

1 **Optimizing systemic insecticide use to improve malaria control**

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9 **Abstract**

10 Long lasting insecticidal nets and indoor residual sprays have significantly reduced
11 the burden of malaria. However, several hurdles remain before elimination can be achieved:
12 mosquito vectors have developed resistance to public health insecticides, including
13 pyrethroids, and have altered their biting behaviour to avoid these indoor control tools.
14 Systemic insecticides, drugs applied directly to blood-hosts to kill mosquitoes that take a
15 blood meal, offer a promising vector control option. To date, most studies focus on
16 repurposing ivermectin, a drug used extensively to treat river blindness. There is concern that
17 over-dependence on a single drug will inevitably repeat past experiences with the rapid
18 spread of pyrethroid resistance in malaria vectors. Diversifying the arsenal of systemic
19 insecticides used for mass drug administration would improve this strategy's sustainability.
20 Here, a review was conducted to identify systemic insecticide candidates and consolidate
21 their pharmacokinetic/pharmacodynamic properties. The impact of alternative integrated
22 vector control options and different dosing regimens on malaria transmission reduction are
23 illustrated through a mathematical model simulation. The review identified drugs from four
24 classes commonly used in livestock and companion animals: avermectins, milbemycins,
25 isoxazolines, and spinosyns. Simulations predicted that isoxazoline and spinosyn drugs were
26 promising candidates for mass drug administration, as they were predicted to need less
27 frequent application than avermectins and milbemycins to maintain mosquitocidal blood
28 concentrations. These findings will provide a guide for investigating and applying different
29 systemic insecticides to achieve better mosquito control strategies.

30

31 **Keywords:** systemic insecticide, malaria, mosquito, vector control, computational modelling

32 **Significance:**

33 The widespread use of long lasting insecticidal nets (LLINs) and indoor residual spray
34 has selected for mosquitoes that are resistant to pyrethroids or avoid exposure by feeding
35 outdoors or on livestock. Systemic insecticides, drugs that render a host's blood toxic to
36 feeding mosquitoes, could be an effective control strategy for mosquitoes with pyrethroid
37 resistance and/or outdoor feeding tendencies. Here, a number of existing systemic insecticide
38 candidates are identified and their pharmacokinetic properties in different drug-host-route
39 scenarios consolidated. These data were used to parameterise a mathematical model that
40 illustrated the projected gains achievable in malaria control programmes already employing
41 LLINs. The findings provide a guide for investigating and applying different systemic
42 insecticides to improve mosquito control strategies and reduce malaria transmission.

43 **Introduction:**

44 Long lasting insecticidal nets (LLINs) and indoor residual sprays (IRS) have played
45 significant roles in reducing the burden of malaria (1, 2). However, several hurdles remain
46 before elimination can be achieved. First, pyrethroids are heavily used in LLINs and,
47 previously, IRS (3). As a result, the widespread and sustained use of this single class of
48 insecticides has selected for mosquitoes that are resistant to the primary intervention methods
49 (4, 5). Second, because LLINs and IRS target mosquitoes that feed indoors on humans,
50 mosquitoes have shifted their feeding patterns to avoid exposure. For instance, increasing
51 numbers of mosquitoes have been found to seek their bloodmeals and/or rest outdoors after a
52 new instalment of bed nets (6). Some malaria-transmitting mosquitoes avoid indoor
53 interventions by obtaining their blood meals from animal hosts (7). Though livestock cannot
54 act as parasite reservoirs, bites diverted away from human hosts can act as temporary reprieve

55 from insecticide exposure, increasing vector lifespans, and consequently contributing to
56 perpetuated transmission (8).

57 To build on recent gains in malaria vector control, it is critical to develop a method
58 that is effective against pyrethroid resistant, outdoor feeding/resting, or zoophagic mosquitoes
59 (9). A promising solution is systemic insecticides, drugs that render host blood toxic to a
60 mosquito that takes a blood meal (10). The types of systemic insecticides most relevant to
61 treating mosquitoes are ectoparasiticides, drugs that target ectoparasites (e.g. blood-feeding
62 arthropods), and endectocides, drugs that target both endo- and ectoparasites. Many of these
63 drugs have a mode of action distinct from pyrethroids (11–15), and thus should be effective
64 against mosquitoes that either have mutations specific to pyrethroids or are susceptible. These
65 systemic insecticides have been widely used to treat humans, livestock, and domestic animals
66 for infections ranging from gastrointestinal and systemic nematodes to blood-feeding
67 parasites (16–19).

68 Studies have demonstrated that mass drug administration (MDA) of the systemic
69 insecticide ivermectin to humans and cattle can significantly decrease mosquito population
70 numbers temporarily (20, 21). To attain longer lasting impacts, the optimal use of systemic
71 insecticides requires understanding the pharmacokinetics of the drug in the host to determine
72 the dosing frequency necessary for maintaining lethal blood-drug concentrations.
73 Additionally, understanding the mosquito population's feeding patterns will guide the
74 decision of whether humans or animal hosts should be targeted. Finally, recent history has
75 highlighted the importance of avoiding over-reliance on singular control tools; thus, it would
76 be prudent to both investigate the effects of synergizing the systemic insecticide with extant
77 interventions and expand the arsenal of effective systemic insecticides from the current
78 candidate of interest, ivermectin (22, 23). Here, a review of endectocides and
79 ectoparasiticides is presented to collate the pharmacokinetic properties for different drug-

80 host-route combinations. These data were then used to parameterise a mathematical model to
81 illustrate the projected gains achievable in malaria control programmes already employing
82 LLINs.

83 **Methods**

84 I. Literature review

85 Veterinary and human parasiticides were identified with systemic properties that
86 affected arthropods and were not prohibited nor being phased out of use in most countries.
87 These included avermectins, milbemycins, neonicotinoids, spinosyns, and isoxazolines.
88 Unlike pyrethroids, which target voltage-gated sodium channels (11), avermectins and
89 milbemycins target glutamate-gated chloride channels (12), neonicotinoids and spinosyns
90 target unique sites of the nicotinic acetylcholinesterase receptor (nAChR) (13, 14), and
91 isoxazolines target γ -aminobutyric acid (GABA)-gated chloride channels(15). Further
92 discussion of the parasiticides' structures and modes of action is beyond the scope of this
93 study, but may be reviewed elsewhere (12–15).

94 To determine the relevant pharmacokinetic studies for different systemic insecticide
95 treatments, a review of the electronic literature was conducted. PubMed was searched from
96 inception to July 24, 2018 using the following search terms: (“*systemic insecticide*” OR
97 *endectocide* OR *avermectin* OR *abamectin* OR *doramectin* OR *eprinomectin* OR *ivermectin*
98 OR *selamectin* OR *milbemycin* OR “*milbemycin oxime*” OR *moxidectin*, *ectoparasiticides*
99 OR *isoxazolines* OR *afoxolaner* OR *fluralaner* OR *sarolaner* OR *lotilaner* OR *neonicotinoids*
100 OR *imidacloprid* OR *nitenpyram* OR *spinosyns* OR *spinosad* OR *spinetoram* OR “*N-tert-*
101 *butyl nodulisporamide*”) AND (*pharmacokinetics* OR “*area under the curve*” OR “*area*
102 *under curve*” OR *kinetics* OR “*half-life*” OR *Cmax* OR *Tmax* OR *blood* OR OR *plasma*). The
103 complete list of accepted and rejected studies is available upon request to the corresponding
104 author.

105 Study inclusion was determined in two steps. First, the titles and abstracts were
106 screened to determine studies that were not relevant, not primary research (e.g., letter or
107 review), or purely computational. Irrelevant studies were defined as those focusing on drug
108 mechanism, a drug that was not systemic or ineffective against mosquitoes, or hosts that are
109 not targeted by mosquitoes for blood meals. After the initial screen, the full papers of the
110 remaining studies were reviewed. Inclusion required the reporting of relevant
111 pharmacokinetic parameters in plasma, use of a standardized drug (i.e. generic or a
112 commercially available formula), application of single drug (i.e. no adjuvants or cocktails),
113 and a test-population size $n \geq 3$.

114 From the selected studies, the following data were extracted directly into an Excel
115 spreadsheet: host studied, drug applied, drug name/formula, dose applied, route of
116 administration, the maximum drug concentration reached in the plasma (C_{max}), the time it
117 took to reach C_{max} , the area under the curve, the half-lives for absorption and elimination, the
118 mean residual time, and the volume of distribution. All data were summarized using basic
119 descriptive statistics (mean and standard deviation or standard error when available) for each
120 scenario (host-drug-route of administration). As different classes of drugs require different
121 concentrations to achieve the same toxicity level, the doses for each combination of drug-
122 host-route were not compared. Instead, the analysis focused on the pharmacokinetic metrics
123 that impact the treatment's efficacy, which in turn, can be used to calculate the appropriate
124 dose.

125 II. Data analysis

126 To determine the underlying trends between the pharmacokinetic parameters and each
127 categorical factor (host, drug class, route of administration), a weighted (using the inverse of
128 the variance) three-way ANOVA was conducted in Stata. Hosts with fewer than 10

129 observations were grouped into two categories based on bodyweight: other-small (< 75 kg)
 130 and other-large (> 75 kg).

131 III. Model development

132 To investigate strategies for applying different systemic insecticides to further limit
 133 malaria transmission, models from the literature were modified (24–26) (see **Supplementary**
 134 **Text** for model development and **Table S1** for parameter values). The proportion of bites that
 135 lead to infection, egg laying rate, and death rate of mosquitoes are dependent on the
 136 concentration of insecticide in LLINs (N) and systemic insecticides in livestock or humans
 137 (D_L or D_H , respectively) a mosquito is exposed to. Different host species and routes of
 138 administration are characterised by different rates of adsorption, which were often not
 139 reported. Hence, to allow for comparison, the model represented the systemic insecticide's
 140 pharmacokinetics as a single compartment and the initial insecticide concentration as the
 141 reported C_{max} in the blood after treatment.

$$142 \quad \frac{dD_L}{dt} = -k_{D_L} D_L \quad (1)$$

$$143 \quad \frac{dD_H}{dt} = -k_{D_H} D_H \quad (2)$$

$$144 \quad \frac{dN}{dt} = -k_N N \quad (3)$$

$$145 \quad b_h = a b \left(1 - C_N \frac{N^{H_n}}{N^{H_n} + LC_{50N} [T_N]^{H_n}} \right) \quad (4)$$

$$146 \quad b_m = a c \left(1 - C_N \frac{N^{H_n}}{N^{H_n} + LC_{50N} [T_N]^{H_n}} \right) \quad (5)$$

$$147 \quad \beta_{mc} = \beta_m + \frac{1}{3} \left(\begin{array}{l} (1 - p_h) C_L \frac{D_L^{H_b}}{D_L^{H_b} + F_{50}^{H_b}} + \\ p_h C_H \frac{D_H^{H_b}}{D_H^{H_b} + F_{50}^{H_b}} \end{array} \right) \beta_m \quad (6)$$

$$148 \quad \mu_{mc} = \mu_m + \frac{1}{3} \left(\begin{array}{l} p_h C_N \frac{N^{H_n}}{N^{H_n} + LC_{50N}[T_N]^{H_n}} \mu_N + \\ (1 - p_h) C_L \frac{D_L^{H_d}}{D_L^{H_d} + LC_{50D}[T_D]^{H_d}} \mu_I + \\ p_h C_H \frac{D_H^{H_d}}{D_H^{H_d} + LC_{50D}[T_D]^{H_d}} \mu_I \end{array} \right) \quad (7)$$

149 The impact of insecticides used for livestock treatment, human treatment, and bed net
 150 treatment is diminished as they degrade at rates k_{D_L} , k_{D_H} , and k_N . These rates were
 151 determined by the half-lives recorded from the review. The transmission potential from
 152 vector to human or vice versa (b_h and b_m , respectively) is a function of biting frequency (a),
 153 the proportion of bites that successfully leads to infection in humans or mosquitoes (b and c ,
 154 respectively), the coverage of bed nets (C_N) and whether the LLIN's insecticidal
 155 concentration is above the lethal concentration for killing 50% of the population in a set
 156 amount of time ($LC_{50N}[T_N]$). Mosquitoes lay eggs at a natural rate of β_m , but the number of
 157 eggs laid can be modified with the introduction of certain systemic insecticides (β_{mc}).
 158 Similarly, mosquitoes natural death rate (μ_m) is modified with the introduction of LLINs and
 159 systemic insecticides (μ_{mc}). For both the egg laying rate and death rate, the impact of
 160 different control strategies depends on the proportion of bites on humans (p_H), the coverage
 161 of LLINs and systemic insecticides in livestock or humans (C_N , C_L , C_H , respectively), and the
 162 respective concentration thresholds for reducing fecundity or killing by 50% (F_{50} , $LC_{50N}[T_N]$,
 163 and $LC_{50D}[T_D]$).

164 The relationship between mosquito fecundity or mortality and the concentration of
 165 LLINs or systemic insecticides is not linear, but is captured by Hill kinetics. The F_{50} ,
 166 $LC_{50D}[T_D]$, and Hill coefficients (H_b and H_d for birth and death rates, respectively) were
 167 calculated for lab-reared *Anopheles* for different systemic insecticides by fitting a Hill
 168 equation to published data (27–29) (**Fig. S1-2**). The $LC_{50N}[T_N]$ was calculated for wild
 169 *Anopheles* that displayed a range of resistance to LLINs and the Hill coefficient (H_n) was

170 calculated for lab-reared, permethrin resistant *Anopheles* by fitting a Hill equation to
171 published data (30, 31). The time window (T_N or T_D) associated with each insecticide's
172 LC_{50} was based on previously reported measurements (27–29, 31).

173 IV. Simulations

174 This model was used to explore the impact of synergizing different systemic
175 insecticide treatments and LLINs on permethrin resistant mosquitoes. A new LLIN was
176 replaced every three years, as recommended by the WHO (32). Systemic insecticide
177 treatments were designed to test a range of half-lives (0.1:100 days), dose concentrations
178 ($1:10^5$ ng/mL), F_{50S} (0:480 ng/mL), and $LC_{50D}[T_D]$ s (7:1180 ng/mL), based on data mined
179 from the review. The simulation begins with the initial concentration of drug in the host's
180 blood, approximated by C_{max} . The appropriate dose necessary to achieve C_{max} can be
181 calculated based on pharmacokinetics associated with each host species, as previously
182 documented (33), and is not discussed here. Although many of the systemic insecticides
183 identified in the review remain to be characterised as mosquitocidal candidates, $LC_{50D}[T_D]$ s
184 were identified from the avermectin, moxidectin, isoxazoline and spinosyn classes for
185 *Anopheles gambiae* or *An. arabiensis* and used to establish a range of realistic values. F_{50S}
186 were only reported for a subset of avermectins and moxidectin. Each treatment characterised
187 by half-life, C_{max} , F_{50S} , and $LC_{50D}[T_D]$ was dosed at frequencies ranging from weekly to
188 annually. Strategy outcome was quantified by calculating the relative reduction (RR) in
189 malaria prevalence after 3 years of drug treatment and LLIN coverage (M_{N+D}) relative to 3
190 years of LLINs alone (M_N).

$$191 \quad \text{Relative reduction} = \frac{M_N - M_{N+D}}{M_N} \times 100 \quad (8)$$

192 This framework was applied to evaluate strategies for areas with different levels of baseline
193 malaria, mosquito populations with different feeding behaviours, and different deployment
194 scenarios (targeting livestock only, humans only, or both).

195 **Results**

196 I. Data retrieval

197 From the initial 375 articles returned by the search, 237 full-text articles were
198 assessed for eligibility, and 139 met the eligibility criteria (**Fig. 1a**). The studies reported
199 pharmacokinetic parameters in eight different host categories, ten systemic insecticides, and
200 six routes of administration (**Fig. 1b-d**). The three most commonly studied hosts were cattle,
201 sheep, and dogs. Systemic insecticides studied included five avermectins (abamectin,
202 doramectin, eprinomectin, ivermectin, and selamectin), three isoxazolines (afoxaloner,
203 fluralaner, and lotilaner), one milbemycin (moxidectin), and one spinosyn (spinosad). These
204 insecticides were applied intramuscularly, intraruminally, intravenously, orally,
205 subcutaneously, or topically. Note that intraruminal and intravenous routes of administration
206 are experimental and are not currently operationally feasible; however, they were included to
207 help determine the full range of action possible for each drug.

208 II. Data analysis

209 To evaluate the different treatment scenarios (host, route of administration, and drugs
210 grouped by class), weighted three-way ANOVAs were conducted for each pharmacokinetic
211 parameter. Half-life of elimination and C_{\max} were the only parameters with significant
212 interactions ($p < 0.05$) with host, route, and drug. The significant effectors of half-life were
213 drug class ($p = 0.016$), route of admission ($p = 0.007$), and interactions between host and
214 route ($p < 0.001$) and drug and route ($p = 0.007$). Regardless of route of administration, the
215 order of drugs from shortest to longest half-lives were avermectins < milbemycins <
216 spinosyns < isoxazolines. The median half-life for avermectins and milbemycins was < 10

217 days for all routes of administration, whereas the isoxazolines half-lives were > 10 days (**Fig.**
218 **2a, Fig. S3**). Comparing median half-lives for a given drug class across hosts shows some
219 host-dependency. For instance, the milbemycin had a longer median half-life in dogs (19.4
220 days) than in other hosts (< 10 days) and avermectins have a longer median half-life in cattle
221 than in other hosts (**Fig. 2b, Fig. S4**). When comparing routes of administration for different
222 hosts, topically applied drugs typically achieved longer half-lives than orally applied ones
223 (**Fig. 2c, Fig. S5**).

224 The significant factors for C_{\max} were drug ($p = 0.03$) and interactions between host
225 and drug ($p = 0.002$) and host and route ($p < 0.001$). The order of drugs from lowest to
226 highest C_{\max} was different from that of half-lives: milbemycins < avermectins < isoxazolines
227 < spinosyns (**Fig. S6**). Cattle reported the lowest median C_{\max} for milbemycins, whereas dogs
228 and sheep had the lowest C_{\max} for avermectins (**Fig. 2d, Fig. S7**). There was also a
229 dependency of C_{\max} on host and route (**Fig. 2e, Fig. S8**). Although the intravenous route
230 resulted in the highest C_{\max} for different hosts, due to the drug being directly delivered into
231 the bloodstream, the order of resulting C_{\max} for other routes varied based on host.

232 The spread in half-lives and C_{\max} s seen for a given drug-host-route combination can
233 be attributed to several host factors that may affect some drugs' absorption and,
234 consequently, the plasma concentration. These factors include age, gender, breed, diet,
235 presence of parasite infection, pregnancy, lactation, and whether or not topically treated hosts
236 are restricted from self-licking (34–41). Understanding how these host conditions affect
237 basic pharmacokinetics is critical for designing optimal treatment strategies that can account
238 for these natural variations.

239 III. Basic dynamics of malaria transmission and control methods

240 The model captures the temporal dynamics of malaria transmission in a human
241 population being exposed to mosquito bites. Upon the introduction of the LLIN, a general
242 decline in malaria prevalence (the sum of symptomatic and asymptomatic individuals) is
243 observed, followed by a steady increase as the insecticide in the net degrades and fewer
244 mosquitoes are killed by LLIN exposure (**Fig. 3a**). The addition of treating a blood host with
245 systemic insecticide can further reduce malaria prevalence when applied frequently enough.

246 IV. Dosing strategy design and evaluation

247 To quantify the efficacy of different dosing strategies, the relative reduction (RR) in
248 malaria prevalence after three years of using LLINs and systemic insecticide treated livestock
249 was compared to that of using LLINs alone. For a set dosing frequency, the RR increased as a
250 function of half-life and C_{\max} (**Fig. 3b**).

251 The minimum dosing frequency was calculated to achieve a target RR (here, 10%) for
252 a range of different drugs distinguished by half-life, C_{\max} , F_{50} , and $LC_{50D}[T_D]$ (**Fig. 3c-i**). The
253 drugs with the longest half-lives and highest C_{\max} s needed to be dosed the least often to
254 maintain a sufficiently high concentration to remain lethal to feeding mosquitoes. Given the
255 same half-life and C_{\max} , drugs with higher F_{50} and $LC_{50D}[T_D]$ needed to be dosed more
256 frequently to compensate for the decreased efficacy of drug on mosquito fecundity or
257 lethality.

258 Overlaying the data gathered in the review for drugs with reported F_{50} s and
259 $LC_{50D}[T_D]$ s for *Anopheles gambiae sensu lato* shows the frequency at which these existing
260 drugs would need to be applied to achieve the target 10% relative reduction in malaria
261 prevalence. The avermectins, represented by ivermectin, eprinomectin, and doramectin, have
262 relatively low F_{50} s and $LC_{50D}[T_D]$ s, suggesting that relatively low concentrations of drug in
263 the bloodstream would affect the fecundity and death rates of feeding mosquitoes. However,

264 this impact is limited by these drugs' relatively short half-lives, ranging from 0.4 to 11.1 days
265 (**Table 1**). Depending on the host and route of administration, regimens with dosing
266 frequencies ranging from weekly to quarter-annually would be required to achieve the target
267 10% relative reduction in malaria prevalence. Although ivermectin and eprinomectin have a
268 similar $LC_{50_D}[T_D]$, ivermectin has a stronger effect on fecundity (**Fig. S2**). Consequently,
269 ivermectin would require less frequent dosing than eprinomectin to achieve the same target
270 reduction, given scenarios with the same C_{max} and half-life. Doramectin has a lower impact
271 on fecundity and death rates, with higher F_{50} and $LC_{50_D}[T_D]$ than ivermectin and
272 eprinomectin.

273 Although fluralaner and afoxolaner (both isoxazolines) have higher $LC_{50_D}[T_D]$ s than
274 ivermectin, they are predicted to achieve 10% RR with yearly dosing, due to their longer
275 half-life and higher C_{max} . Similarly, spinosad has a high $LC_{50_D}[T_D]$, a relatively long half-life
276 of 11.3 days, and a much higher C_{max} of 1550.0 ng/mL, and could achieve a 10% RR when
277 dosed biannually. These results are conservative, as the effect of fluralaner, afoxolaner, and
278 spinosad on fecundity are assumed to be zero until this effect has been characterised in
279 mosquitoes.

280 Despite some of the studies evaluating moxidectin reported the longest half-lives and
281 highest C_{max} s, its high F_{50} and $LC_{50_D}[T_D]$ means that it would have to be dosed more
282 frequently (> weekly) or at higher doses to provide an effective complement to LLINs.

283 V. Application to different scenarios

284 This method for evaluating dosing strategies for systemic insecticides can be used to
285 evaluate differences in baseline malaria prevalence in a community, mosquito feeding
286 behaviour, and coverage scenarios. For each scenario, a prediction was made for the dosing
287 frequency necessary for scenarios in which livestock, humans, or both are treated with a

288 systemic insecticide similar to ivermectin (**Table 1**). Unless otherwise mentioned, it was
289 assumed that mosquitoes were indiscriminate feeders, resistant to permethrin, and malaria
290 was mesoendemic.

291 *i. Malaria endemicity*

292 Control methods for varying levels of malaria endemicity were explored by simulating
293 mesoendemic and hyperendemic environments (baseline prevalence between 11% and 50%,
294 or >50%, respectively) (**Fig. 4a-c**) (42). For all levels of endemicity, treating only livestock
295 or only humans resulted in the same amount of relative reduction for a given half-life and
296 C_{\max} because the mosquitoes were simulated as indiscriminate feeders. Treating both
297 livestock and humans had a compounding effect that resulted in the greatest reduction in
298 malaria prevalence and a down-shift in dosing frequencies for a set half-life and C_{\max} . With
299 increasing malaria prevalence, a drug with the same half-life and C_{\max} would need to be
300 dosed more frequently to achieve the same relative reduction in malaria. In a low level
301 mesoendemic environment (malaria prevalence = 25%), LLINs alone play a significant role
302 in reducing transmission; however, additional treatment of livestock and humans could
303 further reduce prevalence and theoretically break transmission. In a high level mesoendemic
304 environment (malaria prevalence = 50%), LLINs alone are not as effective and the additional
305 treatment of livestock and humans could significantly reduce malaria transmission. When
306 malaria is hyperendemic (prevalence = 65%), the addition of systemic insecticide treatment
307 would reduce malaria prevalence relative to LLINs alone; however, to bring malaria
308 transmission under control, longer, sustained treatment and/or the use of drugs with longer
309 half-lives and higher C_{\max} would be necessary.

310 *ii. Mosquito feeding behaviour*

311 Choosing the correct control method for a given community also relies on the
312 bloodmeal preference of the mosquito population (**Fig. 4d-e**) (43). When mosquitoes are
313 zoophilic, malaria transmission can largely be controlled by LLINs because the mosquitoes
314 do not target humans as frequently. Treating livestock with systemic insecticides would be
315 more effective than treating humans, requiring less frequent dosing for a drug with a given
316 half-life and C_{\max} . Malaria in regions with anthropophilic mosquitoes was reduced the most
317 with the treatment of both livestock and humans, with most of the reduction due to the
318 treatment of humans. Dosing frequencies were increased, given the need to maintain high
319 enough lethal systemic insecticide concentrations to affect a greater number of mosquitoes
320 targeting humans for bloodmeals.

321 **Discussion**

322 To date, ivermectin has been the main systemic insecticide considered for its
323 mosquitocidal properties and the only one marketed for human use (44–46). However, there
324 are a range of additional avermectins and different drug classes, such as milbemycins,
325 spinosyns, and isoxazolines, that should be screened as potential candidates for future
326 mosquito control methods in livestock and/or humans. Here, through the combination of a
327 review and a malaria transmission model, it was demonstrated how existing systemic
328 insecticides can be applied to reduce malaria transmission in a range of scenarios. To make a
329 10% reduction in malaria prevalence beyond what is already achieved by LLINs, some of the
330 identified drugs need to be applied at frequencies much higher than the current MDA's
331 annual or bi-annual dosing regimen (19). For instance, it was estimated that many scenarios
332 using moxidectin would need to be dosed at an unrealistic frequency, faster than once a week,
333 to reduce malaria transmission. This supports previous studies that show moxidectin has little
334 impact on mosquitoes (28) and would not be an effective choice for a treatment strategy.
335 Further investigation of these drugs' safety in hosts and effect on mosquitoes is necessary.

336 To design treatments with an operationally realistic dosing frequency (i.e. once or
337 twice a year), drugs that naturally attain higher blood concentrations and have longer half-
338 lives (i.e. isoxazolines and spinosyns) could be selected or alternative ways to achieve higher
339 concentrations of drug for longer periods of time could be applied. Recently, a study
340 demonstrated the tolerability of high doses of ivermectin in humans and the resulting increase
341 in time that the blood was lethal to mosquitoes (47). An alternative to increasing the
342 concentration of the delivered dose, a number of adjuvants have been reported to improve the
343 absorption or extend the half-life of systemic insecticides, such as lipids for lipophilic drugs
344 (48, 49) or efflux pump inhibitors that remove xenobiotics (50–54), respectively. A third
345 promising solution is the development of sustained-release devices, which have been shown
346 to maintain a target concentration for 280 days in livestock (55).

347 In addition to designing a dosing regimen that is effective at reducing the transmission
348 of a vector-borne disease, the secondary effects should also be considered:

349 *Emergence of resistance*

350 As the frequency of insecticide administration is increased to break the malaria
351 transmission cycle, it is imperative to consider how these new treatment regimens will lead to
352 the emergence of resistance in mosquitoes as well as other parasites. To gain some insight,
353 consider how mosquitoes have already developed resistance to the insecticides used in LLINs
354 and IRS (3). The two main mechanisms of insecticide resistance observed so far in
355 mosquitoes can be categorized as metabolic or target site mutations (56). Studying how other
356 arthropods have formed resistance to these systemic insecticides can also shed light on the
357 path of resistance formation in mosquitoes. For instance, macrocyclic lactone resistance has
358 been shown to arise in the cattle tick, fruit fly, and body lice due to increased expression of
359 ATP-binding cassette transporter, P-glycoprotein, and P450 genes (57–59). With strategic use

360 of systemic insecticides that target different mechanisms, monotherapy could be avoided and
361 the development of resistance in mosquitoes could be delayed.

362 Selecting for resistant off-target parasites is also a concern. One study reported
363 ivermectin resistant *Rhipicephalus microplus* found on 50% of cattle being treated regularly
364 with ivermectin for gastrointestinal nematodes (60). Similarly, repeated treatment of
365 ivermectin for onchocerciasis in humans has selected for resistant *Onchocerca volvulus* in
366 Ghana (61). As these systemic insecticides are commonly used to control other parasite
367 infections in humans and livestock, it is critical that dosing regimens and outcome
368 surveillance addresses the formation of resistance in off-target parasites.

369 *Presence in food products*

370 Considering how different systemic drugs are secreted from a host's system is also a
371 critical part of evaluating a new treatment program. For instance, lactating hosts treated with
372 a single-dose of eprinomectin or ivermectin produced milk with detectable drug levels for
373 weeks, thus exposing the nursing young (62, 63). Due to the unknown effects of the drug on a
374 newborn, nursing human mothers in the first week after delivery have been excluded from
375 MDAs of ivermectin (64).

376 Additionally, systemic insecticides from treated hosts becomes incorporated into dairy
377 and meat products (65). Regulations have been established for levels of acceptable residues
378 of a few drugs, such as eprinomectin; yet, most other drugs have not been licensed for use in
379 dairy animals and thus do not have an acceptable limit for drug concentration found in milk
380 (66). It was surmised that the extent of drug excretion and residence time in milk depends on
381 a drug's lipophilicity and route of administration (67, 68). However, more studies are needed
382 to characterise the different drugs' excretion in milk and, subsequently, establish safety limits
383 for suckling young or consumable items.

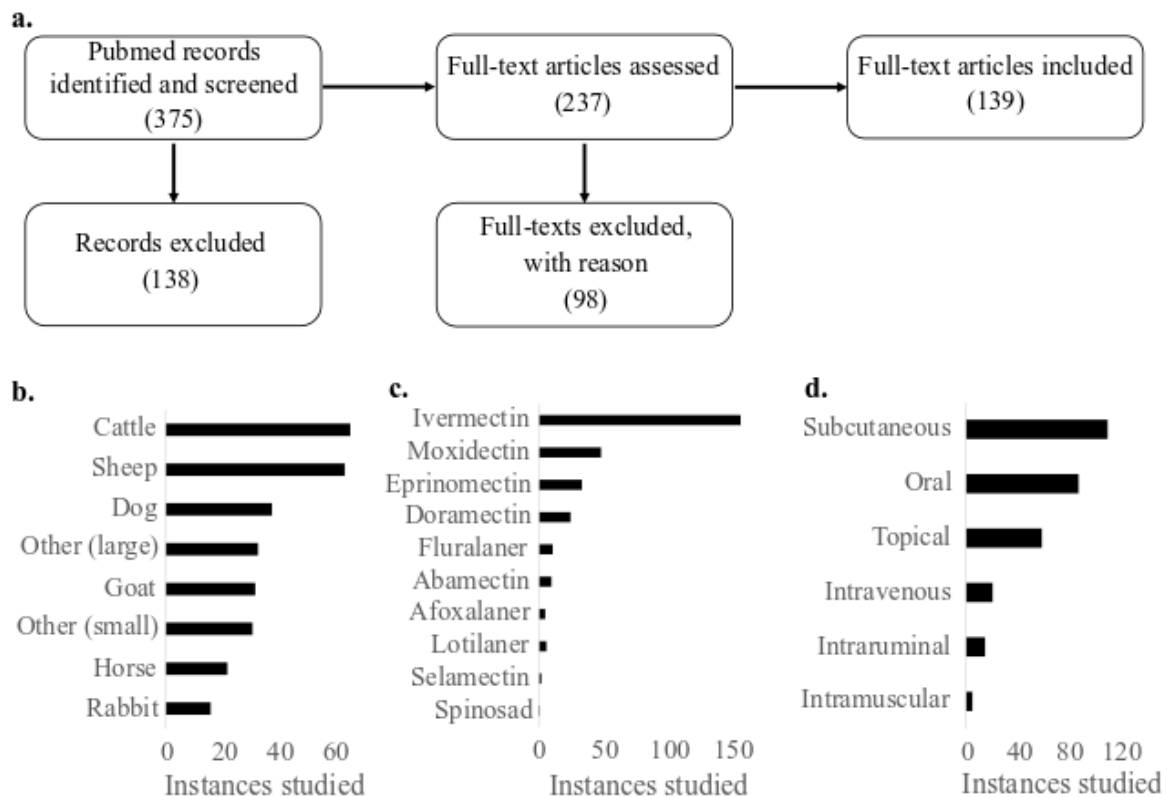
384 **Conclusions**

385 Studies have demonstrated that MDAs of systemic insecticides can significantly
386 decrease mosquito population numbers temporarily. To design effective, long-term vector
387 control strategies with systemic insecticides, their pharmacokinetics and pharmacodynamics
388 need to be understood. Here, multiple systemic insecticides with different mechanisms of
389 action and PK/PD characteristics that could be used in MDAs have been highlighted. The
390 simulations provide a foundation from which to further characterise how wild mosquitoes
391 respond to systemic insecticides. Given the history of mosquitoes forming resistance to the
392 insecticides in LLINs and IRS, having a variety of systemic insecticide strategies that target
393 different mechanisms could help reduce the rate at which mosquito resistance arises to these
394 new methods.

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398 **Competing interests:** The authors declare no competing interests

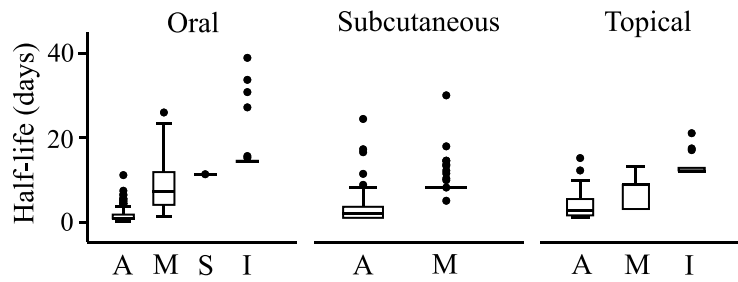
399 **Figures:**



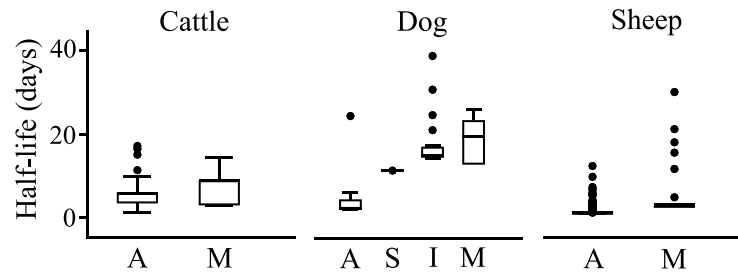
400

401 **Fig. 1.** Identification of existing systemic insecticides' applications. **(a)** A review of PubMed
402 identified relevant studies of existing systemic insecticides. **(b-d)** The included studies
403 covered a range of different hosts, systemic insecticides, and routes of administration.

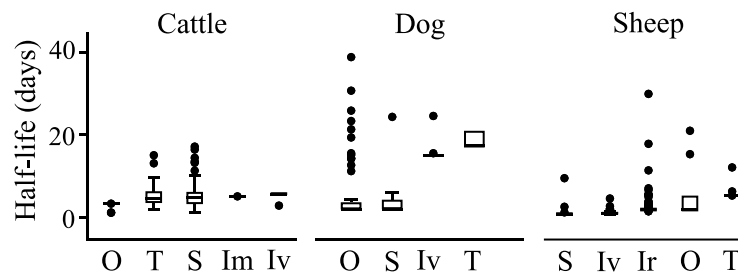
a. Half-life: Route x Drug



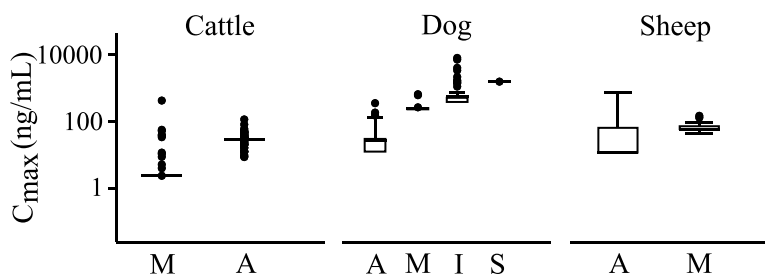
b. Half-life: Host x Drug



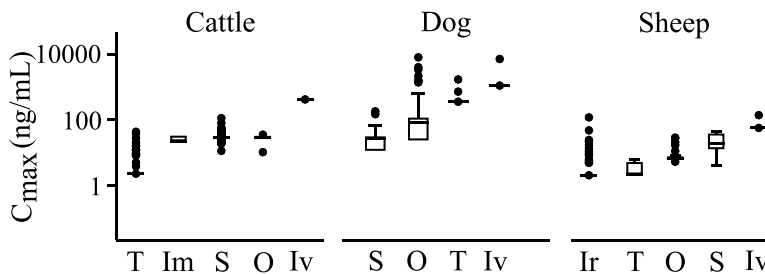
c. Half-life: Host x Route



d. C_{max}: Host x Drug



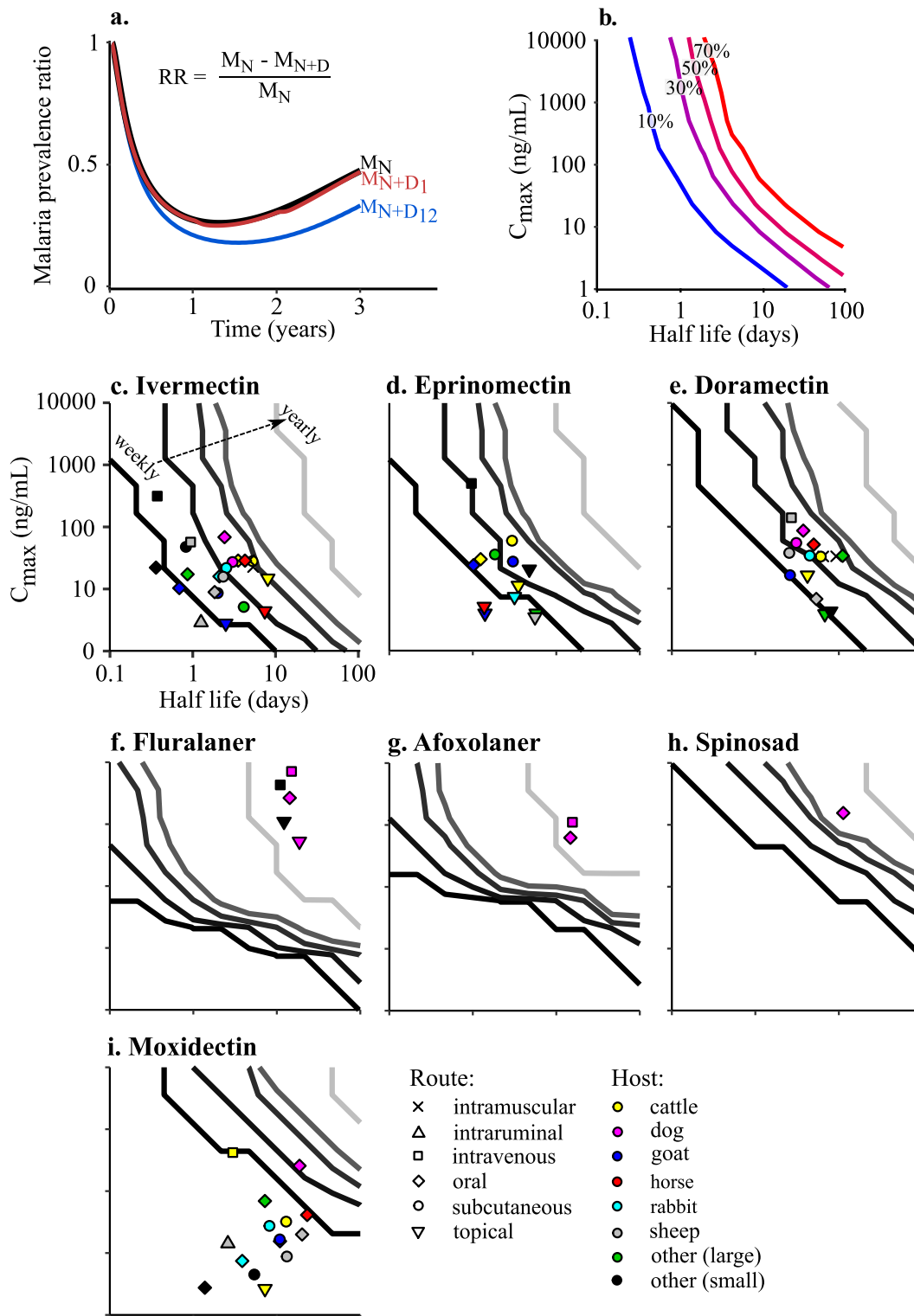
e. C_{max}: Host x Route



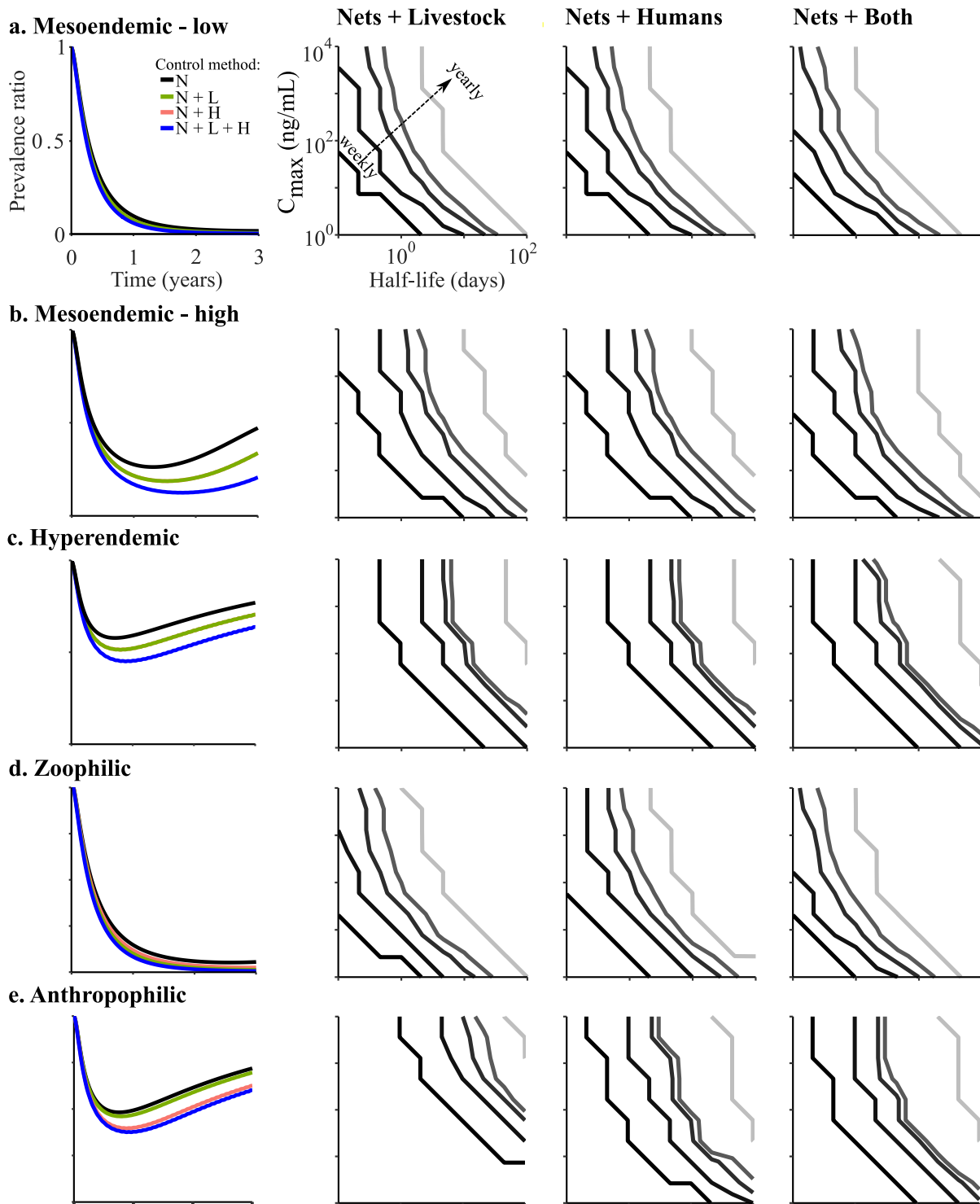
404

405 **Fig. 2.** Half-life and C_{max} are dependent on interactions between drug class, host, and route of
 406 administration. (a) Half-life is affected by the interaction between route of administration and

407 drug class. **(b)** The three most studied hosts show the effect of host and drug class on drug
 408 half-life. **(c)** The interaction between drug application route and host affects the drug half-
 409 life. **(d)** C_{max} is affected by the interaction between host and drug. **(e)** The interaction between
 410 route of administration and host also impacts C_{max} . Abbreviations: Drug classes: A=
 411 Avermectin, I = Isoxazoline, M=Milbemycin, S= Spinosyn; Routes: Im = Intramuscular, Ir =
 412 Intraruminal, Iv = Intravenous, O = Oral, S = Subcutaneous, T = Topical.



414 **Fig. 3.** Modelling malaria transmission and control methods. **(a)** The malaria prevalence ratio
415 is compared for a population using LLINs alone (M_N , black), LLINs with livestock treated
416 yearly with systemic insecticide (M_{N+D1} , red), and LLINs with livestock treated monthly with
417 systemic insecticide (M_{N+D12} , blue). **(b)** For a strategy using LLINs and livestock treated at a
418 set dosing frequency (here, monthly), the relative reduction in malaria prevalence can be
419 calculated for insecticides of various half-lives and C_{max} s. **(c-i)** The dosing frequency
420 necessary to achieve a 10% relative reduction in malaria prevalence can be calculated for
421 insecticides with different pharmacokinetic properties. Overlaying pharmacokinetic values
422 gathered from the review predicts the minimum dosing frequency of existing systemic
423 insecticides in certain host-route scenarios. Contour definitions from left to right: weekly,
424 monthly, quarter-annually, bi-annually, annually. Here, we assume indiscriminate biting
425 behaviour ($p_h = 0.5$) and a mesoendemic environment ($m=10$).



426

427 **Fig. 4.** Effect of different coverage strategies for scenarios with different malaria prevalence
 428 classes and mosquito biting behaviours. The first column compares temporal dynamics of
 429 malaria prevalence for the different scenarios: LLINs alone (N), LLINs and livestock
 430 treatment (N+L), LLINs and human treatment (N+H), LLINs with both hosts treated (N +
 431 both). The three right columns are the predictions for dosing frequency necessary to reduce
 432 malaria prevalence by 10% for each scenario. (a-c) With increasing malaria presence, the
 433 degree to which control methods can reduce malaria prevalence decreases and the frequency
 434 of insecticide reapplication increases (mesoendemic-low: $m = 5$; mesoendemic-high: $m = 10$;
 435 hyperendemic: $m = 20$). Here, an indiscriminate biting behaviour is assumed in mosquitoes (p_H

436 = 0.5), thus N+L and N+H have same outcome. **(d-e)** When mosquitoes are zoophilic ($p_H =$
437 0.35), systemic insecticides do not need to be dosed in livestock or humans as frequently as in
438 other scenarios, due to lower rates of mosquitoes biting humans. Controlling anthropophilic
439 mosquitoes ($p_H = 0.8$) requires an increase in dosing frequency due to the high rate of human
440 bites. Here, $m = 10$. Contour definitions from left to right: weekly, monthly, quarter-annually,
441 bi-annually, annually.

442 **Table 1.** Range of pharmacokinetic and pharmacodynamic parameters collected from the
443 literature review.

	C _{max} (ng/mL)	Half-life (day ⁻¹)	F ₅₀ (ng/mL)	LC ₅₀ [T _D] (ng/mL)
Macrocyclic lactones				
Doramectin	3.8 : 139.8	2.5 : 11.1	9.2	30.6
Eprinomectin	3.4 : 503.0	1.0 : 5.7	1.0	7.6
Ivermectin	2.7 : 316.0	0.4 : 7.8	4.1	7.3
Moxidectin	2.6 : 420.0	1.4 : 23.1	478.4	1178.0
Isoxazolines				
Afoxolaner	621.9 : 1107.0	14.8 : 15.6	0 *	66.8
Fluralaner	513.3 : 7109.0	11.0 : 18.6	0 *	21.2
Spinosyns				
Spinosad	1550.0	11.3	0 *	461.0

444 * F₅₀ remains to be measured for *Anopheles*

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