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► To cite this version:

Hannah C. Slater, Brian D. Foy, Kevin Kobylinski, Carlos Chaccour, Oliver J. Watson, et al.. Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study. *The Lancet Infectious Diseases*, 2020, 20 (4), pp.498-508. 10.1016/S1473-3099(19)30633-4 . hal-02450316

HAL Id: hal-02450316

<https://hal.science/hal-02450316>

Submitted on 23 May 2022

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

3 Hannah C. Slater PhD (1)*, Prof Brian D. Foy PhD (2), Kevin Kobylinski PhD (3), Carlos Chaccour MD
4 (4,5,6), Oliver J. Watson MRes (1), Joel Hellewell PhD (1), Ghaith Aljayyousi PhD (7), Teun Bousema
5 PhD (8,9), Jeremy Burrows PhD (10), Prof Umberto D'Alessandro PhD (11), Haoues Alout PhD (12),
6 Prof Feiko O Ter Kuile PhD (7), Patrick G.T. Walker PhD (1), Prof Azra C. Ghani PhD (1), Menno R. Smit
7 MD (7)

- 8 1) MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease
9 Epidemiology, Imperial College London, London, UK
- 10 2) Arthropod-borne and Infectious Diseases Laboratory, Department of Microbiology,
11 Immunology and Pathology, Colorado State University, Fort Collins, CO, USA
- 12 3) Department of Entomology, Armed Forces Research Institute of Medical Sciences, Bangkok,
13 Thailand
- 14 4) ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain
- 15 5) Instituto de Salud Tropical - Universidad de Navarra, Pamplona, Spain
- 16 6) Ifakara Health Institute, Ifakara, Tanzania
- 17 7) Liverpool School of Tropical Medicine (LSTM), Liverpool, UK
- 18 8) Department of Immunology and Infection, London School of Hygiene and Tropical Medicine,
19 London, UK
- 20 9) Radboud Institute for Health Sciences, Radboud University Medical Centre, Nijmegen, The
21 Netherlands
- 22 10) Medicines for Malaria Venture, Route de Pré Bois 20, 1215 Geneva 15, Switzerland
- 23 11) MRC Unit The Gambia at LSHTM, Fajara, Banjul, The Gambia
- 24 12) ASTRE unit (UMR117), INRA-CIRAD, Montpellier, France

25 *Corresponding author (hslater@path.org, PATH, 2201 Westlake Avenue, Seattle, WA, USA)

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
30 become infectious.

31 **Methods:** We validate an existing population-level mathematical model of the impact of ivermectin
32 on the mosquito population and malaria transmission to entomological and clinical data. The model
33 is extended to include a range of complementary malaria interventions and to incorporate new data
34 on higher doses with a longer mosquitocidal effect. We then simulate the impact of these doses in a
35 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
38 seasonal moderate transmission setting, three rounds of ivermectin-only MDA spaced one month
39 apart with a dose of 3x300µg/kg and 70% coverage is predicted to reduce clinical incidence by 71%
40 and prevalence by 34%. We predict that adding ivermectin MDA to seasonal malaria
41 chemoprevention in this setting would reduce clinical incidence by an additional 77% in under 5-year
42 olds. Adding ivermectin MDA to MDA with antimalarials in this setting is predicted to reduce
43 incidence by an additional 75% (all-ages).

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
11 models to assess the impact of ivermectin (to humans) on malaria prevalence and incidence, using
12 the search terms “ivermectin” AND “malaria” AND (“modelling” OR “modeling”). The search was
13 unrestricted by language or publication date. Using this search and by scanning reference lists of
14 articles, we identified three publications in peer-reviewed journals. Slater et al. found that adding a
15 single dose of ivermectin 150 µg/kg would only have a modest effect on reduction of malaria
16 prevalence if distributed in mass drug administration (MDA) with dihydroartemisinin-piperazine
17 (DHA-P), although higher doses of ivermectin were predicted to have a greater and longer-lasting
18 effect. However, a model developed by Stuckey and colleagues predicted that adding ivermectin to
19 MDA with DHA-P in Zambia would have a negligible additional effect. Finally a theoretical
20 mathematical model by Ngwa et al. predicts that treating symptomatic individuals with ivermectin
21 would reduce the reproduction number of malaria.

22 Added value of this study

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

34 Implications of all the available evidence

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

1 and indoor residual spraying with insecticides, we believe ivermectin is a powerful new tool which
2 can complement existing malaria control efforts.

3

4 **Introduction**

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

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

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

40 The doses of ivermectin typically used for onchocerciasis and lymphatic filariasis control (single doses
41 of 150-200µg/kg) have a short mosquitocidal effect of around 5-6 days¹⁷ and limited impact on
42 mosquito populations¹⁸ and transmission unless distributed frequently¹⁹. Recent clinical trials
43 investigating the impact of higher doses have produced promising results. Three doses of 300µg/kg
44 given over three days has a mosquitocidal effect in humans for 28 days against *Anopheles gambiae*

1 s.s.²⁰ and a single dose of 400µg/kg was effective for at least ten days against *Anopheles minimus*
2 and 6-10 days against *Anopheles dirus*, two of the most important malaria vectors in Southeast
3 Asia^{21,22}. A slow-release ivermectin implant has achieved mosquitocidal concentrations for 40 weeks
4 in cattle¹², and a novel slow-release, gastric-resident, drug delivery technology in development has
5 achieved mosquitocidal concentrations of ivermectin for around 14 days in pigs²³. Fluralaner and
6 afoxolaner, two drugs from the isoxazolines class of endectocides used in veterinary medicine, have
7 also been shown to be toxic to mosquitoes. Preliminary estimates indicate that they could remain at
8 effective mosquitocidal concentrations for 50-90 days, but have not yet been tested for safety in
9 humans²⁴ and regulatory approval for human use may take up to a decade²⁵. The combination of
10 non-ivermectin mosquitocidal drugs administered to cattle alongside ivermectin administered to
11 humans has been suggested as an approach to simultaneously target anthropophilic and zoophilic
12 mosquitoes whilst preventing the development of resistance to ivermectin via a dual-chemistry
13 approach which is recommended in other forms of vector control²⁶.

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

20 **Methods**

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

26 **Malaria transmission model**

27 The deterministic compartmental model incorporates transmission between mosquito and human
28 hosts^{27,29}. Individuals begin life susceptible with a level of maternally-acquired immunity which
29 quickly wanes. Upon inoculation with an infectious bite they either become infected (with a
30 probability determined by their level of pre-erythrocytic immunity), whereupon they either develop
31 clinical disease or asymptomatic infection (determined by their levels of blood-stage immunity).
32 Individuals with clinical disease have a probability of being successfully diagnosed and treated.
33 Treated individuals are prophylactically protected for a duration based on the properties of the
34 antimalarial taken. Untreated individuals with clinical disease are assumed to have symptomatic
35 infection for an average 5 days before transitioning to becoming asymptotically infected.
36 Asymptotically infected individuals remain infected for an average of 310 days²⁷, but their
37 probability of being detectable by microscopy decreases over the course of the infection to capture
38 the effect of decreasing parasite densities. Individuals that are susceptible or have asymptomatic
39 infection can be superinfected which follows the same infection process. The acquisition and loss of
40 immunity is dynamically modelled and determines the probability of infection, the probability of
41 developing symptoms and the detectability and transmissibility of infection. Transmission from
42 mosquitoes to humans is determined by the entomological inoculation rate, which is a product of
43 the mosquito biting rate, sporozoite rate, functions determining the relative biting rate on different
44 subgroups (capturing heterogeneity in exposure and age) and the probability of successful
45 inoculation. Similarly, transmission from humans to mosquitoes is determined by the infectivity of

1 the human, which is based on their infection state, the mosquito biting rate, the age- and
2 heterogeneity-biting rates and the probability of successful infection. We assume a constant and
3 isolated population, with no movement of infected humans or mosquitoes in or out of the
4 intervention area. Details of the model are provided in the Appendix, page 1-11.

5 **Intervention models**

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

19 **Model validation**

20 The model is validated against data from two ivermectin trials: a study across three countries
21 consisting of a single round of ivermectin MDA and focusing on entomological data¹⁸, and a cluster
22 randomised trial (CRT) conducted in Burkina Faso consisting of a single round of ivermectin MDA in
23 the control arm and six rounds of ivermectin MDA in the intervention arm and focusing on clinical
24 incidence in a cohort of children ≤ 5 years old³¹. This model validation is presented in the Appendix,
25 pages 12-17.

26 **Intervention Scenarios**

27 We explore the potential impact of ivermectin on malaria prevalence and clinical incidence for the
28 scenarios shown in Box 1. The scenarios are simulated in three seasonality 'archetypes' that capture
29 a range of transmission in sub-Saharan Africa³²: i) highly seasonal, based on Fatick in Senegal, with a
30 transmission season of approximately 4 months, ii) seasonal, based on Bougouriba in Burkina Faso,
31 with a season of 7-8 months, and iii) perennial, based on Equateur in Democratic Republic of Congo
32 (DRC), with year-round transmission. Unless stated otherwise, all simulations have a mean annual
33 all-age slide prevalence of 30%.

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

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

1 For all scenarios the intervention is introduced optimally in relation to the location-specific
2 seasonality profile of each simulation, obtained by simulating the model at different start times and
3 selecting the time that results in the greatest reduction in cumulative incidence. Results are
4 expressed as a percentage reduction in prevalence or incidence in the one year after the start of the
5 intervention (further details Appendix page 11).

6

7

8 **Role of Funding Source**

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

12

13 **Results**

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

20

21 **Ivermectin only MDA**

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

35

36 **Ivermectin MDA with SMC**

37 Figure 3 and Table 1 show the estimated impact of population-wide ivermectin MDA in combination
38 with SMC. Adding ivermectin MDA is predicted to increase the reduction in clinical cases in children
39 <5 years old compared to SMC alongside existing core interventions. In a highly seasonal setting, we
40 predict that SMC alone reduces clinical cases by 58% but adding population-wide ivermectin MDA

1 increases this figure to 87% (1x400µg/kg) or 90% (3x300µg/kg) in the year after the start of the
2 intervention. This corresponds to an incremental impact on top of SMC alone of 69% and 77%,
3 respectively. The reduction in clinical incidence is predicted to be lower in a setting with a longer
4 transmission season. Here, the incremental impact of ivermectin is 51% (1x400µg/kg) and 58%
5 (3x300µg/kg). The impact of expanding SMC distribution to all individuals under the age of 10 is
6 shown in the Appendix, pages 25-26.

7 Delivering SMC to children <5 years old and ivermectin MDA population-wide (≥5 years old) is also
8 predicted to reduce population level prevalence – whereas SMC alone is predicted to reduce all-age
9 prevalence by only 19-21%, adding ivermectin (1x400 µg/kg dose) is predicted to reduce all-age
10 prevalence by 52% (highly seasonal setting) or 45% (seasonal setting).

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

12 The impact of MDA with DHA-P and ivermectin in a highly seasonal moderate transmission setting
13 with three rounds spaced one month apart is shown in Figure 4a,d, and in a perennial moderate
14 transmission setting with three rounds spaced one month apart in Figure 4b,e or three rounds
15 spaced four months apart in Figure 4 c,f. MDA with DHA-P and ivermectin is predicted to be most
16 effective in a seasonal transmission setting; predicted reduction in clinical incidence is 91% (DHA-P +
17 1x400µg/kg ivermectin) and 94% (DHA-P + 3x300µg/kg ivermectin) compared to 74% with DHA-P
18 alone (Table 1). In a perennial setting, a greater reduction in burden is achieved by spacing the
19 rounds evenly throughout the year – in this scenario, the incremental impact of ivermectin in
20 addition to DHA-P is also greater (Table 1).

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

22 Figure 5 shows the impact of MDA with DHA-P and ivermectin in a seasonal low transmission setting.
23 Adding ivermectin to DHA-P prevents the rebounds in transmission between rounds and is predicted
24 to prolong the overall impact of the MDA intervention.

25 **Discussion**

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

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

42 SMC is widely conducted, extremely effective, and a key intervention in in the Sahel region which
43 experiences some of the highest rates of malaria worldwide. We predict that administering

1 ivermectin to the population ≥ 5 years old could not only increase the impact of SMC in children
2 under 5, but could also increase the population-level benefit, reducing clinical incidence across the
3 whole population.

4 Our results suggest that the 3x300 $\mu\text{g}/\text{kg}$ dose is only marginally more impactful than the 1x400 $\mu\text{g}/\text{kg}$
5 dose. Although the hazard-ratio area under the curve (and above 1) is 78% greater for 3x300 $\mu\text{g}/\text{kg}$
6 compared to 1x400 $\mu\text{g}/\text{kg}$ (Figure 1c), the highly non-linear effect of increased mortality on the
7 proportion of mosquitoes completing sporogony and becoming infectious means that the duration
8 the hazard ratio is above some threshold is more important than the magnitude of the hazard ratio.
9 Even for a hazard ratio of 2, the proportion of mosquitoes surviving long enough to complete
10 sporogony is 63% lower than in the absence of ivermectin. The hazard ratio is >2 for 14 days with
11 3x300 $\mu\text{g}/\text{kg}$ and for 10 days with 1x400 $\mu\text{g}/\text{kg}$. The difference between the two regimens is greater
12 in a highly-seasonal compared to a perennial setting (Figure 2) because, with the former,
13 ivermectin's effective window covers a greater proportion of annual transmission.

14 A key assumption in the ivermectin model is that the hazard ratios observed in a clinical laboratory
15 setting can be applied to the known mortality rates of wild mosquitoes. For example, we assume
16 that a mosquito dying twice as quickly in the laboratory after a certain dose of ivermectin would also
17 die twice as quickly in the wild, albeit with a considerably higher baseline mortality rate. In the
18 model, we assume that the mean baseline lifespan of an *Anopheles gambiae* mosquito is 10 days in
19 the wild whereas the lifespan of mosquitoes in laboratory experiments is around 14-30 days^{20,33}.

20 The model accurately captures changes in entomological outcomes observed in the field; however,
21 these field data are limited (Appendix, page 14). Future entomology data collected in CRTs is
22 therefore needed to validate or refine this assumption. Although the results presented here assume
23 all mosquitoes are *Anopheles gambiae s.s.*, there is no evidence that other African vectors would be
24 less sensitive^{12,33,34}.

25 Further limitations include that the 3x300 $\mu\text{g}/\text{kg}$ hazard estimates were derived directly from data¹³
26 whereas the 1x400 $\mu\text{g}/\text{kg}$ hazard ratios were estimated using a PK-PD model. The data used to derive
27 both sets of hazard ratios were from a trial where ivermectin was co-administered with DHA-P.
28 Preliminary data suggest an interaction between these drugs that increases ivermectin
29 bioavailability, peak concentration, and mosquito killing effect compared to that of ivermectin
30 alone²¹. Additionally, it remains to be determined whether the observed effect of ivermectin solely
31 reflects that of the parent compound, or whether there is also an active ivermectin metabolite with
32 mosquitocidal properties²¹.

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

38 CRTs are needed to provide empirical evidence on the effectiveness and safety of ivermectin. An
39 earlier small CRT of repeated ivermectin MDA in Burkina Faso³¹ found a 19.6% reduction in episodes
40 of clinical incidence in a cohort of children ≤ 5 years old (Appendix, pages 15-17). Whilst the
41 1x400 $\mu\text{g}/\text{kg}$ dose has been used for lymphatic filariasis control, the 3x300 $\mu\text{g}/\text{kg}$ dose has never been
42 delivered at scale to whole populations. An ongoing CRT in The Gambia (NCT03576313) will provide
43 evidence on the safety and acceptability of this higher dose (3x300 $\mu\text{g}/\text{kg}$) when given in
44 combination with DHA-P. Questions remain surrounding the feasibility of delivering this intervention

1 at scale and the implications and potential adherence issues of treating populations with a drug that
2 may provide them no direct benefits (if they do not have any other infections that ivermectin treats).

3 The appetite from national malaria control programs and funders to implement ivermectin MDA still
4 needs to be ascertained. These decisions will depend in part on estimates of cost-effectiveness in
5 comparison to other malaria interventions, particularly other novel vector control tools that might
6 be targeted in areas with high transmission and high coverage of existing vector control tools. Mass
7 ivermectin distribution in Loa loa endemic regions may require a test-and-not-treat strategy, as it can
8 cause adverse events in Loa loa infected individuals³⁵.

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

16 As of September 2019, two ivermectin CRTs are underway (in The Gambia and Burkina Faso) and
17 there are three more (that we are aware of) planned to start in 2019 or 2020. These trials are being
18 conducted in different transmission settings with different doses and distribution schedules,
19 different malaria vectors, and different coverages of other interventions. Models that have been
20 validated against clinical and entomological data, such as the one presented here, will offer a useful
21 way to compare results from these diverse trials, to synthesise evidence, and provide a robust
22 framework to extrapolate from these trials to wider-scale impact predictions.

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8 **Conflicts of Interest**

9 Dr. Chaccour reports grants from Unitaid and Bill and Melinda Gates Foundation during the conduct
10 of the study. Dr. Foy has a patent 16/275,172 pending. Dr. Bousema reports grants from Bill and
11 Melinda Gates Foundation during the conduct of the study. Dr. D'Alessandro reports grants from
12 MRC Joint Global Health Trial Scheme during the conduct of the study. All other authors declare no
13 conflicts of interest.

14 15 **Disclaimers**

16
17 Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to
18 its presentation and/or publication. The opinions or assertions contained herein are the private
19 views of the author, and are not to be construed as official, or as reflecting true views of the
20 Department of the Army or the Department of Defense.

21
22 ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya

23 24 **Funding Sources**

25 This work was funded by an Imperial College Junior Research Fellowship to HCS with additional
26 financial support from the Bill and Melinda Gates Foundation.

27 HCS and CC received additional financial support from Bill and Melinda Gates Foundation under the
28 Ivermectin development roadmap (OPPP1177135) and from Unitaid under the Project Preparation
29 Facility of the BOHEMIA grant (2018-30-ISG)

30 31 **Contributors**

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

37 38 **References**

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7 **Figure legends**

8 Figure 1: (a) Modelled drug concentrations of 3x300µg/kg and 1x400µg/kg doses of ivermectin⁴¹
9 estimated using a PK-PD model⁴¹ fitted to data in Smit et al.¹³. (b) Data (dark pink points, with 95%
10 confidence intervals) and modelled relationship between drug concentrations and *Anopheles*
11 *gambiae* mosquito mortality (dark pink line) obtained using local polynomial regression, and the
12 dose-response relationship (light pink line) used in a previous modelling study²⁸. (c) Hazard ratios for
13 *Anopheles gambiae* mosquito mortality of 3x300µg/kg and 1x400µg/kg doses of ivermectin using
14 relationships from (a) and (b).

15

16 Figure 2: Clinical incidence per 1,000 all-age population (a,b,c) and annual mean slide prevalence
17 (c,d,e) after three rounds of ivermectin one month apart in three different transmission settings. The
18 vertical pink lines indicate the timing of the ivermectin MDA rounds. Coverage is assumed to be 70%
19 of all individuals over the age of 5. The baseline scenario assumes standard interventions only
20 (LLINs, access to diagnosis and treatment).

21

22 Figure 3: Clinical incidence per 1,000 children ≤5 years old after four rounds one month apart of
23 SMC, SMC + 1x400µg/kg ivermectin or SMC + 3x300µg/kg ivermectin in a highly seasonal (a) and
24 seasonal (b) transmission setting with a pre-intervention mean annual slide prevalence of 30%. We
25 assume ivermectin coverage of 70% in individuals over the age of five and SMC coverage of 90%
26 children aged 3-59 months. The baseline scenario assumes standard interventions only (LLINs, access
27 to diagnosis and treatment).

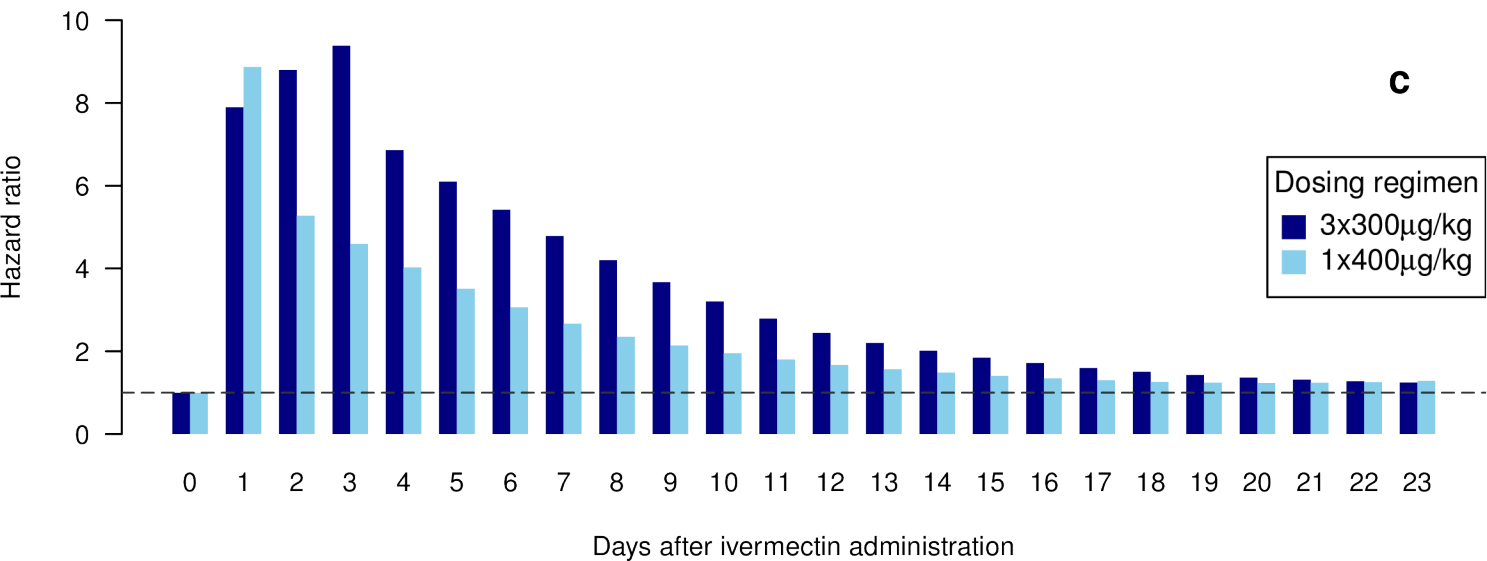
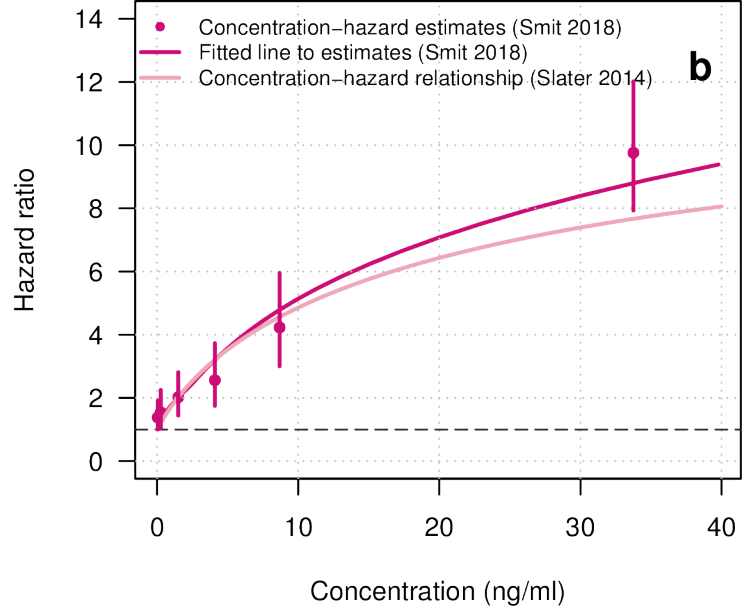
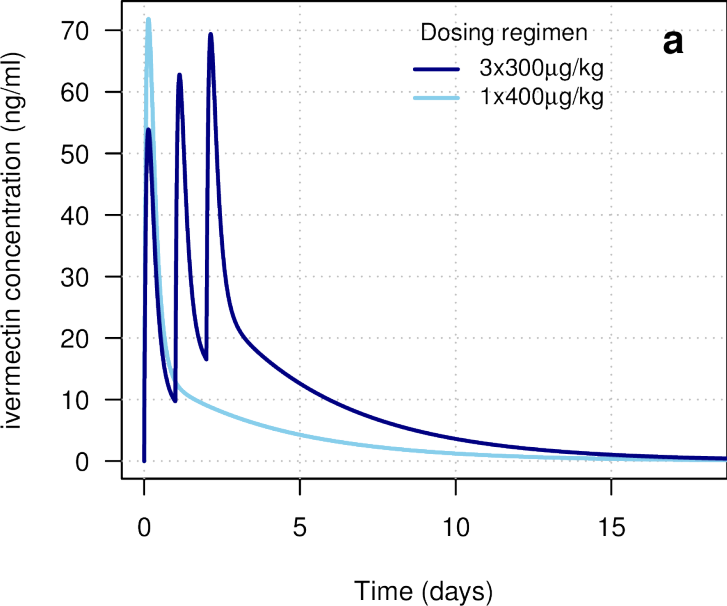
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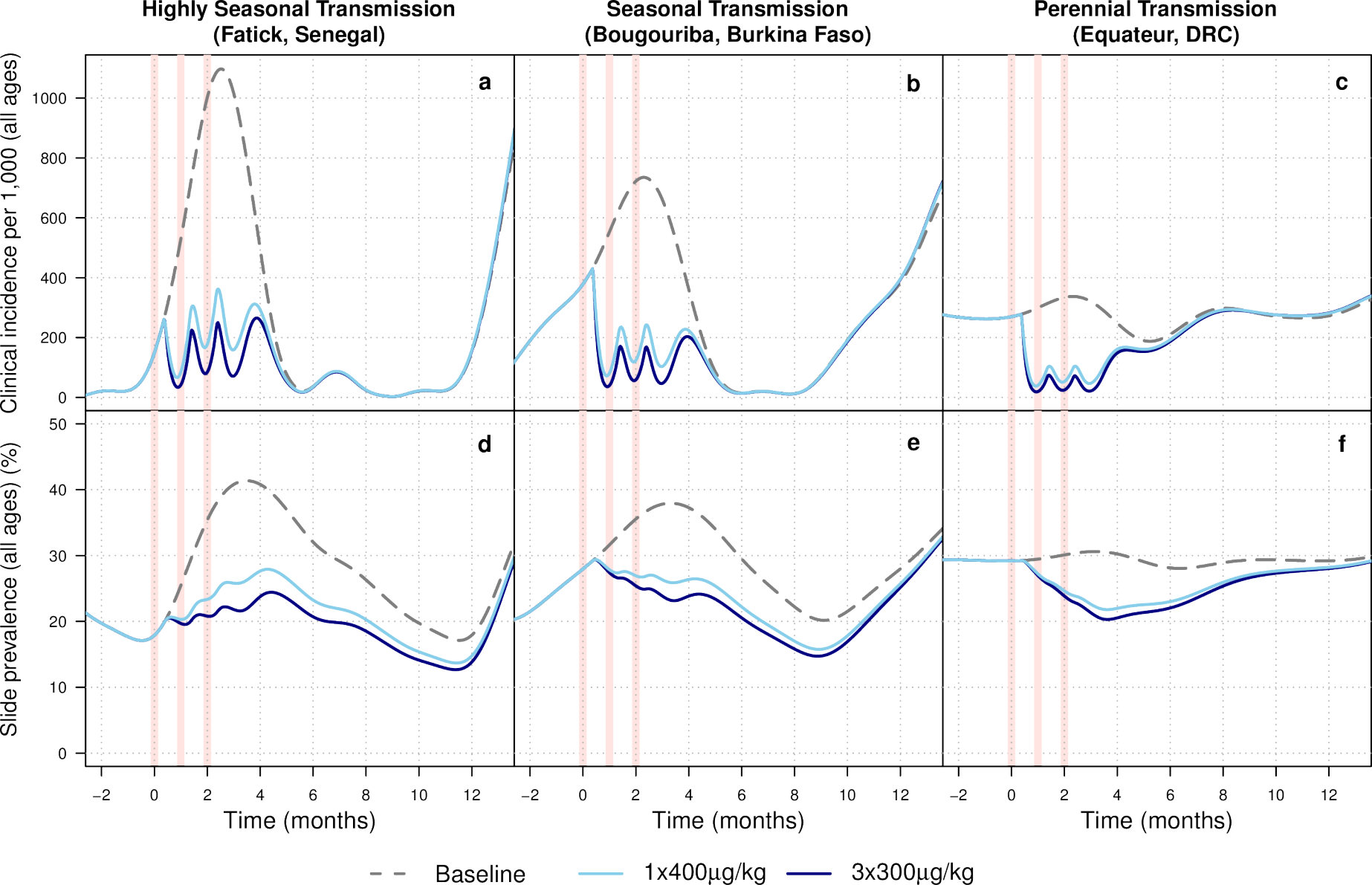
29 Figure 4: Clinical incidence per 1,000 all-age population (a,b,c) and annual mean slide prevalence
30 (d,e,f) after three rounds of MDA with DHA-P, MDA with DHA-P + 1x400µg/kg ivermectin or MDA
31 with DHA-P + 3x300µg/kg ivermectin in a highly seasonal moderate (a,d), and perennial moderate
32 (b,e and c,f) transmission setting. The rounds are conducted either one month apart (a,d and b,e) or
33 four months apart (c,f). Coverage is assumed to be 70% of all individuals over the age of 5. The
34 baseline scenario assumes standard interventions only (LLINs, access to diagnosis and treatment).

35

36 Figure 5: Clinical incidence per 1,000 all-age population (a) and annual mean slide prevalence (b)
37 after three rounds of MDA with DHA-P, MDA with DHA-P + 1x400µg/kg ivermectin or MDA with
38 DHA-P + 3x300µg/kg ivermectin in a highly seasonal low transmission setting. Coverage is assumed

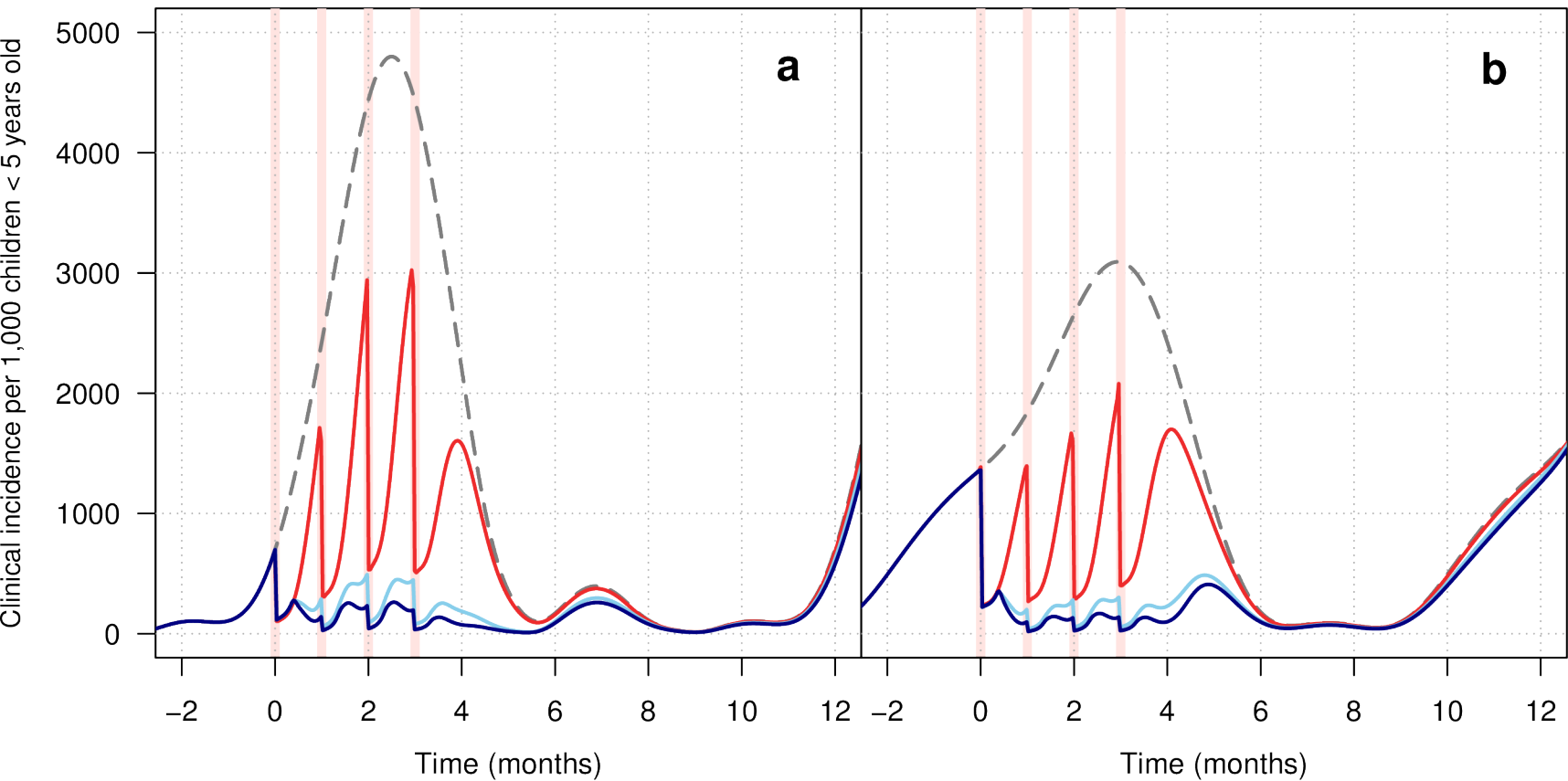
- 1 to be 70% of all individuals over the age of 5. The baseline scenario assumes standard interventions
- 2 only (LLINs, access to diagnosis and treatment).
- 3





Highly Seasonal Transmission
(Fatick, Senegal)

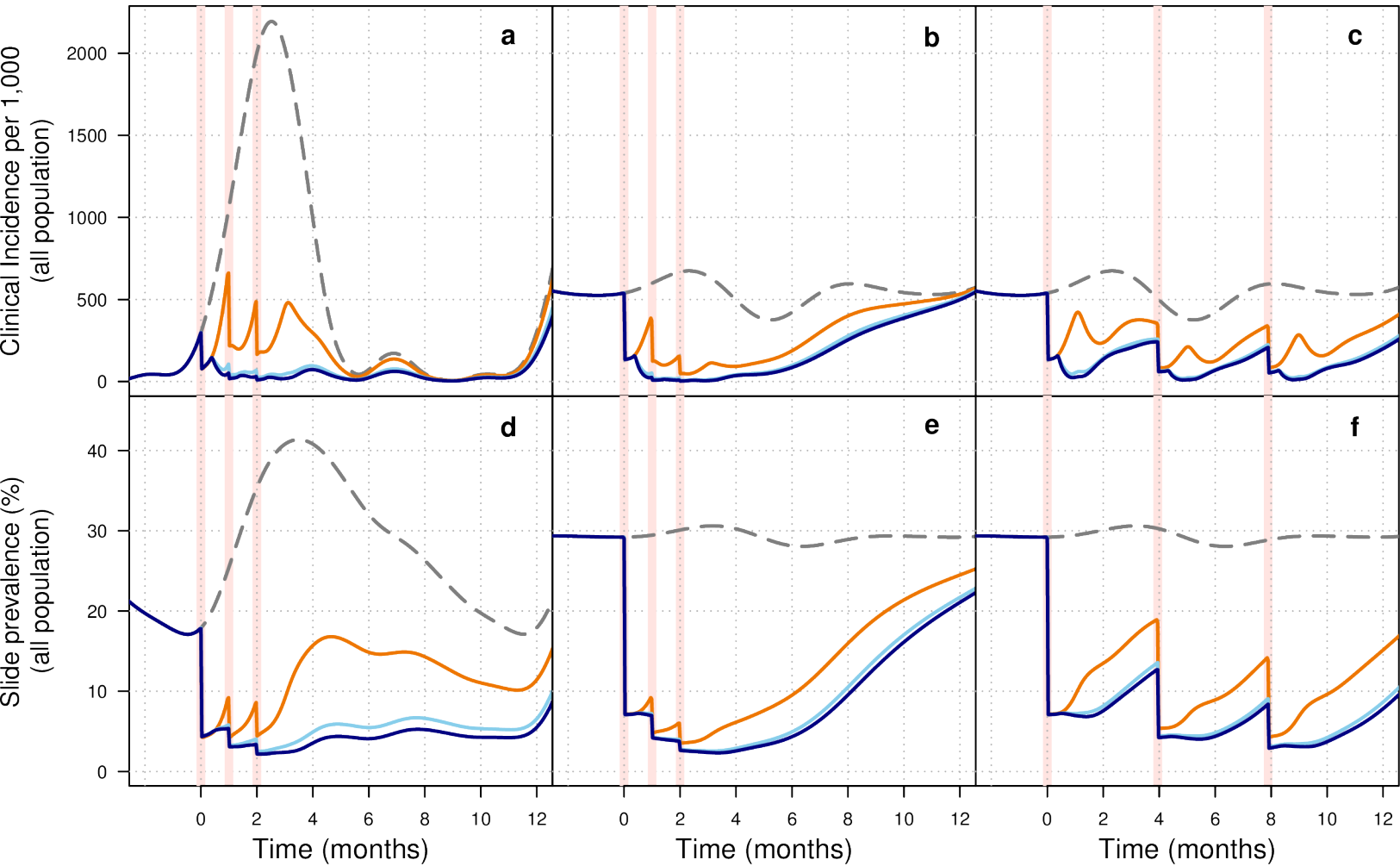
Seasonal Transmission
(Bougouriba, Burkina Faso)



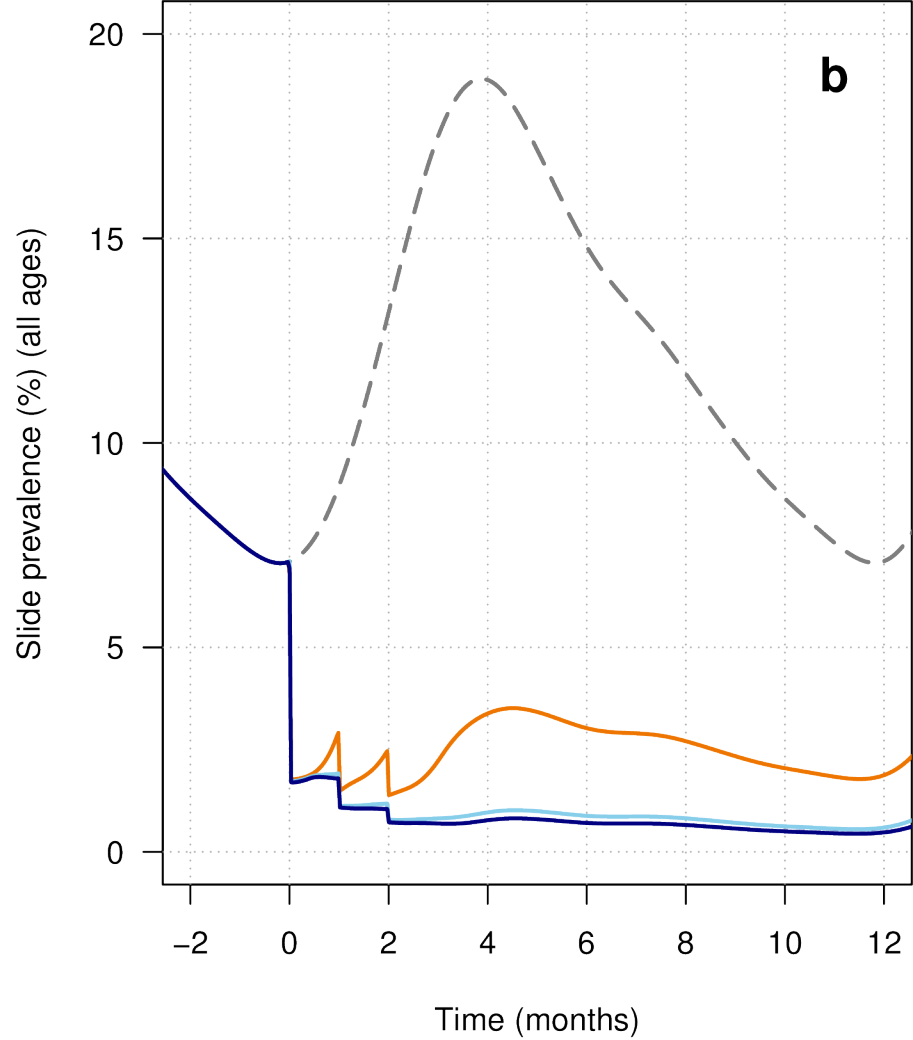
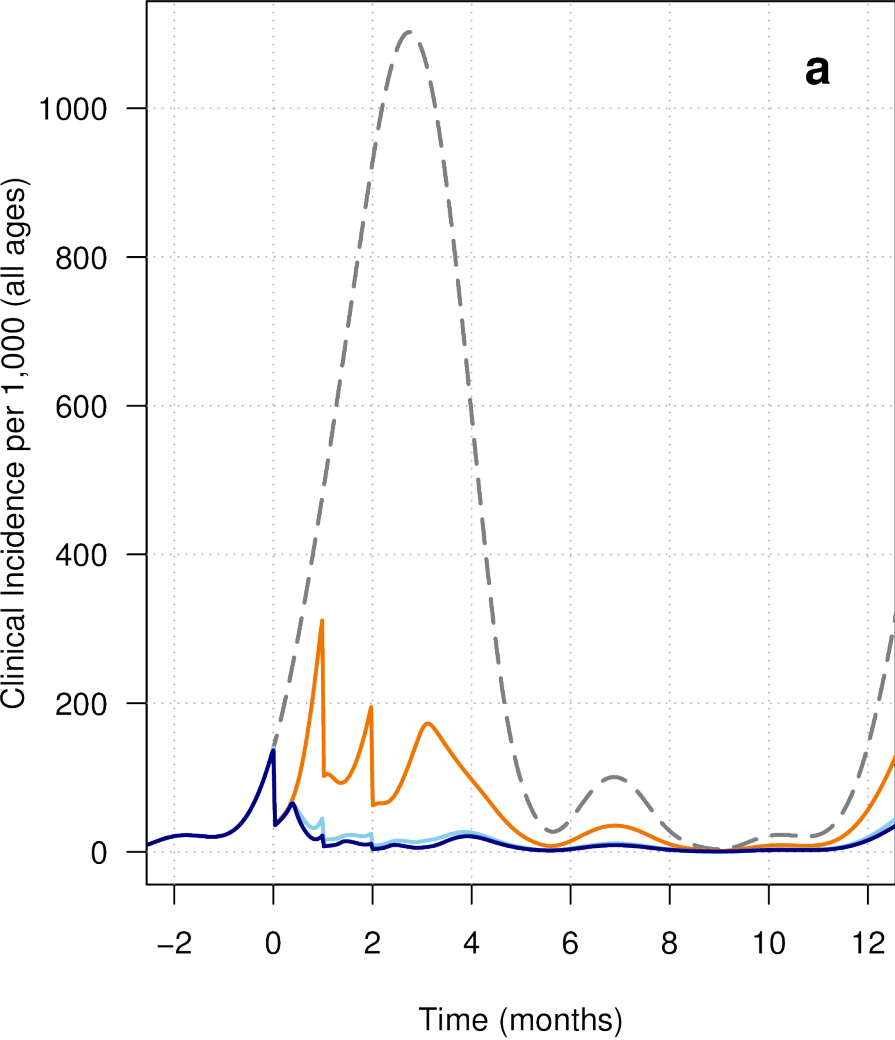
Highly Seasonal Transmission
(Fatick, Senegal)

Perennial Transmission
(Equateur, DRC)

Perennial Transmission
(Equateur, DRC)



-- Baseline — MDA (DHA-P) — MDA (DHA-P) + 1x400µg/kg — MDA (DHA-P) + 3x300µg/kg



-- Baseline — MDA (DHA-P) — MDA (DHA-P) + 1x400 μ g/kg — MDA (DHA-P) + 3x300 μ g/kg

Box 1: Details of intervention scenarios

Complementary intervention	Ivermectin interventions	Intervention Frequency	Example transmission setting
Continue standard interventions already in place (LLINs, access to diagnosis and treatment)	<ul style="list-style-type: none"> • None • Ivermectin-1x400 MDA • Ivermectin-3x300 MDA 	3 rounds one month apart	Highly seasonal (based on Fatick, Senegal), moderate transmission
			Seasonal (based on Bougouriba, Burkina Faso), moderate transmission
			Perennial (based on Equateur, DRC), moderate transmission
SMC (with sulfadoxine-pyrimethamine and amodiaquine (SP-AQ)) to children 3-59 months old and continue standard interventions	<ul style="list-style-type: none"> • None • Ivermectin-1x400 MDA • Ivermectin-3x300 MDA 	4 rounds one month apart	Highly seasonal (based on Fatick, Senegal), moderate transmission
			Seasonal (based on Bougouriba, Burkina Faso), moderate transmission
MDA (with dihydroartemisinin-piperazine (DHA-P)) to all eligible population and continue standard interventions	<ul style="list-style-type: none"> • None • Ivermectin-1x400 MDA • Ivermectin-3x300 MDA 	3 rounds one month apart	Highly seasonal (based on Fatick, Senegal), moderate transmission
			Perennial (based on Equateur, DRC), moderate transmission
			Highly seasonal (based on Fatick, Senegal), low transmission
		3 rounds four months apart	Perennial (based on Equateur, DRC), moderate transmission

Ivermectin only

Ivermectin dose	Percentage reduction in clinical incidence in all population over 1 year after start of intervention		Percentage reduction in mean slide prevalence in all population over 1 year after start of intervention	
	1x400µg/kg	3x300µg/kg	1x400µg/kg	3x300µg/kg
Highly seasonal (Fatick, Senegal)	62%	71%	27%	34%
Seasonal (Bougouriba, BF)	49%	55%	21%	26%
Perennial (Equateur, DRC)	28%	31%	13%	15%

SMC and ivermectin MDA

Complementary intervention	Percentage reduction in clinical incidence in children <5 years old over 1 year after start of intervention (compared to baseline)			Percentage reduction in clinical incidence in children <5 years old over 1 year after start of intervention (compared to SMC only)	
	None	1x400µg/kg	3x300µg/kg	1x400µg/kg	3x300µg/kg
Highly seasonal (Fatick, Senegal)	58%	87%	90%	69%	77%
Seasonal (Bougouriba, BF)	48%	75%	78%	51%	58%

MDA with DHA-P and ivermectin

Complementary intervention	Percentage reduction in clinical incidence in all population over 1 year after start of intervention (compared to baseline)			Percentage reduction in clinical incidence in all population over 1 year after start of intervention (compared to MDA only)	
	None	1x400µg/kg	3x300µg/kg	1x400µg/kg	3x300µg/kg
Highly seasonal (Fatick, Senegal) 3 rounds 1 month apart	74%	91%	94%	67%	75%
Perennial (Equateur, DRC) - 3 rounds 1 month apart	50%	66%	68%	31%	36%
Perennial (Equateur, DRC) - 3 rounds 4 months apart	57%	79%	81%	51%	57%

Complementary intervention	Percentage reduction in slide prevalence in all population over 1 year after start of intervention (compared to baseline)			Percentage reduction in slide prevalence in all population over 1 year after start of intervention (compared to MDA only)	
	None	1x400µg/kg	3x300µg/kg	1x400µg/kg	3x300µg/kg
Highly seasonal (Fatick, Senegal) 3 rounds 1 month apart	60%	82%	86%	55%	64%
Perennial (Equateur, DRC) - 3 rounds 1 month apart	58%	70%	72%	28%	32%
Perennial (Equateur, DRC) - 3 rounds 4 months apart	64%	78%	79%	38%	43%

Table 1. Predicted reductions in malaria clinical incidence and prevalence for all intervention scenarios described in box 1. Ivermectin only: Percentage reductions in clinical incidence (all ages)

and annual mean slide prevalence (all ages) from simulations shown in Figure 2 (BF = Burkina Faso). SMC and ivermectin MDA: Absolute and incremental (in addition to SMC) percentage reduction in clinical incidence (in children <5 years old), in simulations shown in Figure 3. MDA with DHA-P and ivermectin: Absolute and incremental (in addition to MDA with DHA-P) percentage reduction in clinical incidence and slide prevalence in simulations shown in Figure 4. Equations for all 'percentage reduction' equations are in the Appendix, page 10.