

1 **Ivermectin as a novel complementary malaria control tool to reduce incidence and**
2 **prevalence: a modelling study**

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26 **Summary**

27 **Background:** Ivermectin has been identified as a potential new vector control tool to reduce malaria
28 transmission. Mosquitoes feeding on a bloodmeal containing ivermectin have been shown to have a
29 reduced lifespan, meaning they are less likely to live long enough to complete sporogony and become
30 infectious.

31 **Methods:** In this study, we validate an existing population-level mathematical model of the impact of
32 ivermectin on the mosquito population and malaria transmission to entomological and clinical data.
33 The model is extended to include a range of complementary malaria interventions and to incorporate
34 new data on higher doses with a longer mosquitocidal effect. We then simulate the impact of these
35 doses in a range of usage scenarios in different transmission settings.

36 **Findings:** Mass drug administration (MDA) with ivermectin is predicted to reduce prevalence and
37 incidence and is most effective in areas with a relatively short transmission season. In a highly seasonal
38 moderate transmission setting, three rounds of ivermectin-only MDA spaced one month apart with a
39 dose of 3x300µg/kg and 70% coverage is predicted to reduce clinical incidence by 71% and prevalence
40 by 34% We predict that adding ivermectin MDA to seasonal malaria chemoprevention in this setting
41 will reduce clinical incidence by an additional 77% in under 5-year olds. Adding ivermectin MDA to
42 MDA with antimalarials in this setting is predicted to reduce incidence by an additional 75%.

1 **Interpretation:** Ivermectin is a novel vector control tool that targets residual transmission, it has an
2 excellent safety profile and has operationally synergistic distribution schedules with existing malaria
3 interventions. Based on modelling predictions in this study, we propose that this drug could be a
4 valuable addition to the malaria control toolbox, both in areas with persistently high transmission
5 where existing vector control is insufficient and in areas approaching elimination to prevent
6 resurgence.

7 **Funding:** Imperial College Junior Research Fellowship

8 **Research in context**

9 Evidence before this study

10 We searched PubMed and ScienceDirect on August 17th, 2019, for studies using mathematical models
11 to assess the impact of ivermectin (to humans) on malaria prevalence and incidence, using the search
12 terms “ivermectin” AND “malaria” AND (“modelling” OR “modeling”). The search was unrestricted by
13 language or publication date. Using this search and by scanning reference lists of articles, we identified
14 three publications in peer-reviewed journals. Slater et al. found that adding a single dose of ivermectin
15 200 µg/kg would only have a modest effect on reduction of malaria prevalence if distributed in mass
16 drug administration (MDA) with dihydroartemisinin-piperazine (DHA-P), although higher doses of
17 ivermectin were predicted to have a greater and longer-lasting effect. However, a model developed
18 by Stuckey and colleagues predicted that adding ivermectin to MDA with DHA-P in Zambia would have
19 a negligible additional effect. Finally a theoretical mathematical model by Ngwa et al. predicts that
20 treating symptomatic individuals with ivermectin would reduce the reproduction number of malaria.

21 Added value of this study

22 We present the first population-level mathematical model of the impact of ivermectin on the
23 mosquito population and malaria transmission that has been validated to clinical and entomological
24 field data. Furthermore, the model incorporates new empirical data on higher doses with a longer
25 mosquitocidal effect and has been extended to assess ivermectin alone and in combination with a
26 range of complementary malaria interventions, including mass drug administration and seasonal
27 malaria chemoprevention. By simulating impact in a range of usage scenarios in different transmission
28 settings, our study shows that mass drug administration with ivermectin is predicted to reduce
29 prevalence and incidence and is most effective in areas with a relatively short transmission season.
30 When used in combination with seasonal malaria chemoprevention or mass drug administration with
31 antimalarials, we predict that ivermectin will increase and prolong the impact of these interventions.

32 Implications of all the available evidence

33 Our modelling results indicate that ivermectin alone, and to a greater extent when combined with
34 antimalarial drugs, is predicted to have a major and prolonged effect on malaria prevalence and
35 incidence in a range of transmission settings. We predict that adding ivermectin mass drug
36 administration to current interventions can increase impact and help sustain reductions in
37 transmission. Due to the operationally synergistic opportunities of co-administering ivermectin with
38 other interventions that have the same distribution schedule (mass drug administration with
39 antimalarials, and seasonal malaria chemoprevention), and the fact that ivermectin can directly target
40 residual transmission that remains even with high coverage of long lasting insecticidal nets and indoor
41 residual spraying with insecticides, we believe ivermectin is a powerful new tool which can
42 complement existing malaria control efforts.

43

1 Introduction

2 Despite increasing coverage of vector control (long lasting insecticidal nets (LLINs) and indoor residual
3 spraying (IRS) with insecticides) and improved access to diagnosis and treatment, there were still an
4 estimated 435,000 deaths from malaria in 2017¹. Novel control methods targeting aspects of the
5 transmission cycle currently missed by existing interventions may be needed to further reduce malaria
6 burden. LLINs have contributed most to reductions in transmission² but provide imperfect protection
7 against human-vector contact, missing outdoor and early-biting mosquitoes. IRS targets only indoor-
8 feeding and indoor-resting mosquitoes. Furthermore, there is evidence that mosquitoes are changing
9 their behaviour to feed at times when people are not protected by these interventions³. Worryingly,
10 insecticide resistance to the main chemicals has been reported worldwide⁴, resulting in reduced
11 efficacy in killing mosquitoes.

12 IRS and LLINs will likely remain the cornerstones of malaria control but there is an urgent need for
13 additional tools to supplement them. Several novel vector control approaches are being trialled⁵,
14 including attractive targeted sugar baits⁶ and eave tubes⁷. Mosquitocidal drugs, such as the
15 avermectin class of endectocides, are a potentially impactful novel approach to vector control.
16 Endectocides work by killing mosquitoes that feed on humans or animals that have recently taken
17 them. Ivermectin is the only drug in the class that is available for human use, and studies have shown
18 that it is toxic to mosquitoes, delays refeeding⁸, reduces fecundity⁹ and locomotor activity¹⁰, and may
19 inhibit sporozoite development¹¹. Ivermectin has many attractive qualities as a novel malaria control
20 tool. Unlike IRS and LLINs, it targets mosquitoes regardless of feeding location or time. It can be given
21 to cattle, so could be dual-administered to both humans and cattle in areas with zoophilic malaria-
22 transmitting mosquitoes¹². Furthermore, it has a novel model of action, reducing the likelihood of
23 cross-resistance with existing insecticides⁹.

24 Mass ivermectin administration could be combined in an operationally opportunistic manner with
25 current interventions already being carried out on a large scale across malaria endemic regions. Single
26 dose mass drug administration (MDA) with ivermectin (and other anti-helminthic drugs) is carried out
27 to control neglected tropical diseases (NTDs) across Africa¹³ - extending the dosing schedule and
28 frequency of administration in line with the malaria transmission season could have an impact on
29 malaria transmission. Seasonal malaria chemoprevention (SMC), the monthly distribution of
30 antimalarial drugs to children 3-59 months old during the peak months of transmission is being
31 implemented in 12 countries in the Sahel region of Africa¹. Combining SMC with population-wide
32 ivermectin distribution could further protect children from being re-infected and reduce malaria
33 transmission. Finally, MDA with antimalarials has been trialled in several malaria endemic countries
34 to either accelerate toward elimination¹⁴, reduce malaria burden¹⁵ or contain the spread of
35 artemisinin resistant parasites through local elimination¹⁶; ivermectin could be combined with this
36 intervention to increase and prolong impact.

37 The doses of ivermectin typically used for onchocerciasis and lymphatic filariasis control (single doses
38 of 150-200µg/kg) have a short mosquitocidal effect of around 5-6 days¹⁷ and limited impact on
39 mosquito populations¹⁸ and transmission unless distributed frequently¹⁹. Recent clinical trials
40 investigating the impact of higher doses have produced promising results. Three doses of 300µg/kg
41 given over three days has a mosquitocidal effect in humans for 28 days against *Anopheles gambiae*
42 *s.s.*²⁰ and a single dose of 400µg/kg was effective for at least ten days against *Anopheles minimus* and
43 6-10 days against *Anopheles dirus*, two of the most important malaria vectors in Southeast Asia^{21,22}. A
44 slow-release ivermectin implant has achieved mosquitocidal concentrations for 40 weeks in cattle¹²,
45 and a novel slow-release, gastric-resident, drug delivery technology in development has achieved

1 mosquitocidal concentrations of ivermectin for around 14 days in pigs²³. Fluralaner and afoxolaner,
2 two drugs from the isoxazolines class of endectocides used in veterinary medicine, have also been
3 shown to be toxic to mosquitoes. Preliminary estimates indicate that they could remain at effective
4 mosquitocidal concentrations for 50-90 days, but have not yet been tested for safety in humans²⁴ and
5 regulatory approval for human use may take up to a decade²⁵. The combination of non-ivermectin
6 mosquitocidal drugs administered to cattle alongside ivermectin administered to humans has been
7 suggested as an approach to simultaneously target anthropophilic and zoophilic mosquitoes whilst
8 preventing the development of resistance to ivermectin via a dual-chemistry approach which is
9 recommended in other forms of vector control²⁶.

10 The growing body of evidence that higher doses of ivermectin have a prolonged efficacious duration,
11 as well as the development of other slow release or long lasting endectocides has led to calls to better
12 understand the potential impact of these drugs on malaria transmission¹⁷. In this study, we use a
13 mathematical model to estimate the impact of ivermectin MDA and to provide guidance on the
14 potential scenarios in which they could complement existing malaria interventions to further reduce
15 malaria transmission and burden.

16 **Methods**

17 We previously developed a malaria transmission model²⁷ to capture the impact of ivermectin²⁸ on
18 vector survival. Here we extend the model to: i) incorporate a range of complementary malaria
19 interventions, ii) allow a wider range of mosquitocidal drug profiles, iii) track the parity rate of vector
20 populations, and iv) allow for correlation between who receives drugs each round in mass
21 administration interventions.

22 **Malaria transmission model**

23 The deterministic compartmental model incorporates transmission between mosquito and human
24 hosts^{27,29}. Individuals begin life susceptible with a level of maternally-acquired immunity which quickly
25 wanes. Upon inoculation with an infectious bite they either become infected (with probability
26 determined by their level of pre-erythrocytic immunity), whereupon they either develop clinical
27 disease or asymptomatic infection (determined by their levels of blood-stage immunity). Individuals
28 with clinical disease have a probability of being successfully diagnosed and treated. Treated individuals
29 are prophylactically protected for a duration based on the properties of the antimalarial taken.
30 Untreated individuals with clinical disease are assumed to have symptomatic infection for an average
31 5 days before transitioning to becoming asymptotically infected. Asymptotically infected
32 individuals remain infected for an average 310 days²⁷, but their probability of being detectable by
33 microscopy decreases over the course of the infection to capture the effect of decreasing parasite
34 densities. Individuals that are susceptible or have asymptomatic infection can be superinfected which
35 follows the same infection process. The acquisition and loss of immunity is dynamically modelled and
36 determines the probability of infection, the probability of developing symptoms and the detectability
37 and transmissibility of infection. Transmission from mosquitoes to humans is determined by the
38 entomological inoculation rate, which is a product of the mosquito biting rate, sporozoite rate,
39 functions determining the relative biting rate on different subgroups (capturing heterogeneity in
40 exposure) and age and the probability of successful inoculation. Similarly, transmission from humans
41 to mosquitoes is determined by the infectivity of the human, which is based on their infection state,
42 the mosquito biting rate, the age- and heterogeneity-biting rates and the probability of successful
43 infection. We assume a constant and isolated population, with no movement of infected humans or
44 mosquitoes in or out of the intervention area. Details of the model are provided in the Appendix, page
45 1-11.

1 **Intervention models**

2 We assess the impact of ivermectin MDA by assuming that a proportion of bloodmeals taken by
3 mosquitoes contain ivermectin (determined by the coverage of ivermectin in the human population).
4 Mosquitoes ingesting ivermectin transition to a new compartment where they experience an elevated
5 mortality rate for the rest of their life. The ‘ivermectin-fed’ compartments are tracked for each day
6 post ivermectin-administration, each with a unique mortality rate to capture the elevated but waning
7 mosquitocidal effect of ivermectin over time as the concentration in human blood decreases. The
8 elevated mortality rates are estimated using a pharmacokinetic (PK)-pharmacodynamic (PD) model³⁰
9 which has been fitted to human ivermectin plasma concentrations and corresponding mosquito
10 mortality data from feeding experiments conducted using *Anopheles gambiae sensu stricto*²⁰. Delayed
11 refeeding, reduced egg laying and reduced sporogonic development are not explicitly modelled as
12 these effects are minimal compared to the mosquitocidal effects²⁸. We also incorporate the impact of
13 existing malaria interventions – including LLINs, SMC and MDA – using existing intervention models²⁹.

14 **Model validation**

15 The model is validated against data from two ivermectin trials: a study across three countries
16 consisting of a single round of ivermectin MDA and focusing on entomological data¹⁸, and a cluster
17 randomised trial (CRT) conducted in Burkina Faso consisting of a single round of ivermectin MDA in
18 the control arm and six rounds of ivermectin MDA in the intervention arm and focusing on clinical
19 incidence in a cohort of children ≤ 5 years old¹⁹. This model validation is presented in the Appendix,
20 pages 12-17.

21 **Intervention Scenarios**

22 We explore the potential impact of ivermectin on malaria prevalence and clinical incidence for the
23 scenarios shown in Box 1. The scenarios are simulated in three seasonality ‘archetypes’ that
24 encapsulate the range of transmission in sub-Saharan Africa³¹: i) highly seasonal, based on Fatick in
25 Senegal, with a transmission season of approximately 4 months, ii) seasonal, based on Bougouriba in
26 Burkina Faso, with a season of 7-8 months, and iii) perennial, based on Equateur in Democratic
27 Republic of Congo (DRC), with year-round transmission. Unless stated otherwise, all simulations
28 have a mean annual all-age slide prevalence of 30%.

29 Ivermectin is recommended for all individuals $>15\text{kg} / \geq 90\text{cm}$, however, for simplicity we assume all
30 children <59 months are below this threshold, and all children ≥ 59 months are above this threshold.
31 Coverage of ivermectin is defined using the number of all individuals ≥ 5 years old as the denominator.
32 Ivermectin is also not recommended for pregnant women, which is why we only consider modest
33 coverage estimates (maximum of 70%).

34 We consider two ivermectin regimens: a single dose of $400\mu\text{g}/\text{kg}$ (1x400) and three consecutive daily
35 doses of $300\mu\text{g}/\text{kg}$ per day (3x300). The former is the highest dose currently recommended for
36 lymphatic filariasis MDAs, and the latter is the dose that was viewed as most promising in a recent
37 clinical trial²⁰.

38 For all scenarios the intervention is introduced optimally in relation to the location-specific seasonality
39 profile of each simulation, obtained by simulating the model at different start times and selecting the
40 time that results in the greatest reduction in cumulative incidence.

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1 **Role of Funding Source**

2 The sponsor of the study had no role in study design, data collection, data analysis, data interpretation,
3 or writing of the report. The corresponding author had full access to all the data in the study and had
4 final responsibility for the decision to submit for publication.

5

6 **Results**

7 The estimated pharmacokinetic profiles of the two dosing regimens are shown in Figure 1a. These
8 were combined with the mosquito hazard ratios estimated in Smit et al.²⁰ for each time after
9 ivermectin administration that mosquitoes were fed on the treated individuals' blood (day 2+4hours,
10 d7, d10, d14, d21, d28) to estimate the relationship between drug concentration and the mosquito
11 hazard ratio (Figure 1b). Figures 1a-b were then combined to estimate the daily hazard of mortality of
12 mosquitoes biting each day (Figure 1c).

13

14 **Ivermectin only MDA**

15 We first simulated the impact of ivermectin only, assuming all other interventions continued at their
16 current coverage levels (Figure 2, Table 1). The impact of ivermectin is predicted to be greatest in the
17 setting with the shortest transmission season, with a predicted reduction in clinical incidence of 62%
18 and 71% for the 1x400µg/kg and 3x300µg/kg doses respectively. The intervention is predicted to be
19 less effective in areas with perennial transmission, where the equivalent reductions are 28% and 31%
20 respectively. We predict that ivermectin has a greater impact on incidence than on prevalence. This is
21 because the intervention prevents new infections by killing infected and infectious mosquitoes rather
22 than clearing older asymptomatic infections. The sensitivity of these results to the impact of repeat
23 ivermectin distribution assuming different durations and magnitudes of mosquitocidal effect
24 (including a hypothetical mosquitocidal drug with a 90-day efficacious period), population coverage
25 levels, number of rounds and timing between rounds and transmission intensities, and exploring the
26 impact of importation of infected individuals into the intervention area, as well as synergies between
27 interventions is shown in the Appendix, pages 18-28.

28

30 **Ivermectin MDA with SMC**

31 Figure 3 and Table 1 show the estimated impact of population-wide ivermectin MDA in combination
32 with SMC Adding ivermectin MDA is predicted to increase the reduction in clinical cases in children <5
33 years old compared to SMC alongside existing core interventions. In a highly seasonal setting, we
34 predict that SMC alone reduces clinical cases by 58% but adding population-wide ivermectin MDA
35 increases this figure to 87% (1x400µg/kg) or 90% (3x300µg/kg) in the year after the start of the
36 intervention. This corresponds to an incremental impact on top of SMC alone of 69% and 77%,
37 respectively. The reduction in clinical incidence is predicted to be lower in a setting with a longer
38 transmission season. Here, the incremental impact of ivermectin is 51% (1x400µg/kg) and 58%
39 (3x300µg/kg). The impact of expanding SMC distribution to all individuals under the age of 10
40 (alongside ivermectin to individuals over the age of 10) is shown in the Appendix, pages 25-26.

41 Delivering SMC to children <5 years old and ivermectin MDA population-wide (≥5 years old) is also
42 predicted to have a dramatic impact on population level prevalence – whereas SMC alone is predicted

1 to reduce all-age prevalence by only 19-21%, adding ivermectin (1x400 µg/kg dose) is predicted to
2 reduce all-age prevalence by 52% (highly seasonal setting) or 45% (seasonal setting).

3 **Ivermectin and DHA-P MDA for burden reduction**

4 The impact of MDA with DHA-P and ivermectin for burden reduction in a highly seasonal moderate
5 transmission setting with three rounds spaced one month apart is shown in Fig. 4a,d, and in a
6 perennial moderate transmission setting with three rounds spaced one month apart in Fig. 4b,e or
7 three rounds spaced four months apart in Fig. 4 c,f. MDA with DHA-P and ivermectin is predicted to
8 be most effective in a seasonal transmission setting; predicted reduction in clinical incidence is 91%
9 (DHA-P + 1x400µg/kg ivermectin) and 94% (DHA-P + 3x300µg/kg ivermectin) compared to 74% with
10 DHA-P alone (Table 1). In a perennial setting, a greater reduction in burden is achieved by spacing the
11 rounds evenly throughout the year – in this scenario, the incremental impact of ivermectin in addition
12 to DHA-P is also greater (Table 1).

14 **Ivermectin and DHA-P MDA for elimination**

15 Figure 5 shows the impact of MDA with DHA-P and ivermectin in a seasonal low transmission setting.
16 Here adding ivermectin to DHA-P prevents the rebounds in transmission between rounds and is
17 predicted to prolong the overall impact of the MDA intervention.

18 **Discussion**

19 Our modelling results predict that ivermectin alone, and to greater extent when combined with
20 antimalarial drugs, could have a major and prolonged effect on malaria prevalence and incidence
21 across a range of transmission settings. We predict that adding ivermectin MDA to current
22 interventions can increase impact and sustain reductions in transmission. Due to the operationally
23 synergistic opportunities of co-administering ivermectin with other interventions that have the same
24 distribution schedule (MDA with antimalarials, SMC), and the fact that ivermectin can directly target
25 residual transmission that remains even with high coverage of vector control, ivermectin may be a
26 promising new complementary malaria tool.

27 In a seasonal setting, adding ivermectin MDA to SMC has a greater incremental impact on reducing
28 prevalence and incidence compared to adding ivermectin MDA to DHA-P MDA, however the total
29 impact of the latter intervention is greater. During SMC, a large proportion of the population remain
30 untreated and unprotected, therefore adding an intervention that reduces the infectious vector
31 population means that these individuals will also receive a benefit. However, MDA with DHA-P
32 provides prophylaxis to a larger proportion of the population, so reducing the infectious vector
33 population with ivermectin has a lower additional impact as a large proportion cannot be re-infected
34 anyway.

35 SMC is widely conducted, extremely effective, and a key intervention in in the Sahel region which
36 experiences some of the highest rates of malaria worldwide. We predict that administering ivermectin
37 to the population ≥5 years old could not only increase the impact of SMC in children under 5, but could
38 also increase the population-level benefit, reducing clinical incidence across the whole population.

39 Our results suggest that the 3x300µg/kg dose is only marginally more impactful than the 1x400µg/kg
40 dose. Although the hazard-ratio area under the curve (and above 1) is 78% greater for 3x300 µg/kg
41 compared to 1x400µg/kg (Figure 1c), the highly non-linear effect of increased mortality on the
42 proportion of mosquitoes completing sporogony and becoming infectious means that the duration
43 the hazard ratio is above some threshold is more important than the magnitude of the hazard ratio.
44 Even for a hazard ratio of 2, the proportion of mosquitoes surviving long enough to complete

1 sporogony is 63% lower than in the absence of ivermectin. The hazard ratio is >2 for 14 days with
2 3x300 µg/kg and for 10 days with 1x400 µg/kg. The difference between the two regimens is greater in
3 a highly-seasonal compared to a perennial setting (Figure 2) because, with the former, ivermectin's
4 effective window covering a greater proportion of annual transmission.

5 A key assumption in the ivermectin component of the model is that the hazard ratios observed in a
6 clinical laboratory setting can be applied to the known mortality rates of wild mosquitoes. For
7 example, we assume that a mosquito dying twice as quickly in the laboratory after a certain dose of
8 ivermectin would also die twice as quickly in the wild, albeit with a considerably higher baseline
9 mortality rate. In the model, we assume that the mean baseline lifespan of an *Anopheles gambiae*
10 mosquito is 10 days in the wild whereas the lifespan of mosquitoes in laboratory experiments is
11 around 14-30 days^{20,32}.

12 The model accurately captures changes in entomological outcomes observed in the field; however,
13 these field data are limited (Appendix, page 14). Future entomology data collected in CRTs is therefore
14 needed to validate or refine this assumption. The results presented here assume all mosquitoes are
15 *Anopheles gambiae s.s.*, however, there is no evidence that other African vectors would be less
16 sensitive^{12,32,33}.

17 Further limitations include that the 3x300µg/kg hazard estimates were derived directly from data¹³
18 whereas the 1x400µg/kg hazard ratios were estimated using a PK-PD model. The data used to derive
19 both sets of hazard ratios were from a trial where ivermectin was co-administered with DHA-P.
20 Preliminary data suggest an interaction between these drugs that increases ivermectin bioavailability,
21 peak concentration, and mosquito killing effect compared to that of ivermectin alone²¹. Additionally,
22 it remains to be determined whether the observed effect of ivermectin solely reflects that of the
23 parent compound, or whether there is also an active ivermectin metabolite with mosquitocidal
24 properties²¹.

25 The results presented here assume a constant and isolated population, with no movement of infected
26 humans or vectors into or out of the intervention area. Although in a sensitivity analysis (see Appendix,
27 pages 24-25) we did not find a major impact of this assumption, further exploration of the effect of
28 this intervention in models that capture spatial linkage between populations is warranted.

29 To provide empirical evidence for the utility of ivermectin across different settings CRTs are needed.
30 An earlier small CRT of repeated ivermectin MDA in Burkina Faso¹⁹ found a 19.6% reduction in
31 episodes of clinical incidence in a cohort of children ≤5 years old (Appendix, pages 15-17). Whilst the
32 1x400µg/kg dose has been used for lymphatic filariasis control, the 3x300µg/kg dose has never been
33 delivered at scale to whole populations. An ongoing CRT in The Gambia (NCT03576313) will provide
34 evidence on the safety and acceptability of this higher dose (3x300 µg/kg) when given in combination
35 with DHA-P. Questions remain surrounding the feasibility of delivering this intervention at scale and
36 the implications and potential adherence issues of treating populations with a drug that may provide
37 them no direct benefits (if they do not have any other infections that ivermectin treats).

38 The appetite from national malaria control programs and funders to implement ivermectin MDA still
39 needs to be ascertained. These decisions will depend in part on estimates of cost-effectiveness in
40 comparison to other malaria interventions, particularly other novel vector control tools that might be
41 targeted in areas with high transmission and high coverage of existing vector control tools. Mass
42 ivermectin distribution in Loa-Loa endemic regions may require a test-and-not-treat strategy, as it can
43 cause adverse events in Loa-Loa infected individuals³⁴.

1 New longer lasting ivermectin formulations^{12,23} or other mosquitocidal drugs²⁴ offer a promising new
2 opportunity for malaria control, however, the benefit of current formulations of ivermectin should
3 not be underplayed. Ivermectin is known to be safe and accepted by communities who have received
4 MDAs for decades as part of the control of lymphatic filariasis and onchocerciasis. Ongoing CRTs using
5 ivermectin will provide an opportunity to evaluate the impact of mosquitocidal drugs and provide
6 evidence to guide decision making for both current and new longer lasting versions of these drugs.

7 As of September 2019, in addition to the ivermectin CRT underway in The Gambia, there are four more
8 trials (that we are aware of) planned to start in 2019 or 2020. These trials are being conducted in
9 different transmission settings with different doses and distribution schedules, different malaria
10 vectors, and different coverages of other interventions. Models that have been validated against
11 clinical and entomological data, such as the one presented here, will offer a useful way to compare
12 results from these diverse trials, to synthesise evidence, and provide a robust framework to
13 extrapolate from these trials to wider-scale predictions.

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Contributors

HCS performed the transmission modelling analysis and processed all model outputs. HCS, BDF, KK, CC, TB, PGTW, MRS designed the analysis. GA produced the PK/PD modelling outputs. BDF, KK, HA, FTK, MRS collected data. HCS, OJW, JH developed the model code. HCS wrote the first draft of the manuscript. All authors contributed to writing and editing the manuscript. All authors approved the final manuscript.

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