

The Impact of Household Size on Malaria Reduction in Relation with Alterations in Mosquito Behavior by Malaria Parasite

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In the present study the impact of household size together with behavioral alterations caused by parasite on malaria transmission is investigated using a discrete agent-based model of mosquito host-seeking behavior earlier calibrated against experimental data. The rate of transmission was shown to decrease with the typical size of household. Depending on the assumptions, one can observe different thresholds for a significant decrease of the disease reproduction number.

1 INTRODUCTION

Malaria can be regarded as socioeconomic disease, as it prevails in many developing countries with high level of poverty and a prevalence of slums, with residents living in highly populated agglomerates with poor quality of housing and high average size of the household.

Large household size increases the probability of bringing the source, the carrier and the recipient in the dangerously close integration, as it was conjectured in the early study by Sidney Price James (1930), [15]. The example of malaria incidence in England indicated that the number of malaria cases was always higher in cottages, where large families slept together in one room.

Recent study of the malaria trend in Finland over the interval 1750-2006 [13] supports and justifies this hypothesis. Malaria mosquitoes sheltered and survived until the next year in sufficiently wet and warm places inside the house. In the spring mosquitoes activated under more intensive light and

warmer temperatures, causing the disease outbreaks. Reduction of the household size was a key factor causing disappearance of malaria.

Subsequent papers [12, 14] indicate that malaria extermination is substantially more likely, when the average household size drops below four individuals and can also result from the segregation of the sleeping quarters, i.e., nighttime arrangements of small households.

Malaria mosquitoes tend to return to the same location for feeding and some of the *Anopheles* mosquito species seasonally prefer resting indoors [23, 30], which implies multiple feeding in the same household. The plausible scenario includes feeding on infected individual, resting and successive feeding after the activation of malaria parasite.

In addition to the household size, in this paper we study here the alterations of behavior in mosquitoes caused by parasites [4, 6, 19, 31]. There is evidence that infection modifies the threshold at which females reach saturation, forcing infected females, with already impaired engorging mechanism, to take smaller blood meals [19]. Decreased blood meal size induce mosquitoes to take multiple blood meals from multiple hosts per gonotrophic cycle, [19]. Another common alternation induces the increased attractiveness of infected hosts to mosquitoes, [7, 20]. As it was revealed, a human harbouring parasites at the stage transmissible to mosquitoes attracts twice more mosquitoes than uninfected host, see [20].

We suggest that the behavioral alterations caused by infection are among the key factors that induce the reduction of malaria incidence with the average size of the household. We test this hypothesis with the agent-based model of mosquito host-seeking behaviour. In earlier work, we restricted the model of mosquito host-seeking behavior to situation of mosquitoes and host in a hut, and calibrated parameters related to mosquito attraction to human against real data. Additionally, we calibrated parameters that defined the efficiency of control measures, such as long-lasting insecticidal nets, see [25]. In the present study we omit all parameters related to human protection, but adopt the model for village-scale experimental conditions. We simulate the community-scale experiment with different number of people in the household using four different assumptions: no alterations in mosquito behavior caused by parasite, doubled attractiveness of infected individuals, multiple bites for infected mosquitoes per night and both alterations together. With simple assumptions supported by experimental evidence we demonstrate that the transmission is suppressed when the household size decreases.

The simulations are performed here at a short-time scale of one night. Since a development of malaria parasite to transmissible stage requires an incubation period for both mosquitoes and humans, we assume the fraction of infected individuals and mosquitoes constant, but test the contact rates for different fractions. Note that, in principle, the simulation results can be extended

to long time periods using continuous-time ODE models of malaria transmission: for each fraction computed by an ODE model, the state-dependent transmission parameters can be taken as calibrated by our agent-based model simulations.

Here we assume fully vulnerable humans using no protective measures against mosquitoes. In further studies we will consider the trials with a fraction of people using a control measure, such as LLIN (Long Lasting Insecticidal Net) or IRS (Insecticide Residual Spray). This potentially enables to obtain epidemiological parameters that are otherwise hard to retrieve from experiments.

The rest of the paper is organized as follows. In Section 3 we present the modeling approach, the selections and parametrizations for the various factors needed for the modeling, as well as four modifications of the model: one assuming no alterations in mosquitoes by the parasites; the second version with the enhanced attractiveness of infected people; the third version with multiple biting for infected mosquitoes and the last situation with both of the alterations included into simulations. Section 4 describes the numerical details behind the simulations, and Section 5 gives the results of the model runs. The last section contains the conclusions and discussion.

2 MODELLING

2.1 Mosquito movement and attraction to host

Our attraction model is based on the assumption that mosquitoes estimate the direction of odor increase (the gradient) by the mechanism of klinotaxis, as it is conjectured in [32]. During klinotaxis, a mosquito samples the host odor at one location, then changes location and repeats sampling, using its memory of the concentration to chose the next position [3, 8].

Mimicking the klinotaxis, the flight of mosquitoes is modeled here by a random walk. Suppose that at time step $n - 1$ a mosquito-agent is at position \mathbf{x}^{n-1} . It randomly selects a new candidate position \mathbf{x}^n by

$$\mathbf{x}^n = \mathbf{x}^{n-1} + \delta\mathbf{W}, \quad (1)$$

from a 2D proposal distribution. In the experimental runs the parameters \mathbf{x}_0 , σ were matched to imitate the real flight speed of the mosquito, which falls in the range 0.4-1.1 m/s for most species of mosquitoes, as it was concluded in [28]. Herewith, the increment $\delta\mathbf{W} \sim N(\mathbf{x}_0, \sigma^2 I)$ was sampled as a random point on a circle centered at \mathbf{x}^{n-1} with radius $R = 0.4$ m, with a random number from $N(0, \sigma^2)$ with $\sigma = 0.1$ added in the radial direction.

To reduce the CPU computational time, one simulation step covers 2 seconds. In present simulations spatial units are taken in meters. We note that

more detailed models for the flight of insects do exist, see [9, 16, 24, 26]. However, we found that the above simple approach was sufficient for the purposes of the present study.

In the absence of any attraction towards a host, the flight of the mosquito is given by the above random walk. Next, we add a mechanism that enables us to simulate the movement towards host in the presence of attraction. There are several mechanisms enabling mosquitoes to find a human host. Basically, they are able to sense carbon dioxide (CO_2) exhaled by humans at a long distance and to smell chemical odors emitted from human body. Many substances, associated with human sweat, were identified as attractive for mosquitoes, such as nonanol, lactic acid, ammonia, phenol and many other compounds contained in the sweat, [2, 10, 11, 21, 29]. Apart from that, mosquitoes are able to sense human at a distance using the heat sensors around their mouthparts to detect the warmth of a human's body. They also discern movement, colors, shapes and patterns via vision. In general, mosquitoes are unable to recognize the human prey from a distance greater than 80 meters, see [3].

As we initially restrict the model to the hut experiment situation, the concentration of attractive odor, emitted from individual host, is modeled as a solution of the diffusion equation with a point source, the Gaussian kernel centered at a spacial position of the host \mathbf{x}^h :

$$C(\mathbf{x}, \mathbf{x}^h) = \exp \left[-\frac{d^2(\mathbf{x}, \mathbf{x}^h)}{2\sigma_a^2} \right], \quad (2)$$

where \mathbf{x} is the position of mosquito, C stands for a concentration that enables a mosquito to sense the host at a distance $d(\mathbf{x}, \mathbf{x}^h)$. The standard deviation of the Gaussian σ_a determines a maximal distance at which the mosquito is able to sense the host. Naturally, in more complex situations the concentration may be given by other means, such as convection-diffusion models, taking into account the spatial geometry, wind, etc, see [8]. Note that real odor concentrations are not used here, as we scale the concentrations and, moreover, only need the ratios of an attraction potential function as defined below. The movement towards the host is defined as a random accept-reject walk, where the acceptance probabilities are calibrated to fit the measured effects of attractants and repellents.

In community-level situation we also mimic the movement of mosquitoes by klinotaxis, where the total concentration of CO_2 is given by the sum of all the individual concentrations.

We employ the main features of the Metropolis algorithm, see [22]. Suppose that at each point \mathbf{x} we have an attraction potential $p(\mathbf{x})$ that depends on the concentration and other attraction factors. We take a step from point \mathbf{x}^{n-1}

to a next candidate point \mathbf{x}^n . If the respective function values are p_{n-1}, p_n , the new point is accepted with probability

$$\alpha_d(\mathbf{x}^n | \mathbf{x}^{n-1}) = \min \left(1, \frac{p_n}{p_{n-1}} \right) \tag{3}$$

The CO₂ concentration is regarded as a main attraction factor for mosquitoes. To account for the other, complex short-distance attraction factors in a parsimonious way, we simply define the attraction potential as a function

$$p(\mathbf{x}) = \exp(C(\mathbf{x})/\sigma_{acc}) \tag{4}$$

with a scaling factor σ_{acc} that depends on the distance to the host. A linear distance dependency of σ_{acc} was introduced in order to reflect the increasing 'greediness' of mosquito in the plume of the host,

$$\sigma_{acc}(\mathbf{x}) = \begin{cases} \sigma_{acc}^1 + \sigma_{acc}^2 d(\mathbf{x}, \mathbf{x}^h), & d(\mathbf{x}, \mathbf{x}^h) \leq 80 \\ \sigma_{acc}^{\max}, & d(\mathbf{x}, \mathbf{x}^h) > 80 \end{cases} \tag{5}$$

The function increases from the minimum value σ_{acc}^1 with a slope given by the parameter σ_{acc}^2 until it is replaced by a constant.

Figure 1 exhibits the broken line for σ_{acc} , as well as the resulting probability of accepting the steps away from host. Note that the parameters of σ_{acc} can be bounded so that the acceptance probability given by (3) is practically 1 at the distance of 80m from a host, i.e., the movement becomes purely

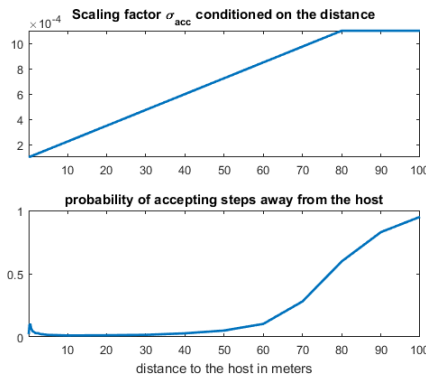


FIGURE 1
Scaling factor σ_{acc} conditioned on distance to the host (top), average probability of accepting steps taken away from the host as a function of distance to the host (bottom).

random outside the concentration plume. For more details see the next section for numerical implementation below.

In community-scale simulations we assume that the scaling factor σ_{acc} depends on the distance to the closest host.

The algorithm essentially mimics the well-know Simulated Annealing optimization method, introduced in [17], just with the 'annealing temperature schedule' replaced with the 'greediness scale', associated with the distance from mosquito to the host. As seen in Figure 1, the rate of acceptance for steps away from the host decays when the insect approaches the host.

Remark 1. *In [25] the model parameters were calibrated against the field data [18]. Here we skip the details of mosquito behavior indoors, as the absolute positions of people in the households are not taken into account. Instead, we assume that after entering the house a mosquito selects the hosts randomly with given probabilities, as explained in the next Section. The above random walk model is used to simulate the mosquito behaviour outdoors, i.e., the attraction towards the households. Note also that any other physical conditions, such as wind, are neglected.*

2.2 Modelling behaviour alterations and household size effect

Infection with malaria parasites has been shown to alter the behavior of mosquitoes, with effects varying depending on parasite life stage, [5]. When a female mosquito ingests malaria parasites from a human host, the parasite must undergo several developmental stages before becoming infectious. During this pre-infectious period, female mosquitoes are less attracted to host, [4] and exhibit lower persistence of feeding attempts, [1].

After incubation period (which typically lasts ten to fourteen days), mosquito is able to infect a new vertebrate host. Mosquitoes with the parasite at a fully developed stage have been reported to be more attracted to hosts, more persistent in feeding attempts and feeding on more hosts per feeding attempt than uninfected females, [5]. This set of behavioral changes associated with infection seems likely to be an evolutionary mechanism that had been developed by malaria parasite that enhances the spread of infection [5].

In this paper we study the impact of two behavioral alterations: an enhanced attractiveness of the infected individual for mosquitoes, see [20], and multiple biting typical for infected mosquitoes due to their damaged engorging system, see [31].

Initially, we study the effect of the household size on mosquito-human contact rate where no alterations is assumed. Then, we investigate the impact of each of the alterations separately (varying the typical size of the household) and finally, we study the composite effect of both alterations using similar simulation settings.

In all of the settings a mosquito randomly selects the host after entering the house. We use an equiprobable choice of the host in case of no infected hosts. But malaria parasites at transmissible gametocyte stage has been reported to enhance the attractiveness of humans-carriers to the parasite's vector, [7, 20]. The humans harboring parasite's gametocytes attracts twice as many mosquitoes, as uninfected one, as it has been experimentally verified in [20]. The mechanism underlying this manipulation is unknown, but it is likely that the parasites change infected individual's breath or body odor and temperature, [20].

In the case of doubled attractiveness of infected humans we assume that the probability of being selected is twice higher for infected individual in comparison to uninfected one [7, 20]. To model this, we define a total attractiveness of the household as the number of uninfected hosts N_{uninf} plus twice the number of infected hosts N_{inf} :

$$N_{tot} = N_{uninf} + 2N_{inf}.$$

Then, the probability of selecting the infectious host is $2/N_{tot}$, whereas for uninfected it comprises $1/N_{tot}$.

In general, several parasites appear to increase the biting rate of their insect vectors, commonly by impairing the vector's ability to obtain a full blood meal and thereby inducing the vector to bite several times before it is fully engorged, [19]. Examples include the protozoan *Leishmania* in sandflies, the plague bacterium *Yersinia pestis* transmitted by the tropical rat flea *Xenopsylla cheopis*, and trypanosomes in tse-tse flies. As has been experimentally demonstrated, the mosquito *Anopheles gambiae* infected with sporozoites of the parasite *Plasmodium falciparum* bites more people during a single night than uninfected mosquitoes, [19].

The mechanisms underlying this influence are not totally explored but mostly result from at least two manipulation processes. First, the parasite increases the mosquito's motivation to continue a meal after it has been interrupted, thus increasing the probability that it bites several times. Second, the parasite decreases the amount of blood obtained at each biting attempt, thereby increasing the number of bites required to obtain a given amount of blood. Some evidence for the latter mechanism has been provided by the observation that sporozoites of the parasite *Plasmodium gallinaceum* lower the apyrase activity in the salivary glands of infected *Aedes aegypti*. As a result, an infected mosquito's ability to locate blood is impaired, and it probes for a longer time than do uninfected mosquitoes, [19].

For the multiple biting alteration we assume that an infected mosquito takes up to 5 bites per night (depending on the number of physically available hosts) and tends to feed on multiple hosts, [31]. Uninfected mosquito bites

only once per night. Each mosquito is tracked separately, and we score the number of bites taken, bitten hosts and many other relevant factors, see the next section for more details.

Remark 2. *We assume that there is a chance that mosquito $p_{hut} = 0.01$ abandons the house after every successive feeding.*

3 CALCULATIONS

As the test case we consider a village consisting of 100 individuals inhabiting a number of equally-sized households located in the domain of 0.5 km^2 size. The houses are placed no closer than 40m from one another. Each house is of the size 10 m^2 .

Overnight 10-hour trials are simulated with mosquitoes initially randomly placed inside of the domain. Since we are interested only in relative numbers, the simulations can be performed for a fixed number of mosquitoes. In this study the simulations were run for 1200 mosquitoes. This number was taken sufficiently big to insure computationally stable output. Additionally, each experiment was averaged over 3 repetitions to enhance the accuracy. For spatial averaging new positions of households are randomly generated at each successive repetition of the algorithm.

To assess the rate of transmission, a reproductive number R_0 , defined as a number of secondary cases caused by one infectious human through a generation of infections in mosquitoes [27] was measured:

$$R_0 = \frac{mbca^2}{rg}. \quad (6)$$

Here g is the death rate of mosquitoes and a stands for mosquito-human contact rate, m denotes the number of female mosquitoes per human, b is the probability of transmission of sporozoite from infected mosquito to susceptible human, and c gives the probability of transmission of the sporozoite from infected human to mosquito.

These transmission parameters depend on geographical location, season and human population density in the region, among the other relevant factors. However, the contact rates can be obtained from model simulations. Since we are interested in a relative decrease of the reproduction number, we can set the constant $mbc/rg = 1$. Moreover, to account for asymmetric contact rates between infected mosquitoes and uninfected humans and uninfected mosquitoes and infected humans, we modify the above formula in a following way:

$$R_0 = \bar{a}\tilde{a}, \quad (7)$$

where \bar{a} and \tilde{a} stand for infected mosquitoes to uninfected humans and uninfected mosquitoes to infected humans contact rates, correspondingly. The asymmetry in contact rates arises from different initial proportion of infected people (see [6]). Additionally, the difference in contact rates increases from behavioral alterations.

Remark 3. *In this study we assume no mosquito protection for humans. Bu the modelling approach can be considered for situations with a fraction humans using a control measure, such as LLIN (Long Lasting Insecticidal Net) or IRS (Insecticide Residual Spray). This allows to compute epidemiological parameters that are hard to measure from experiments.*

Enhanced attractiveness of infected individuals As it was described above, we model the enhanced attractiveness of infected human as twice higher probability of being selected in comparison to uninfected individual. But we assume that all the individuals are equally attractive for infected and uninfected mosquitoes.

Multiple bites for infected mosquitoes For simplicity, we assume that infected mosquito makes up to 5 bites during the night, depending on the number of physically available hosts. At the same time, uninfected mosquito bites only once. Additionally, we assume that infected mosquito never bites same host twice (this is an evolutionary mechanism that had been developed by the malaria parasite that enables to intensify the spread of infection, [31]). So if a mosquito stays in the house after biting one of the hosts, it selects another host at random, excluding the hosts that already was bitten. After biting the host, infected mosquito leaves the house with probability $p_{hut} = 0.01$. Technically, when mosquito has bitten one of the hosts, this host becomes 'invisible' for mosquito for the rest of simulation. We create the mask of size $[N_m, N_h]$, where we mark bitten hosts separately for each mosquito. After that, the distance from mosquito to the host is set to infinity, which implies no impact from this particular host to the total concentration.

Combining the alterations When combining the alterations, we recompute the total attractiveness of the household for infected mosquito after each successive feeding (in case if mosquito does not leave the house):

$$N_{tot} = N_{uninf} + 2N_{inf},$$

where N_{uninf} and N_{inf} denote the number of uninfected and infected hosts that were not previously bitten.

The probability of selecting the infectious host is $2/N_{tot}$, whereas for uninfected it comprises $1/N_{tot}$, as it was previously described.

4 RESULTS

As a result, we compare simulated contact rates and relative reproduction numbers for 10, 5, 4, 3 and 2 -people households, see Figures (2), (3) and (4). The simulations are performed for different constant fractions of infected hosts and mosquitos, see below.

In case of no behavioural alterations we still do observe that the infected mosquito - uninfected human contact rates \bar{a} are systematically lower, when the household size drops below 3 people threshold, see Figures (2). For all the other household sizes the contact rates \bar{a} are quite similar.

Simultaneously, uninfected mosquito - infected human contact rates are fairly similar for all of the household sizes, see Figure (3). As for the reproduction numbers in case of no alterations, we mostly observe that the smaller households result in a lower rate of transmission. We do not observe a substantial difference between 3, 4 and 5- people households. But the smallest 2-people household size systematically results in a much lower R_0 in comparison to all the other cases, regardless of the proportion of initially infected individuals, see Figure (4). We can also state that 10-people household mostly results in a higher R_0 in comparison with smaller households, but is not significantly higher in comparison to 5 and 4-people households

When the infected human is twice more attractive, infected mosquito - uninfected human contact rates \bar{a} are close regardless of the household size, but the complementary uninfected mosquito - infected human contact rates are systematically lower, when the household size is less than 3 people, see Figure (3). Resulting reproduction numbers R_0 are close for 5,4 and 3 - people households, regardless of initial fraction of infected people. Simultaneously, 10-people household results in systematically higher R_0 in comparison to the smaller household sizes, while 2-people household results in a substantially lower R_0 in comparison to 5, 4 and 3-people household sizes, see Figure (4). In this case we can state two thresholds for typical household size: less than 6 and less than 3, which corresponds to a significant reduction of the reproduction number. This observations are consistent with experimental conclusions from [13].

The second alteration, multiple bites taken by infected mosquitoes, results in infected mosquito - uninfected human contact rates decreasing with the household-size, except for the case with 10 and 5 individuals, which display inverse dependency.

Finally, when combining the two alterations, we observe infected mosquito - uninfected human contact rates similar to the previous case, i.e.,

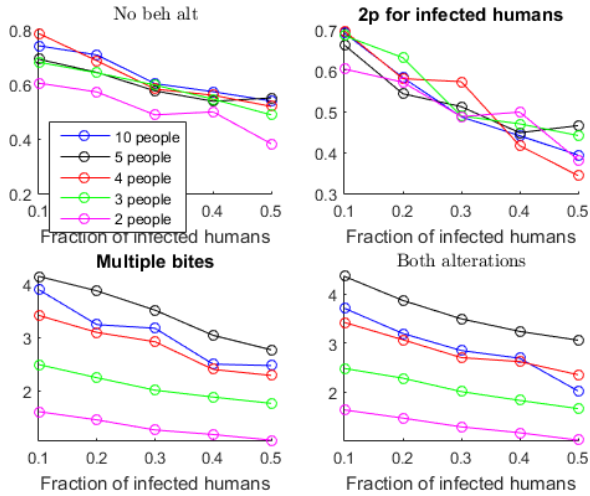


FIGURE 2 Infected mosquito - uninfected human contact rates \bar{a} conditioned on proportion of infected individuals in the village for different household sizes.

generally decreasing with the size of the household, see Figure (2). As in case of doubled attractiveness of an infected individual, the uninfected mosquito - infected human contact rates are systematically lower, when the household size is less than 3 people, see Figure (3). The threshold for reproduction number R_0 is below that of 4 people.

5 DISCUSSION

In the present paper we studied the effect of the household size on malaria transmission rates using an agent-based model of mosquito host-seeking behaviour. We simulated the community-scale experiment using four different assumptions: no alterations in mosquito behaviour caused by parasite, doubled attractiveness of infected individuals, multiple bites for infected mosquitoes per night and both alterations in combination. We were varying the household size from 2 to 5 people, and we also considered 10-people household.

In general, the reproduction numbers always displayed a decrease with the household size. Depending on the assumptions, we could observe different thresholds for a substantial reduction in disease transmission.

When no alterations were assumed and we studied purely the impact of the household size, a significant reduction in transmission appears, if the household size is below 3 individuals, which is consistent with [12, 13] and [14].

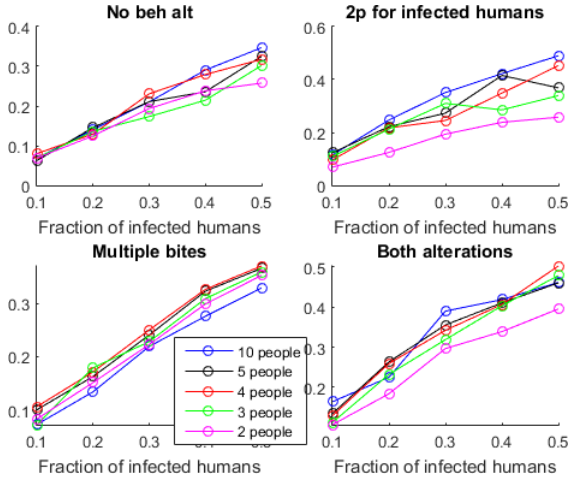


FIGURE 3 Uninfected mosquito - infected human contact rates \bar{a} conditioned on proportion of infected individuals in the village for different household sizes.

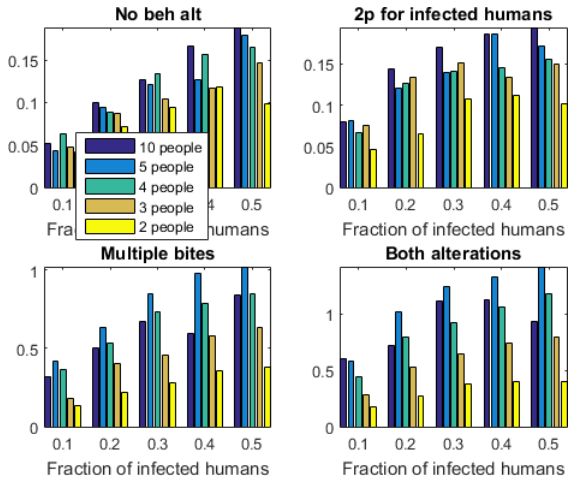


FIGURE 4 Reproduction number $R_0 = \frac{\bar{a}\bar{a}bc}{g}$ conditioned on proportion of infected individuals in the village for different household sizes

In case when we additionally assume doubled attractiveness of infected people, we observe the second threshold, below 6 individuals, in addition to the previous case. When we assume multiple bites for infected mosquitoes, but equal attractiveness of the humans, the decrease in reproduction number is

observed when the size is below 4 household members. Finally, when assuming both alterations, we observe same threshold as in the previous case.

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