MAJOR ARTICLE

# The Potential Impact of Adding Ivermectin to a Mass Treatment Intervention to Reduce Malaria Transmission: A Modelling Study

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***Background.*** Ivermectin (IVM), used alongside mass treatment strategies with an artemisinin combination therapy, has been suggested as a possible tool for reducing malaria transmission. Mosquitoes ingesting a bloodmeal containing IVM have increased mortality, reducing the probability that the parasite completes sporogony.

***Methods.*** Human pharmacokinetic data and mortality data for mosquitoes taking bloodmeals containing IVM are used to quantify the mosquitocidal effect of IVM. These are incorporated into a transmission model to estimate the impact of IVM in combination with mass treatment strategies with artemether-lumefantrine on transmission metrics.

***Results.*** Adding IVM increases the reductions in parasite prevalence achieved and delays the reemergence of parasites compared to mass treatment alone. This transmission effect is obtained through its effect on vector mortality. IVM effectiveness depends on coverage with the highest impact achieved if given to the whole population rather than only those with existing detectable parasites. Our results suggest that including IVM in a mass treatment strategy can reduce the time taken to interrupt transmission as well as help to achieve transmission interruption in transmission settings in which mass treatment strategies alone would be insufficient.

***Conclusions.*** Including IVM in mass treatment strategies could be a useful adjunct to reduce and interrupt malaria transmission.

***Keywords.*** ivermectin; malaria; mass drug administration; mass screen and treat.

Ivermectin (IVM) has been suggested as a possible tool for reducing *Plasmodium falciparum* malaria transmission [1–3]. Vectors that feed on human or animal hosts that have recently taken IVM have a reduced lifespan [2–13], along with possible reductions in sporogony and delayed refeeding frequency [10, 11]. The mosquitocidal impact of IVM is thought to last for about 6 day after host ingestion [12]. Thus, IVM could potentially temporarily reduce vector abundance as well as preventing onward transmission of parasites ingested following a bite taken on a malaria-infected individual.

IVM has been suggested for use alongside mass screening and treatment (MSAT) or mass drug administration (MDA) with artemisinin combination therapies (ACTs) [1]. ACTs are highly effective in clearing the asexual parasite population from the human host, but gametocytes persist for an average of almost 2 weeks after treatment [14]. Adding IVM means that mosquitoes ingesting these gametocytes would be killed before the parasites complete sporogony, thus reducing the onward transmission of malaria from these treated but gametocytemic individuals. One study in Senegal found a 79% reduction in the proportion of mosquitoes with infectious sporozoites 2 weeks after mass IVM distribution [15].

Vector control has resulted in dramatic reductions in malaria transmission [16, 17]. However, the development of insecticide resistance could halt or reverse the gains made to date [18]. IVM offers a potential vector control

Received 6 March 2014; accepted 12 June 2014; electronically published 20 June 2014.

Presented in part: 6th MIM Pan-African Malaria Conference 2013, Durban, South Africa, 6–11 October 2013.

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**The Journal of Infectious Diseases® 2014;210:1972–80**



DOI: 10.1093/infdis/jiu351

tool with a new mode of action and no existing resistance concerns. It also targets both indoor and outdoor biting mosquitoes equally, thereby avoiding the selective survival of outdoor biters that has been observed after the wide-scale deployment of bed nets [19, 20].

Vector control has been used alongside mass drug treatment in various malaria-endemic regions around the world [21]. In 1 study on an island in Vanuatu, malaria was eliminated using MDA and bed nets after an intensive 9-week intervention [22]. Other studies, although failing to eliminate malaria, reduced transmission for sustained periods before it returned to precontrol levels. In these studies, it is hard to disentangle the relative impacts of mass treatment and vector control, but it is important to note that, of the 4 studies in which MDA was successful in interrupting transmission for several years, all combined mass treatment with vector control [22–25].

Here we investigate the potential impact of mass IVM distribution coadministered with MSAT or MDA on malaria transmission in different malaria-endemic settings. The effect of IVM on mosquito mortality is modeled in a 3-stage process: first, the pharmacokinetic (PK) profile of the drug is estimated using data from the published literature. Second, a proportional hazards survival model is fitted to vector survival data, incorporating the PK profile of IVM as a covariate. Finally, this is incorporated into an existing malaria transmission model [14].

## METHODS

### Pharmacokinetics of IVM

Nine studies containing PK time series data for a total of 126 individuals taking IVM doses between 86–857 μg/kg were identified [26–34] (detailed in Supplementary 1). The dynamics of drug concentration in the human blood were modeled using the following equations:

$$\frac{dG}{dt} = -aG$$

$$\frac{dB}{dt} = aG - cB$$

where $G$ and $B$ are the concentrations of IVM in the gut and blood, respectively. The initial conditions are $G(0) = G_0$ (where $G_0$ is the IVM dose in μg/kg) and $B(0) = 0$. These equations can be solved to give:

$$B(t) = a\ G_0\left(\frac{e^{-ct} - e^{-at}}{a - c}\right)$$

This function was fitted to the PK time series data using maximum likelihood methods.

### Effect of IVM on Mosquito Survival

Twelve studies on impact of IVM on mosquito mortality were identified [2–13] (detailed in Supplementary 1). The studies consisted of mortality data for 14 490 mosquitoes, of which 11 794 were *Anopheles*. In 8 of the studies, the mosquitoes were fed on human blood (the other 4 studies fed mosquitoes on rats, mice, monkeys, cattle, and dogs). The initial doses ingested by the animal or human host varied between 6–2500 μg/kg. Three of the studies mixed the IVM with the blood in vitro and fed the mosquitoes using artificial membrane feeders, while in the remaining studies the mosquitoes were fed directly on the human or animal host. The mosquitoes fed between 0 and 44 days after host IVM ingestion to capture the waning mosquitocidal impact of IVM as the concentration of drug in the blood decays.

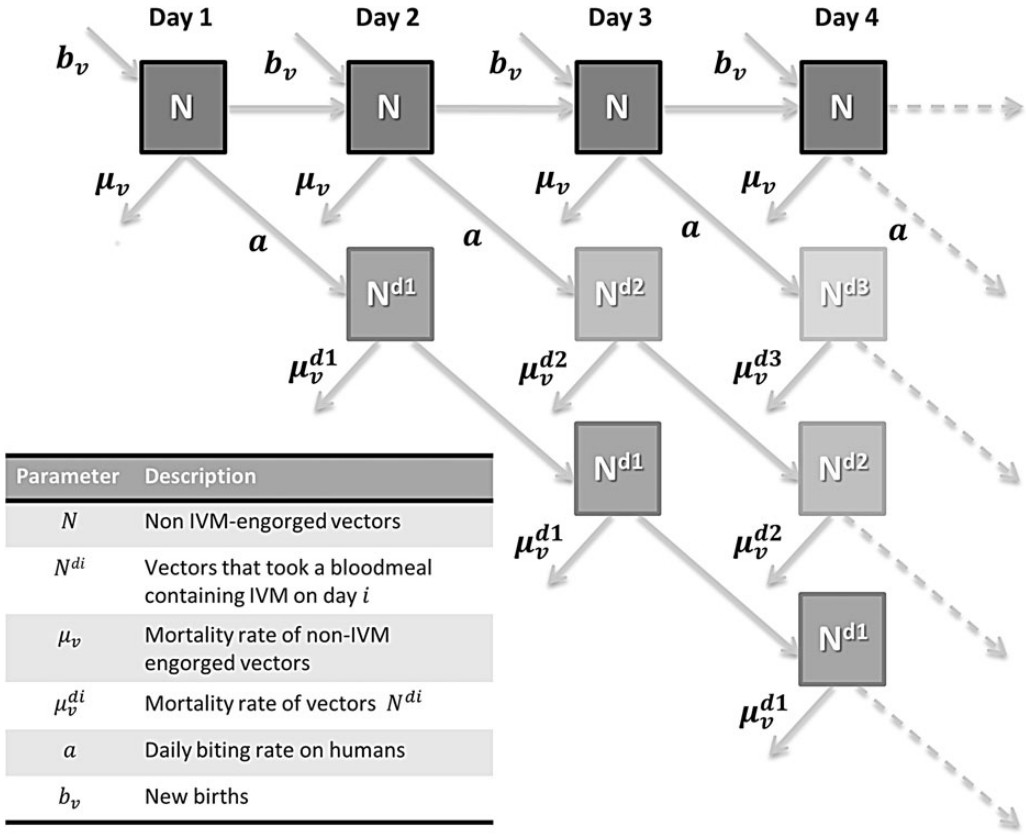
We assume that a vector biting on a given day after host IVM ingestion will experience an increased risk of death and, moreover, it will die at a new constant mortality rate governed by the amount of IVM in the human blood at the time the bloodmeal was taken. The PK curve is used to estimate the concentration of IVM in the host blood at the time that the bloodmeal is taken. A proportional hazards survival model is then used to describe how this concentration of IVM affects mortality. The relationship between the concentration of IVM ingested by the mosquito and its mortality is modeled using a second-order polynomial function. Additional binary covariates were included to describe whether the mosquito was in the *Anopheles* genus, whether it was specifically *A. gambiae*, and whether the bloodmeal was taken directly from the human or animal host or from a membrane feeder with blood and IVM mixed in vitro. The model was fitted using Efron's tied times likelihood method using the survival package in R, and the set of covariates retained for the final model was determined using a stepwise regression based on the Akaike information criterion. Further details on the PK and IVM data and models are presented in Supplementary 2.

### Modeling Framework

The effect of IVM on vector mortality is modeled by expanding the vector component of the malaria model presented in [14]. A simplified version of the model is presented in Figure 1. Here, vectors biting on day $i$ after IVM administration will move to a new compartment $N^{di}$ where they have an increased mortality rate $\mu_v^{di}$, informed by the survival model (values presented in Figure 2*C*). They remain in this compartment until they die. Alongside tracking the IVM status of the mosquitoes, we concurrently track whether they are susceptible, exposed (infected but not infectious), or infectious. Mosquitoes in any state can take a bloodmeal containing IVM but that any subsequent bloodmeals after the first IVM bloodmeal do not further increase the mortality rate. Full model equations are presented in Supplementary 2.

### Implementing Interventions

We model the impact of adding mass IVM distribution to a MSAT or MDA program with an antimalarial, here assumed




| Parameter | Description |
|---|---|
| $N$ | Non IVM-engorged vectors |
| $N^{di}$ | Vectors that took a bloodmeal containing IVM on day $i$ |
| $\mu_v$ | Mortality rate of non-IVM engorged vectors |
| $\mu_v^{di}$ | Mortality rate of vectors $N^{di}$ |
| $a$ | Daily biting rate on humans |
| $b_v$ | New births |

**Figure 1.** Schematic of the vector component of the model incorporating IVM-induced increased mortality in mosquitoes. The structure is mirrored for the different infectious states (susceptible, exposed, and infectious). Abbreviation: IVM, ivermectin.

to be artemether-lumefantrine (AL). The parameters describing the effectiveness of AL are taken from [35]. For MSAT, the population is tested for malaria parasites using a malaria diagnostic (assumed to be a rapid diagnostic test [RDT] unless stated otherwise) at a coverage level of 90%; all positive-testing individuals receive AL, which has 95% efficacy at clearing parasites. RDTs are assumed to detect all patent clinical infection and a proportion of patent asymptomatic infection, depending on the acquired immunity of the individual being tested. For polymerase chain reaction (PCR), we assume all individuals with patent and subpatent infection are identified. Both diagnostics are assumed to have 100% specificity. For MDA, 90% of individuals receive AL regardless of their infection status. Successfully treated individuals enter a treated state for a mean of 5 days (where infected individuals have a reduced infectivity to vectors) before clearing asexual parasites. We assume a fixed lag time of 12.5 days between any model state and onward infectiousness (ie, presence of gametocytes). After clearing asexual parasites, individuals enter a period of protective prophylaxis before returning to a susceptible state. All individuals ≥5 years old are given 3 daily doses of IVM regardless of their malaria status at a coverage level of 90% (we assume IVM is always distributed using an MDA strategy unless explicitly stated otherwise). We assume that the coverage levels of MSAT or MDA with AL and IVM are uncorrelated with each other. We consider MSAT or MDA with AL + IVM given either in a single annual round, or 4 rounds a year at monthly intervals.

### Interruption of Transmission

We used the model to estimate the transmission scenarios in which combinations of MSAT or MDA with AL + IVM can interrupt malaria transmission. The threshold used to define interruption of transmission was set such that the probability of having ≤1 person infected (out of a population of 1000 individuals) is >99% (which corresponds to an all-age prevalence <0.0149%) for 50 consecutive days. This result is simulated in a constant (perennial) transmission setting and a highly seasonal transmission setting (based on rainfall patterns observed in Fatick, Senegal) under a range of initial mean annual all-age parasite prevalence values between 0% and 30%. The optimal time to start treatment (with the aim of interrupting transmission) in the highly seasonal setting is defined as the time at which the interruption of transmission

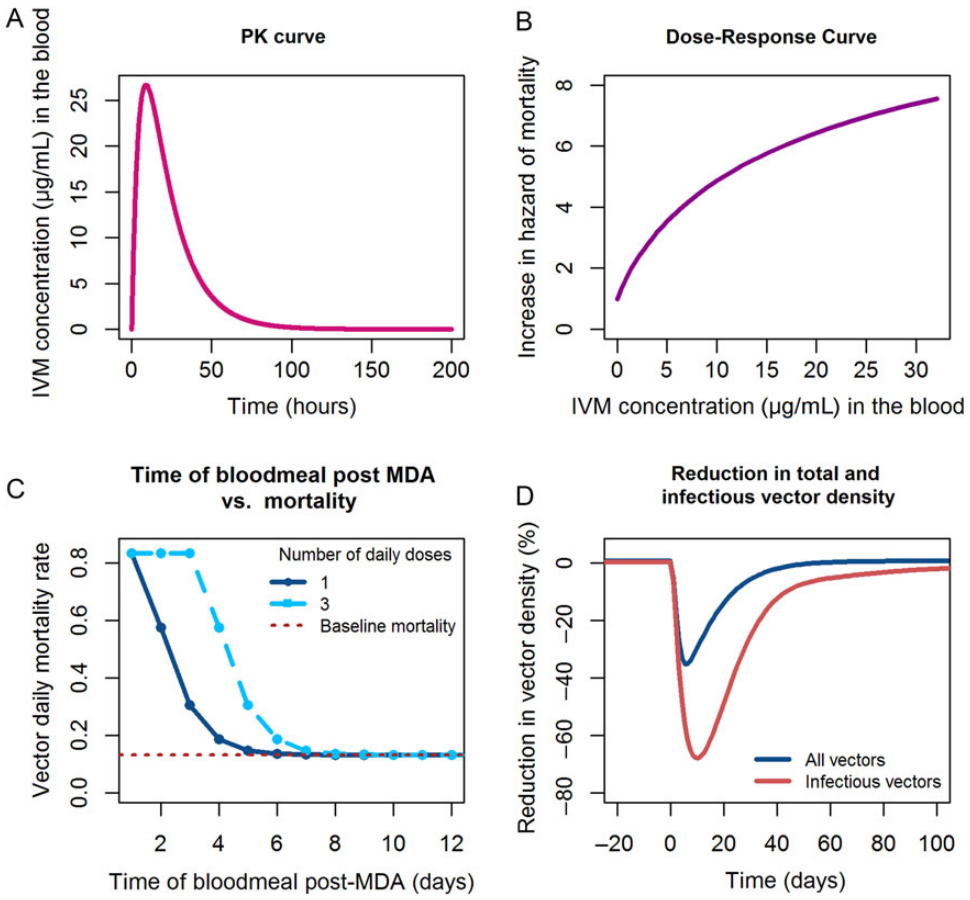



**Figure 2.** *A*, PK curve for IVM assuming an initial dose of 150 μg/kg. The final parameters were: $a = 0.057474$, $c = 0.193504$. *B*, Dose-response curve for IVM given by the equation $\exp(0.836\ C - 0.0738\ C^2)$ where C is the log IVM concentration. The *x*-axis shows the dose of IVM in the host's blood (in μg/kg) at the time the vector takes the bloodmeal, while the *y*-axis shows the increase in hazard of mortality. *C*, Estimated mortality rates for vectors biting on a given day post host IVM ingestion, based on the concentration of IVM in the host blood during the previous 24 hours and assuming vectors are *Anopheles gambiae* and IVM dose is 150 μg/kg. *D*, Reduction in total vector density and infectious density after 3 daily doses of IVM given to the population at a coverage of 90% using the mortality rates shown in 2*C*. Abbreviations: IVM, ivermectin; MDA, mass drug administration; PK, pharmacokinetic.

condition is met the quickest. Four mass treatment regimens are considered in this analysis: (1) MSAT with AL, (2) MSAT with AL + IVM, (3) MDA with AL, and (4) MDA with AL + IVM. Four monthly rounds are conducted each year, and treatment is continued until the interruption of transmission condition is met.

## RESULTS

### Impact of IVM on the Vector Population

Figure 2*A* shows the best-fit PK curve for IVM assuming an initial dose of 150 μg/kg, while Figure 2*B* shows the relationship between IVM dose and the hazard of mortality. The daily vector mortality rates following ingestion of IVM are shown in Figure 2*C*. The maximum additional vector mortality rate occurs within 24 hours of host IVM ingestion, with mortality rates returning to baseline levels approximately 6 days after ingestion. The covariates used in the final survival model are shown in Table 1. *Anopheles*, and in particular *A. gambiae* vectors, are more susceptible to the lethal effects of IVM compared to

**Table 1. Covariates Used in the Proportional Hazards Survival Model**

| Covariate | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|
| Log IVM concentration (linear term) | 2.308 (2.225, 2.394) | <.0001 |
| Log IVM concentration (quadratic term) | 0.929 (.923, .935) | <.0001 |
| *Anopheles* genus | 1.559 (1.441, 1.687) | <.0001 |
| *Anopheles gambiae* complex | 1.481 (1.381, 1.589) | <.0001 |
| Bloodmeal taken directly from host | 3.131 (2.93, 3.345) | <.0001 |
| Wild reared mosquito | 0.944 (.862, 1.033) | .209 |

Abbreviations: CI, confidence interval; IVM, ivermectin.

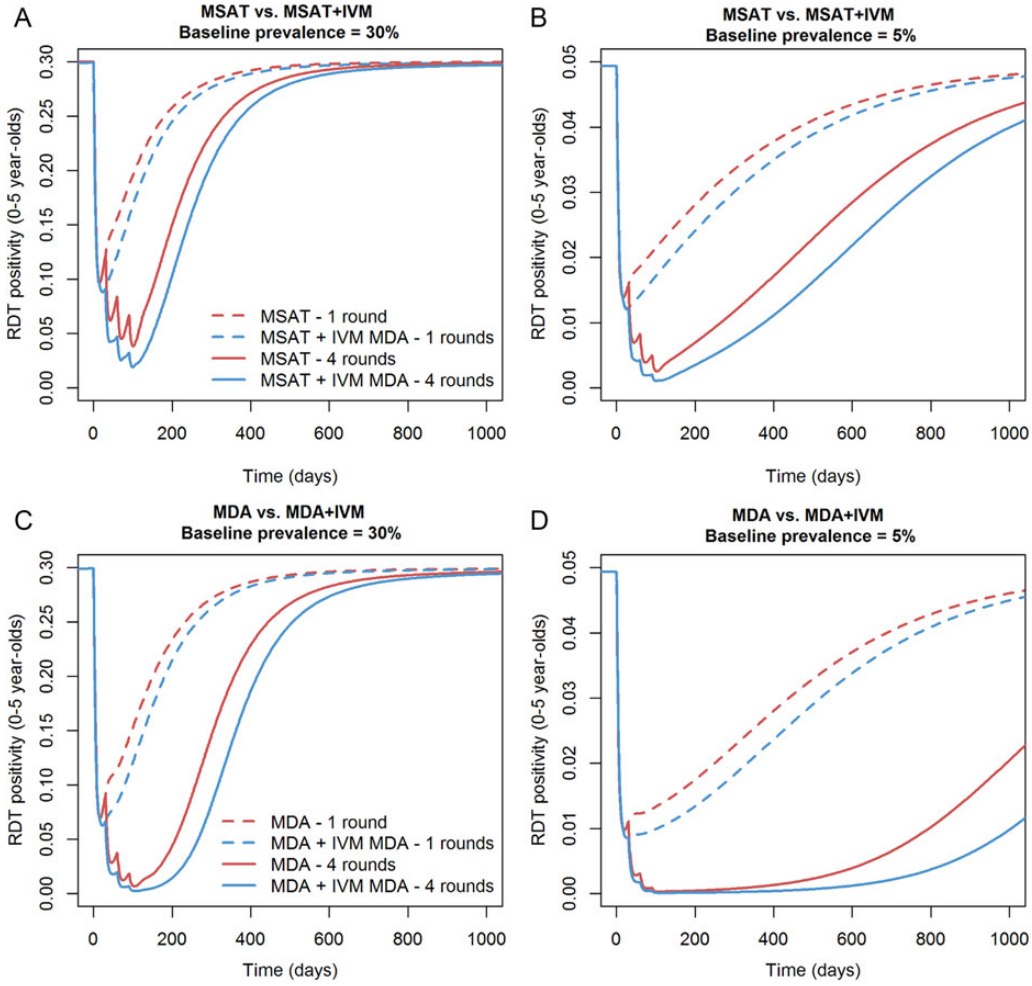



**Figure 3.** Impact of including mass IVM administration alongside MSAT with AL using RDTs (*A* and *B*) or alongside MDA with AL (*C* and *D*) at 2 precontrol prevalence levels (30% [*A–C*] and 5% [*B–D*]). The dashed lines show the impact of a single round of MSAT/MDA or MSAT/MDA + IVM, while the solid lines show the impact of 4 rounds given at monthly intervals of MSAT/MDA or MSAT/MDA + IVM. Abbreviations: AL, artemether-lumefantrine; IVM, ivermectin; MDA, mass drug administration; MSAT, mass screening and treatment; RDTs, rapid diagnostic tests.

other mosquito types. Vectors taking blood from a human or animal host have a hazard of mortality 3 times greater than vectors feeding from a membrane feeder.

The impact on the vector population of treating 90% of the population aged ≥5 with 3 daily doses of IVM (no MSAT or MDA with AL) is shown in Figure 2*D*. The total vector population in reduced by a maximum of 35% from its precontrol level and is suppressed for approximately 30 days. Importantly, the infectious vector population is reduced by 68% for approximately 60 days.

### Impact of IVM on Transmission

Figure 3 shows the impact of including IVM alongside MSAT with AL using RDTs (3*A–B*) and MDA with AL (3*C–D*) in 2 transmission settings. For all treatment scenarios presented here, adding IVM is predicted to result in a greater reduction in RDT-positivity and more sustained period of reduced RDT-positivity than MSAT or MDA alone. After 4 treatment rounds, including IVM delays the return to precontrol prevalence by approximately 50 days when the baseline RDT-positivity is 30% and by 100 days using MSAT or 200 days using MDA when baseline RDT-positivity is 5% (Figure 3). MDA is more effective than MSAT at reducing prevalence, especially in low-transmission settings. IVM adds a greater additional benefit to MSAT than to MDA in terms of the maximum reduction achieved, but the slowed return to precontrol levels is similar for both strategies. Four treatment rounds (solid lines) are clearly preferable to a single round (dashed lines), in terms of both magnitude and duration of impact.

In Figure 4*A* and 4*B*, we now consider giving IVM to RDT-positive individuals only (ie, distributing IVM using an MSAT strategy). We see that an MSAT strategy for IVM (red line) has almost no impact on RDT-positivity compared to not using IVM at all (gray line). Therefore, to impact community-level

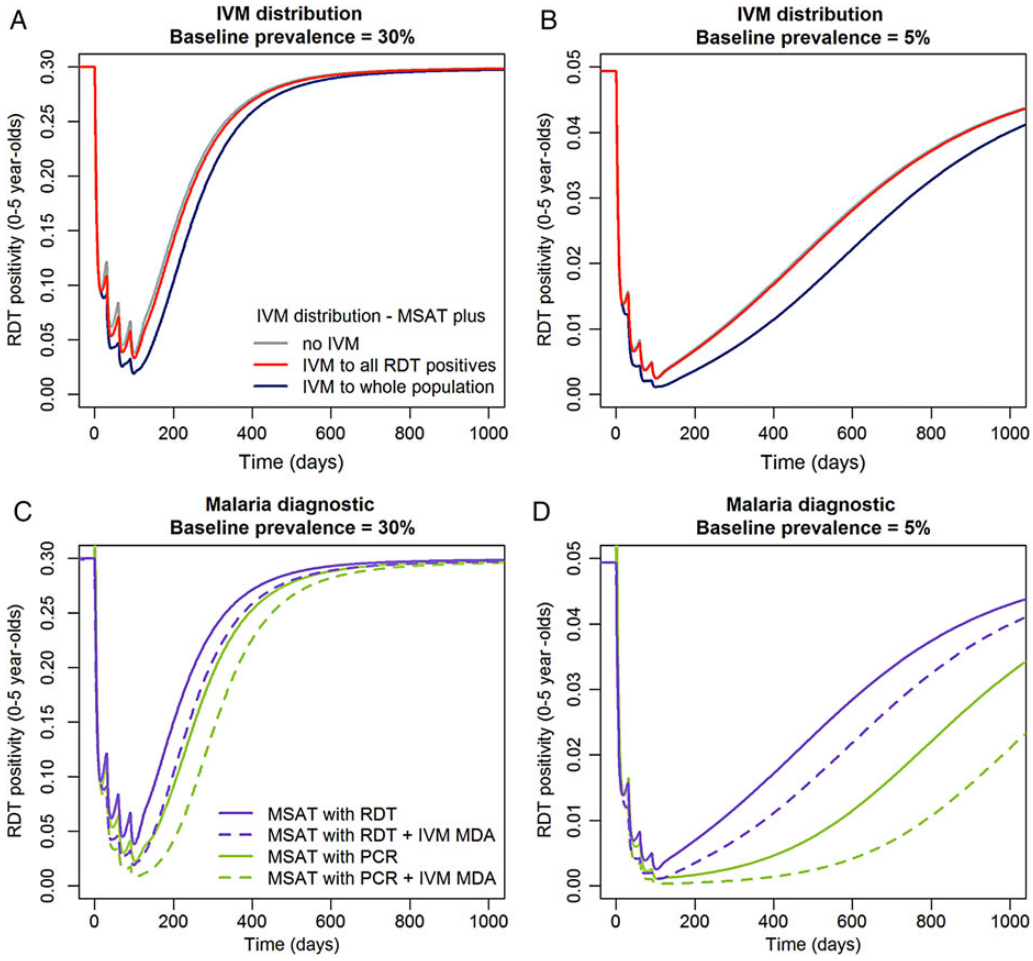



**Figure 4.** *A* and *B*, Effectiveness of MSAT with AL + IVM or MSAT—comparing 2 IVM distribution strategies: only giving IVM to individuals that are malaria RDT-positive (orange line), or giving IVM to all individuals in the population (dark blue line). *C* and *D*, Effectiveness of MSAT with AL alone (solid lines) versus MSAT with AL + IVM (dashed lines)—comparing 2 malaria diagnostics: RDT (purple lines) and PCR (green lines). Abbreviations: AL, artemether-lumefantrine; IVM, ivermectin; MSAT, mass screening and treatment; PCR, polymerase chain reaction; RDT, rapid diagnostic test.

transmission, IVM should ideally be distributed using an MDA approach (dark blue line).

Figure 4*C* and 4*D* compares the effectiveness of 2 malaria diagnostics (RDT and PCR) with either MSAT with AL or MSAT with AL + IVM. Using PCR to detect malaria-infected individuals leads to a greater and more sustained reduction in RDT-positivity compared to using an RDT, as it reaches the subpatent asymptomatic infections which are missed using an RDT. In low-transmission settings (Figure 4*D*) MSAT using PCR + IVM can result in a substantial reduction in malaria prevalence, lasting over a year. In a higher-intensity transmission setting, the effectiveness of MSAT using an RDT + IVM is almost the same as that of MSAT with PCR and no IVM. This combination (MSAT using RDT + IVM) could be used to achieve the same results as MSAT with PCR in regions where using PCR is not feasible.

We investigated the sensitivity of the model results to 4 key assumptions: (1) IVM dosing regimen, (2) vector mortality rates after ingesting a bloodmeal containing IVM, (3) sporogony-inhibiting impact of IVM, and (4) reduced mosquito refeeding frequency resulting from IVM ingestion (full methods and results in Supplementary 3). We found that distributing IVM on days 13 is as effective as distributing on days 1 and 5. A single IVM dose is inferior to both these schedules, but is still considerably better than not using IVM at all. Increasing the duration of the mosquitocidal effect of IVM has a greater impact than increasing the magnitude of the mosquitocidal effect on reducing infectious vector density and host parasite prevalence. Assuming that IVM inhibited sporogony and that IVM resulted in reduced mosquito refeeding resulted in negligible changes in parasite prevalence.

### Interrupting Transmission

Figure 5 shows the expected time to interruption of transmission for different baseline parasite prevalence levels under

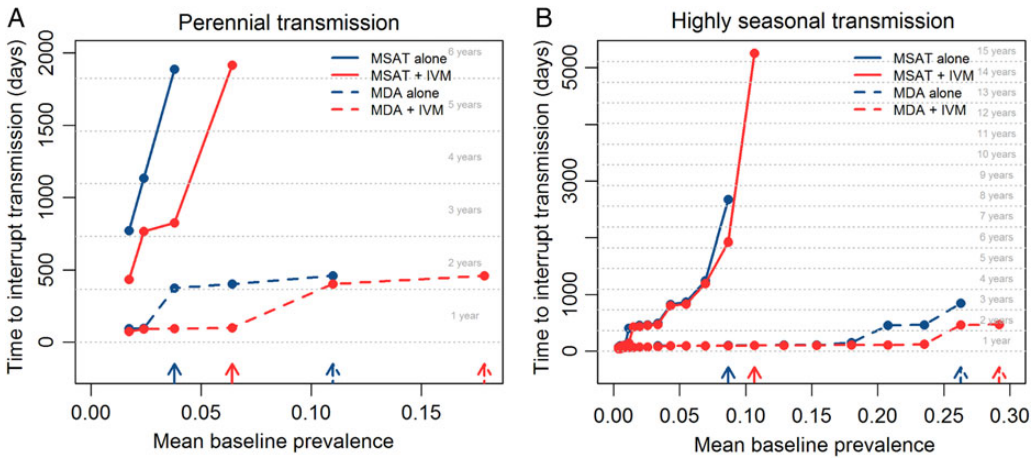



**Figure 5.** Time to interrupt transmission in a perennial (*A*) and a highly seasonal (*B*) transmission setting using MSAT (solid lines) or MDA (dashed lines) with AL with IVM (red lines) and without IVM (dark blue lines). The arrows represent the maximum mean all-age prevalence at which interruption of transmission can be achieved using each intervention. It is assumed that 4 treatment rounds are conducted a year with a month interval between each and that RDT is used as the diagnostic. Abbreviations: AL, artemether-lumefantrine; IVM, ivermectin; MDA, mass drug administration; MSAT, mass screening and treatment; RDT, rapid diagnostic test.

different treatment strategies. We predict that adding IVM reduces the number of years of intervention required to interrupt transmission and achieves interruption of transmission in higher-prevalence scenarios compared to MSAT or MDA alone. In a perennial transmission setting (Figure 5*A*), MDA alone interrupts transmission in areas with mean prevalence <11%. If IVM is added, transmission is interrupted in areas with a prevalence <18%. Using MSAT, these figures are <4% without IVM and <6% with IVM.

In a highly seasonal setting, the optimal time to start 4 rounds of MSAT/MDA + IVM with the aim of interrupting transmission is at the start of the dry season. MDA + IVM interrupts transmission in areas with a mean annual prevalence <30%, whereas MDA alone interrupts transmission when prevalence is <26%. Adding IVM reduces the time to interrupt transmission when prevalence is above 18%; below this level, IVM offers little additional benefit. For MSAT, adding IVM achieves interruption of transmission in higher-prevalence scenarios compared to MSAT alone (11% versus 9%), and reduces the time to achieve this goal when prevalence is above 7%.

The added benefit of using IVM alongside MDA or MSAT is predicted to be greater in a perennial compared to a highly seasonal transmission setting. MDA + IVM is the most effective strategy, and achieves interruption of transmission most rapidly and for the widest range of transmission scenarios. MSAT + IVM is more effective than MSAT alone, but is only suitable if prevalence is below approximately 5% in perennial transmission settings or 10% in highly seasonal transmission settings. In all of these scenarios, it should be borne in mind that this threshold is achieved in the local population and hence transmission can be continually reseeded through imported infections.

## DISCUSSION

Our results demonstrate that including mass IVM administration alongside MSAT or MDA with an ACT could substantially increase reductions in *P. falciparum* malaria transmission, resulting from greater and more sustained reductions in vector density and parasite prevalence. This in turn could increase the probability of interrupting transmission. The objective of any mass drug program is to interrupt malaria transmission for a sustained period of time, with failure to do so resulting in a return to precontrol levels with potential for increased morbidity [36]. Including IVM in the intervention could be beneficial, as it slows the rate of increase in prevalence, potentially reducing the number of years of treatment needed to interrupt transmission, or allowing transmission to be interrupted in areas with higher baseline prevalence.

A large MSAT study conducted in Burkina Faso failed to interrupt transmission, and in fact no reduction in clinical incidence was observed 12 months later, possibly due to the high initial prevalence in the study locations, undetected submicroscopic infections sustaining transmission, or the suboptimal timing of the treatment rounds [37]. In the Yanomami area of Brazil, an "aggressive active case detection" method was used, whereby a high proportion (60%–90%) of the community were tested for malaria on a monthly basis, resulting in a 45% reduction in clinical incidence between 1998 and 2001 [38].

We predict that giving IVM on days 1, 2, and 3 has an almost identical impact to giving IVM on days 1 and 5, thus the most operationally suitable schedule for the region should be selected. Although a single IVM dose is less effective, it remains considerably better than not using IVM and might be a feasible option

in resource-limited areas or hard-to-reach populations. Operationally, adding IVM to an MSAT or MDA program should be straightforward because health workers are typically stationed in a village for 3 consecutive days to give the ACT. IVM is suitable for use in all areas of Africa apart from regions where Loa Loa is coendemic [39]. For an MSAT strategy, PCR is the preferred diagnostic as it ensures all patent infections are identified, leaving no undetected reservoir of infection. This is particularly important in areas that are nearing elimination, as subpatent infections can account for 20%–50% of all human-to-mosquito transmission [40]. We predict that MSAT with an RDT plus IVM could be equally as effective as MSAT with PCR, suggesting that using IVM could be an important way to increase and sustain reductions in transmission resulting from MSAT in areas where PCR is unfeasible. If RDT specificity is less than 100%, the predicted benefits of MSAT would be even greater, as a proportion of uninfected individuals would be incorrectly identified as positive and benefit from a period of prophylactic protection after receiving the ACT [35]. Achieving high population coverage is critical; we predict that only distributing IVM to RDT-positive individuals has almost no impact on transmission reduction. Thus, at a population level, the effectiveness of IVM is due to its impact on the total vector population, rather than a reduction in onward transmission of gametocytes persisting in the blood after ACT treatment. Many African populations have been receiving IVM for decades as part of onchocerciasis or lymphatic filariasis control programs. However, these MDA programs rarely achieve coverage above 90%; mean coverage levels of 80.3% and 83.4% were reported in Kenya [41], 77% in Tanzania [42], and 73.1% in Sierra Leone [43].

Compared to other transmission-blocking drugs, IVM is an attractive prospect. It has an excellent safety profile, with adverse experiences typically mild to moderate and easily managed [44]. The drug can be given to the entire population apart from children weighing <15 kg or <5 years old. Pregnant women were previously excluded, but IVM is now recommended for pregnant and lactating women in high-onchocerciasis-transmission areas [44]. IVM additionally has the advantage of providing a beneficial impact against other diseases commonly found in malaria-endemic regions, such as onchocerciasis, lymphatic filariasis, scabies, and other helminths [45]. Program managers would need to ensure the malaria IVM distribution schemes are beneficial to helminth control efforts, and to monitor the potential emergence of IVM resistance.

Our model results are most sensitive to the duration of the mosquitocidal effect of IVM. In contrast, the impact of sporogonic inhibition and delayed refeeding frequency on transmission was found to be small. However, much of the data used to derive the daily mortality rates for vectors are from laboratory studies where mosquitoes live for considerably longer than in the wild. The vector mortality data were taken from a range of sources, and consisted of data on different vector species, IVM doses, and host bloodmeal species. Similarly, the IVM PK data are from a heterogeneous group of individuals (ie, fasting or nonfasting, healthy or onchocerciasis infected). To fully test the validity of this model, field studies measuring IVM PK in target populations and the lifespan of wild mosquito populations after IVM MDA are needed. Similarly, a study measuring the reduction in prevalence or clinical incidence after rounds of MSAT + IVM versus MSAT alone would enable the model output to be verified.

One major concern surrounding mass ACT treatment strategies is the potential for emergence of drug resistance [46]. Including IVM in a mass treatment program using an ACT could limit or delay the development or proliferation of artemisinin resistance by reducing the number of rounds required to interrupt transmission and reducing onward transmission of resistant parasites present in the blood in the 7 days after treatment.

In summary, our results suggest that IVM could be a key component of any MDA or MSAT program, potentially providing increased and sustained reductions in malaria transmission, and reducing the time taken to interrupt transmission. Successful implementation in the field requires high population coverage and a good understanding of the transmission intensity and seasonality pattern of the study site to ensure that treatment rounds are conducted at optimal times and that interruption or transmission is feasible.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

***Acknowledgments.*** We thank Kevin Kobylinski for valuable advice and for providing the raw data collected at Brian Foy's lab [10] and Jason Richardson's lab [11]. We also thank Jamie Griffin, Thomas Churcher, Michael White, Chris Drakeley, and Bruno Moonen for useful discussions and advice.

***Financial support.*** This work was supported by a grant from the Bill and Melinda Gates Foundation. L. O. was supported by a Medical Research Council (MRC) fellowship. T. B. is supported by a grant from the Bill and Melinda Gates Foundation (OPP1034789).

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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