality: 66.9% in the 12 µg/kg group Controls: 3.9% (significant) 24-hour LC50: between 6 and 12 ng/ml	24-hour Lethal Dose 50: 9.9 µg/kg Significant decrease in oviposition and egg-hatching in survivors
Bockarie 1999 *(20)*	field collections	MDA for LF	*An. punctulatus* *An. koliensis*	400 mcg/Kg (once, orally) + 6 mg/kg DEC	≤ 4 days	3-day mortality: 61%, if collected ≤4 days post treatment Controls: 1–10% (significant) 9-day mortality: 100% if collected ≤4 days post treatment Controls: 18–23% (significant)	70% of deaths within 24 hours of collection Survival rates similar for both species
Foley 2000 *(21)*	treated subjects	human volunteer *(1)*	*An. farauti*	250 mcg/Kg (once, orally)	Same day to 44 days	3-day mortality: 100%, if fed on the same day Controls: 4% (significant) 3-day mortality: 80%, if fed 7 days post treatment 9-day mortality: 100%, if fed 7 days post treatment Controls: 4–6% (significant)	
Fritz 2009 *(4)*	membrane	in vitro mixture (blood + ivermectin)	*An. gambiae* *An. arabiensis*	0.01–1000 ppb	N/A	**Survival rates similar for both species** [time of mortality assessment not stated]-LC50: 19.8 ppb [time of mortality assessment not stated]-LC95: 77.7 ppb	

Reference	Method (1)	Method (2)	Species	Dose	Timespan dose to feeding	Most relevant results	Additional observations
Fritz 2009 *(4)*	treated subjects	cattle	*An. gambiae* *An. arabiensis*	600 µg/kg (once, subcutaneously)	1 to 23 days	3-day mortality: 100%, if fed 1 day post treatment Controls: 10% (significance not reported) 3-day mortality: 62%, if fed 13 days post treatment 9-day mortality: 88%, if fed 13 days post treatment Controls: 10–38% (significance not reported)	No oviposition or significant reduction in oviposition in mosquitoes fed up to 17 days post treatment
Chaccour 2010 *(8)*	treated subjects	human volunteers *(25)*	*An. gambiae*	200 µg/kg (once, orally)	1 and 14 days	3-day mortality: 84%, if fed 1 day post treatment Controls: 38% (significant) 9-day mortality: 96%, if fed 1 day post treatment Controls: 73% (significant) No difference in mortality when fed 14 days after treatment.	A non-measured proportion of mosquitoes in the ivermectin group were noted to show lack of movement coordination, lethargy, inability to fly and paralysis.
Kobylinski 2010 *(5)*	membrane	in vitro mixture (blood + ivermectin)	*An. gambiae*	0.5 to 64 ng/ml	N/A	3-day mortality: 75% in the 32 ng/ml group Controls 10–20% (significance not reported) 3-day mortality: 90% in the 64 ng/ml group Controls 10–20% (significance not reported) [5 day]-LC50: 22.4 ng/ml (18-26.9)	Sublethal concentrations significantly reduced mosquito re-blood feeding rates. Multiple sublethal blood meals further increased mortality. Adult size of *An. gambiae* did not alter susceptibility to ivermectin.
Sylla 2010 *(22)*	field collections	MDA for onchocerciasis	*An. gambiae* *An. arabiensis*	150 mcg/Kg (once, orally)	3 groups: pre, 1 to 6 days and ≥ 7 days post MDA	***An. gambiae*** 5-day mortality: 70%, if collected 2 days post MDA Controls: 16–22% (significant) No difference from controls if collected after day 6 ***An. arabiensis*** 5-day mortality: 50%, if collected 1–6 days post MDA Controls: <20% (significant)	
Kobylinski 2011 *(23)*	field collections	MDA for onchocerciasis	*An. gambiae*	150 mcg/Kg (once, orally)	1–12 days post MDA		Sporozoite rate reduction of 79% in mosquitoes collected 2 weeks following MDA in treated villages compared to a sporozoite rate increase of 246% in control villages (significant)
Butters 2012 *(24)*	membrane	in vitro mixture (blood + ivermectin)	*An. gambiae*	5 different concentrations (not stated)	N/A		Sublethal concentrations induced significant knockdown and inhibited recovery, but had no effect on the re-blood feeding rate.

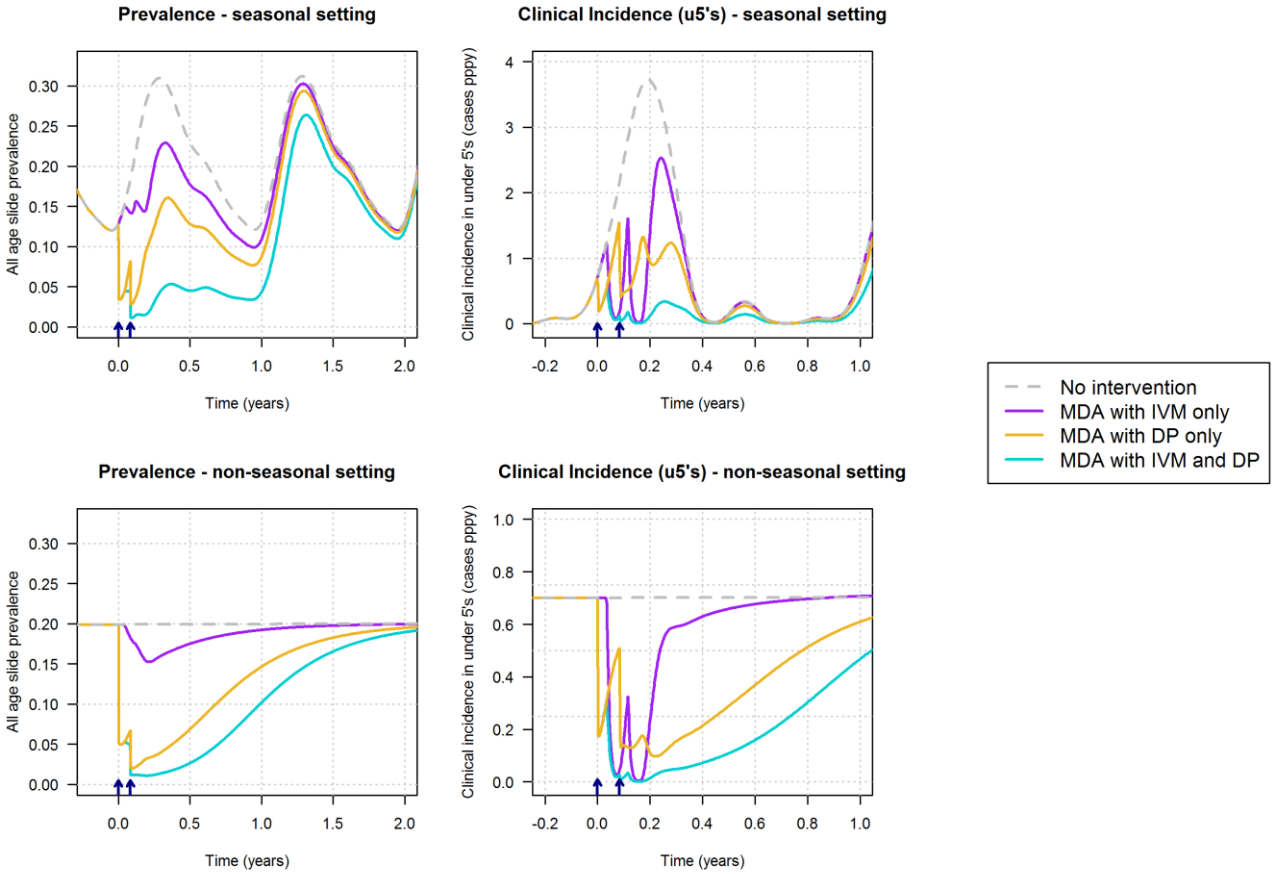
Reference	Method (1)	Method (2)	Species	Dose	Timespan dose to feeding	Most relevant results	Additional observations
Fritz 2012 *(25)*	membrane	in vitro mixture (blood + ivermectin)	*An. arabiensis*	0.1 to 100 ppb	N/A	9-day mortality: 70%, in the 10 ppb group 9-day mortality: 100%, in the 100 ppb group Controls 10% (significance not reported) [9-days]-LC50: 7.9 ppb (6.2–9.9)	LC95: 128.1 ppb (62.1–264.4)
Kobylinski 2012 (*26)*	membrane	in vitro mixture (blood + ivermectin)	*An. gambiae*	not stated	N/A	7-day LC50 = 15.9 ng/ml (14.6, 17.3)	Sublethal concentrations significantly inhibited *P. falciparum* sporogony.
Bastiaens 2012 *(27)*	treated subjects	Swiss mice, Wistar rats and Cynomolgus monkeys	*An. stephensi*	mice and rats: 400 mcg/Kg, Monkeys: 200 and 400 mcg/Kg	1–5 days	Similar results for all three species. 3-day mortality: 70–100%, if fed 1–2 days post treatment Controls: 0–28% (significant)	
Naz 2013 *(28)*	field collections	cattle	*An. culicifacies, An. stephensi*	200 mcg/Kg (once, subcutaneously)	1 to 28 days post dose	***An. culicifacies*** 3-day mortality: 65%, if fed 1 day post treatment Controls: 9% 9-day mortality: 80%, if fed 1 day post treatment Controls: 17% ***An. stephensi*** 3-day mortality: 80%, if fed 1 day post treatment Controls: 10% 9-day mortality: 80%, if fed 1 day post treatment Controls: 25%	Significance only reported for the 12-day cumulative mortality.
Yamada 2013 *(29)*	membrane	in vitro mixture (blood + ivermectin)	*An. arabiensis*	0.5 to 7.5 ppm (blood meal repeated daily)	N/A	24-hour mortality: 90% at 7.5 ppm 2-day mortality: 98% at 7.5 ppm 3-day mortality: 100% at 7.5 ppm	Ivermectin knocked down females almost immediately after blood feeding and killed most within 12 hours.
Alout 2014 *(30)*	field collections	MDA for onchocerciasis or LF	*An. gambiae*	150 mcg/Kg (once, orally) +/- albendazole	Pre- and 1–12 days post MDA	3-day mortality: 65%, if collected 2 days post MDA 5-day mortality: 68%, if collected 2 days post MDA Controls: 16–22% (significant) Survivorship reduced by 33.9% for 1 week post MDA	Significant reduction of sporozoite rates reduced by >77% for 2 weeks following the MDAs Parity rates were significantly reduced for more than 2 weeks after the MDAs.
Kobylinski 2014 *(6)*	membrane	in vitro mixture (blood + ivermectin)	*An. dirus* *An. minimus* *An. campestris* *An.*	-	N/A	***An. dirus*** [7 days]-LC50 = 55.6 ng/ml ***An. minimus*** [7 days]-LC50 = 16.3 ng/ml ***An. campestris*** [7 days]-LC50 = 26.4 ng/ml ***An. sawadwongporni*** [7 days]-LC50 =27.1 ng/ml	Preliminary data suggest that ivermectin is sporontocidal to *Plasmodium vivax* in *An.dirus.*

Reference	Method (1)	Method (2)	Species	Dose	Timespan dose to feeding	Most relevant results	Additional observations
			sawadwongporni				
Ouedraogo 2015 *(7)*	membrane	blood from treated volunteers	*An. gambiae, An. funestus*	200 mcg/Kg (once or twice, orally)	1–7 days	***An. gambiae*** 3-day mortality: 33%, if fed 1 day post treatment (one dose) 3-day mortality: 31%, if fed 3 days post treatment (two doses) Controls: 6% (significant) 10-day mortality: 59%, if fed 1 day post treatment (one dose) 10-day mortality: 66%, if fed 3 days post treatment (two doses) Controls: 21% (significant) 10-day LC50: 5.97 ng/ml ***An. funestus*** 3-day mortality: 19%, if fed 1 day post treatment (one dose) 3-day mortality: 22%, if fed 3 days post treatment (two doses) Controls: 3% (significant) 10-day mortality: 40%, if fed 1 day post treatment (one dose) 10-day mortality: 51% if fed 3 days post treatment (two doses) Controls: 5% (significant)	The artemether-lumefantrine-ivermectin combination was well-tolerated and produced a 4- to 7-fold increase in mortality in mosquitoes that fed 1 day after ivermectin. Day 7 ivermectin plasma levels were positively associated with body mass index and female gender.
Derua *(31)*	treated subjects	human volunteers	*An. gambiae*	150–200 µg/kg	24 hours	3-day mortality: 66.2% Controls 4% (significant) 9-day mortality: 95% Controls 12% (significant)	None of the *An. gambiae* in the ivermectin group laid eggs.
Kobylinski 2015 *(32)*	membrane	in vitro mixture (blood + ivermectin)	*An. dirus*	not stated	N/A		Sublethal concentrations significantly inhibited *P. vivax* sporogony.
Poché 2015 *(33)*	treated subjects	Cattle	*An. coluzzi*	100 & 200 µg/kg	1–21 days	**100 mcg/kg** 3-day mortality 45–63%, if fed < 7 days post treatment 9-day mortality 65–94%, if fed < 7 days post treatment (significant differences only 1 day post treatment)	*An. coluzzi* carrying the *kdr* mutation

Reference	Method (1)	Method (2)	Species	Dose	Timespan dose to feeding	Most relevant results	Additional observations
						200 mcg/kg 3-day mortality 53–77%, if fed < 7 days post treatment 9-day mortality 85–100%, if fed < 7 days post treatment (significant differences until 7 days post treatment)	
Seaman 2015 *(35)*	membrane	in vitro mixture (blood + ivermectin)	*An. gambiae*	11.75 ng/ml	N/A		Mosquito ivermectin susceptibility increased with age and previous blood-feeding. Likely midgut interactions resulting from ivermectin ingestion: blood meal digestion physiological responses, midgut microflora and innate immune responses Gene transcription consistently affected by ivermectin ingestion
Derua 2016 *(34)*	field collections	Larvae	*An. gambiae*	0.001–10 ppm	N/A	24-hour mortality: 38.4% with 0.1 ppm 24-hour mortality: 100% with 1 and 10 ppm	Cx. quinquefasciatus larvae approximately 10-fold more susceptible than *An. gambiae*

Studies assessing the efficacy of ivermectin to kill mosquitoes taking a loaded blood meal. Only studies based on blood meals were included, i.e., no studies using impregnated cotton or sugary solutions. Studies using more than one feeding methodology have been separated by experiment. Efforts have been made to present the results in a uniform manner. Given the duration of the gonotrophic and sporogonic cycles, 3-day and 9-day cumulative mortalities were chosen as the main outcomes. If these were not available, the authors were contacted and values calculated from the raw data provided. If no response was obtained or if the data were not available, the 3-day and 9-day cumulative mortalities were extrapolated from the Kaplan-Meier curves in every publication. If this was not possible, the cumulative mortality was reported together with the original time of assessment. The LC50 is reported with the time used for its assessment. Four studies did not use mortality as a primary endpoint (Kobylinski 2011 & 2015, Butters 2012 and Seaman 2015), but were included because of the importance of their results (sporozoite rate, knockdown/recovery and effect of senescence). One study on Anopheles/Culex larvae was included because of the potential implications of residual ivermectin in latrines.

Annex 2. Modelling the impact of high-dose ivermectin



Modelling estimates of the impact of high-dose ivermectin on malaria prevalence and clinical incidence in highly seasonal (A,B) and non-seasonal (C,D) transmission settings. Two rounds of the intervention are implemented 1 month apart (timings indicated by the navy blue arrows). Coverage of IVM is assumed to be 80% of the population over the age of 5; coverage of dihydroartemisinin-piperaquine (DP) is 80% of the whole population; and the populations covered by the two rounds of intervention are uncorrelated. The ivermectin (IVM) dose is assumed to be 300–600µg/kg for 3 days (coinciding with the dosing regimen for DP). It is assumed that mosquitoes experience increased mortality for 14 days after the start of treatment, but the killing effect wanes over this period such that <0.1% of mosquitoes live long enough to complete sporogony on day 1, but by day 14, 14% of mosquitoes live long enough to complete sporogony (compared to 27% in the absence of IVM). It is assumed that these scenarios are in addition to the case management of clinical cases and ITN usage of 40%. Mean annual prevalence in the presence of these interventions is 25% by microscopy.

Percentage reduction in clinical cases in under 5s in the year after the intervention

	Seasonal setting	Non-seasonal setting
MDA with IVM only	49%	19%
MDA with DP only	59%	52%
MDA with IVM and DP only	89%	76%

Annex 3. List of participants

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