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Original Article

Artificial Natural Selection: Can Supplemental Feeding Domesticate Mosquitoes and Control Mosquito-Borne Diseases?

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Abstract: A new method is proposed for controlling mosquito-borne diseases. In particular, instead of trying to kill mosquitoes, we suggest provisioning them with food from artificial feeders. Because mosquito populations are frequently limited by ecological factors other than blood meals, such as the availability of egg-laying sites, feeding mosquitoes would not necessarily increase the total number of mosquitoes, but could reduce the number of human-drawn mosquito meals. Like mosquito traps, feeders could divert biting mosquitoes away from people by means of lures, but, after diversion, prevent subsequent human bites by satiating the mosquitoes instead of killing them. Mosquito feeders might reduce the problem of the evolution of resistance to control: in an ecology with mosquito feeders, which provide safe and abundant calories for adult female mosquitoes, there could be selection for preferring (rather than avoiding) feeders, which could eventually lead to a population of feeder-preferring mosquitoes. Artificial feeders also offer the chance to introduce novel elements into the mosquito diet, such as anti-malarial or other anti-parasitic agents. Feeders might directly reduce human bites and harnesses the power of natural selection by selectively favoring feeder-preferring (rather than trap-resistant) mosquitoes.

Keywords: mosquito, malaria, plasmodium, selection, vector control

Introduction

The television show *True Blood* proposes the eponymous blood substitute drink in a bottle so vampires do not need to feed on and kill people. Here we essentially ask the following: Could a version of "True Blood" for mosquitoes reduce bites, render mosquitoes unable to transmit blood parasites, and promote the evolution of less-harmful mosquitoes?

Mosquito control methods typically divert mosquitoes away from people but leave mosquitoes worse off for having been diverted. For example, traps and insecticides kill mosquitoes, and bed nets prevent mosquitoes from eating. As a result, heritable features that make mosquitoes less susceptible to these methods can eventually come to dominate the mosquito population; consequently, the evolution of resistance is a major topic in disease control (Braimah et al., 2005; Raymond et al, 2001). Following those who have proposed evolution-resistant parasite control strategies (e.g. Ewald, 2004; Kurzban and Egeth, 2008; Read, Lynch, and Thomas, 2009), we present a new strategy: instead of finding new ways to kill mosquitoes or prevent them from feeding, we propose to divert mosquitoes from people and feed them using artificial feeders. Feeders do not swat, carry insecticide, or contain anti-blood-clotting mechanisms or other host defenses. Because of the relative safety and meal quality of artificial feeders, mosquitoes that continue to feed on *people* could, in contrast to other methods, be selected against.

Feeding mosquitoes from food sources under human control could provide people with two benefits in addition to possibly selecting for human-avoiding mosquitoes. First, the presence of an alternate food source could directly reduce the number of human bites: if a mosquito feeds from a feeder it cannot also take that meal from a person. Second, people could gain control over the mosquito diet and add novel agents, such as anti-malarial medication, to their food. Designing and implementing feeders that would divert and satiate human-biting ("anthropogenic") mosquitoes poses both theoretical and practical problems. Below, we consider some of these problems. For example, what would such a feeder look like? How much food would people need to provide and in what form? Can mosquitoes be provided with quality food without increasing the overall population of mosquitoes? This third question is especially important. Below, we show how in times and regions where factors other than food availability limit mosquito population size, mosquitoes that consume non-human blood can have a selective advantage relative to human-feeding mosquitoes even while the size of the mosquito population remains the same. Finally, we posit that if our theory is sound, then epidemiological simulations, engineering, and empirical testing may be reasonable next steps.

Practical Concerns

Feeding wild mosquitoes something other than human blood drawn by mosquito bites may be possible, but the idea raises certain practical questions. Below, we outline five problems and possible solutions.

How much food would people need to provide?

To keep the world's population of anthropophilic mosquitoes satiated, feeders would have to provide about the same amount of blood that people are already providing through their skin. Only female mosquitoes bite; they do so to acquire protein for laying eggs. They can eat the equivalent of their own body weight in a single meal, or 2-4 milligrams of blood (Klowden and Lea, 1978). In wet seasons, the worst-afflicted regions report an average of several hundred mosquito bites per person per day (Gallup and Sachs, 2001), equivalent to an average blood-loss rate of about one gram (or about 1 ml) of blood per person per day, or about the weight of a paperclip.

This relatively small amount of human blood could be provided to mosquitoes in artificial feeders. However, anthropophilic mosquitoes can also thrive on the blood of a range of vertebrates and invertebrates (Harrington, Edman and Scott, 2001; Styer et al, 2007; Woke, 1937; see Lyimo and Ferguson, 2009 for a review). Anthropophilic mosquitoes have also been reared in labs using an egg/soy protein mixture instead of blood (Griffith and Turner, 1996). Therefore, in the worst-afflicted regions, artificial feeders would need to be stocked with about 1ml/person/day of blood, with the blood perhaps taken from butchered animals or from still-living livestock, or instead it might be possible to stock feeders with a vegetable-based blood substitute formula.

Can an artificial feeder draw mosquitoes away from people?

Mosquitoes are successfully reared in labs by placing food behind a membrane that simulates skin (Rampersad and Ammons, 2007). Mosquito traps take advantage of sensory cues that lure mosquitoes. For example, the CDC light trap uses a light bulb as its main cue and can be made more effective by baiting with CO_2 and octenol, ordinarily reliable cues to the presence of animal life (Magbity *et al*. 2002; Ritchie and Kline, 1995). Mosquitoes are also preferentially attracted to stationary hosts rather than moving, potentially highly defensive hosts (Edman and Kale, 1971; Edman and Scott, 1987). "Artificial cows" are used to attract and kill mosquitoes, and mosquito feeder design can be informed by these precedents (Knols and Meijerink, 1997). The design of mosquito feeders can take advantage of lessons learned from the historical design of mosquito traps and laboratory mosquito feeders: just as traps use mimics and supernormal versions of natural cues to divert mosquitoes from people, so can feeders.[1]

If mosquitoes have access to better food, will mosquito populations increase?

If mosquitoes have safe access to quality food, will the mosquito population increase until swarms are so large that it would be impractical for people to feed them all? Studies suggest that blood meals are often not the limiting factor for the size of mosquito populations; for example, a major factor that limits the size of populations is the availability of aquatic breeding sites (Bradshaw and Holzapfel, 1983; Fincke, Yanoviak and Hanschu, 1997; Jawara *et al*, 2008). The water-limit on mosquito population size explains why there can be orders of magnitude more mosquitoes in wet seasons than dry seasons (Franklin and Whelan, 2009): there is always enough food (people) to go around, but the mosquito population size reflects the availability of standing water. This is why safe, high-quality meals can be expected to increase the fitness of mosquitoes that feed from feeders relative to human-feeders without increasing the size of the mosquito population.[2]

[1] Because mosquito sensory preferences for particular hosts are heritable (Gillies, 1964; Hallem, Dahanukar and Carlson, 2006), an artificial feeder that includes mosquito-attracting cues that humans do not emit would help select for mosquitoes that are not attracted to people, for example, bird feather scent (anthropophilic mosquitoes are also attracted to bird feather scent [Allan, Bernier and Kline, 2006]).

Can an artificial feeder provide a selective advantage over feeding on humans?

Anti-mosquito strategies have evolved among mosquito prey animals, including swatting, grooming, anti-mosquito antibody production, and blood coagulation promoting factors (Klowden and Lea, 1978; Edman and Scott, 1987; Hatfield, 1988). Mosquitoes, in turn, have anti-anti-mosquito strategies such as anti-coagulation elements in saliva and behavioral preferences for approaching less-defensive hosts (see e.g. Edman and Kale, 1971). In this host/parasite arms race, host defenses continue to have a substantial impact on mosquito mortality and reproduction. For example, host movements that disrupt meals negatively impact mosquito fecundity (Hawley, 1985). Anti-mosquito antibodies present in a blood meal can reduce subsequent mosquito survival and fertility by 30% (Hatfield, 1988; Srikrishnaraj, Ramasamy and Ramasamy, 1992).

Mosquito feeders, on the other hand, provide mosquitoes with a "free lunch" in the sense that unlike any organism the mosquito encounters, the feeder is designed to facilitate, rather than defend against, feeding. In addition to benefiting by avoiding swats, feeder-feeding mosquitoes would no longer need salivary anticoagulants and other counter-defenses, possibly leading to selection for their loss. Furthermore, diseases such as malaria lower mosquito fecundity (Hogg and Hurd, 1997), so access to a food source that does not contain a liver (which the malaria parasite needs to reproduce) would directly benefit feeder-feeding mosquitoes.

For mosquitoes, calories are abundant in the form of vertebrate blood, but safe means of foraging are not. To the extent that human-provided mosquito feeders make foraging less costly for mosquitoes, mosquitoes that take advantage of the human-provided meals could benefit relative to mosquitoes that solely feed on swatting, insecticide-ridden, blood-coagulating people. If mosquitoes that feed from feeders survive at a higher rate than mosquitoes that attempt to feed from vertebrates, then in times and places where there are a limited number of quality egg-laying sites, feeder-feeding mosquitoes may be relatively more likely to successfully lay eggs, but the total number of mosquitoes will still be determined by the number of available egg-laying sites.

Through artificial selection, Gillies (1964) elicited an evolved preference for feeding on cows instead of humans among anthropophilic mosquitoes in about six mosquito generations. Gillies (1964) and others observe mosquito generation times of 2-3 weeks, so it is possible that mosquito preferences could begin to be directed away from humans in a relatively short amount of time. However, the rate at which a preference for avoiding people could evolve depends on numerous factors including effects of the food

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[2] However, a potential increase in mosquito populations due to the presence of feeders is still an important concern. In a case where food availability represents an important limit on mosquito populations, the quality of the artificial meal could be titrated downward (perhaps by adding especially harsh anti-malarial compounds) until the reproductive output of mosquitoes that feed from artificial feeders is similar to the reproductive output of mosquitoes that feed from people. Following titration, as long as there is no relative fitness *cost* to feeding from artificial feeders, there will be no selection pressure to avoid feeding from the feeders. And, as long as there is no *overall benefit* to feeding from artificial feeders, there will be no increase in the total number of mosquitoes. Even in this case, feeders can still draw bites away from people, and the downward titration can be removed if food availability ceases to limit the mosquito population size.

source itself, food additives such as antimalarial agents, and the degree of safety given by feeding from a nondefensive food source.

Would mosquito feeders increase the local density of mosquitoes?

Could an artificial feeder increase bites on people near a particular feeder? That is, would an individual want a mosquito feeder in her own backyard? Mosquito traps have historically raised the same engineering problem: how can a trap attract (and kill) local populations of would-be human-biting mosquitoes without attracting large numbers of new mosquitoes to the general area of the trap? Feeder designs can use the same solutions to this problem that previously have been worked out for traps.

One solution used by the miniature CDC light trap is to maintain only a small effective attraction range, about five meters, beyond which mosquitoes are not strongly attracted to the trap cues (Odetoyinbo, 1969). In this way, mosquitoes near to a person and trap are diverted, but mosquitoes that started out further away are not attracted. These traps are used, for example, inside houses. A feeder based on similar short-range cues could attract and feed mosquitoes that were already nearby without attracting additional mosquitoes. More generally, designers of feeders can take advantage of the lessons learned in trap placement in order to divert mosquitoes without attracting more mosquitoes to the area.

A related question is whether feeders might interfere with other successful mosquito interventions like traps, bed nets, eradication, education, "virulence management" (Dieckmann et al, 2002) and "evolutionary epidemiology" (Ewald, 1988). To a large extent, existing strategies could complement or benefit the feeder strategy. Feeders could be used alongside other techniques, such as attempting to remove standing water sources and the use of bed nets. If mosquito traps were used in proximity to feeders, it would be useful to make sure they have at least slightly different attraction cues, in which case traps could help drive the evolution of a feeder-seeking preference. Mosquito eradication through insecticide, sterilization, or genetic manipulation can also occur in tandem with feeders: feeders would still give surviving reproductive mosquitoes something better to bite than people. If there are mosquitoes in your backyard, then even if other control mechanisms happen to be enacted in your community, you might still want to own a mosquito feeder.

Conclusion

Mosquitoes annually transmit malaria and dengue fever to over three hundred million people (Ostera and Gostin, 2011). Providing less-harmful mosquitoes with a selective advantage (safe, quality meals) could help drive the replacement of human-biting mosquitoes with feeder-feeding mosquitoes. If we make mosquitoes better off for having been diverted from feeding on people (rather than worse off, like most traps do), we might achieve control of mosquitoes without producing selection pressures for mosquitoes that are resistant to the mechanism of control. Among other considerations, this strategy does not propose eliminating mosquitoes, a scenario that would have unpredictable ecological effects on mosquito predators and on flowers mosquitoes pollinate. Unlike various plans for releasing genetically modified mosquitoes into the wild (Ostera and Gotsin, 2011;

Shelly and McInnis, 2011), our strategy is based on harnessing the power of natural selection *in nature* by setting up conditions that draw mosquitoes away from people, behaviorally incentivize feeding from artificial feeders instead of preying on people, and creating selection pressures that favors less-harmful mosquito behavior. That is the theory, but implementation requires engineering, and long-term evolutionary outcomes can be difficult to predict.

The proposal here should be understood in the context of work of Ewald (2004), Nowak and May (1994), Hamilton and Zuk (1982), and others, who have extensively analyzed the evolution of virulence, including identifying mechanisms by which parasites can evolve to become less-harmful to hosts. In the mosquito control literature, artificial cows and other traps have been developed that draw biting mosquitoes away from people, and the notion of "zooprophylaxis," or finding ways to shift mosquito preferences from humans and towards animals, has been discussed since at least the 1950s (Saul, 2003). In mosquito laboratory research, various novel means have been devised for feeding mosquitoes without requiring mosquitoes to feed on living humans (Rampersad and Ammons, 2007).

Others have explored potential benefits conferred by selective provisioning of less-harmful parasites. For example, Zivcovik *et. al.* (2010) theorize that human breast milk selectively promotes the colonization of relatively less-harmful bacteria in the gut of the infant, at the evolutionary expense of harmful bacteria (also see Frost, 2011). Similarly, the theory underlying fecal transplants suggests that harmful bacterial colonizations can be overcome by populating the colon with feces taken from a healthy person that contain a less-harmful balance of bacteria (Walker, 2011). And, as Read, Lynch and Thomas (2009) point out in describing a mosquito control plan that would selectively target the most harmful individuals (adult females), it is disease reduction, not insect reduction, that is the true goal of mosquito control strategies. Together, these literatures buttress the concept of a trap-like mosquito feeder that actively maintains wild mosquito populations that are less likely to cause human disease.

In times and places where the spread of disease increases exponentially with the rate of mosquito feeding on people, even a small shift away from feeding on people can have a large impact on human disease (Lyimo and Ferguson, 2009). Safe, quality meals for mosquitoes can be a win-win situation for people and mosquitoes. People and livestock currently lose blood to and are infected with parasites from mosquitoes. If a similar amount of protein could be given away to mosquitoes freely, only the blood parasites would lose. Control with provisioning can also be adapted for other host-parasite systems (see Kurzban and Egeth, 2008), though mosquito bites in particular are a persistent major source of human disease.

Various empirical tests, validations, and engineering related to the new mosquito "domestication" strategy are crucial next steps. The strategy we introduce rests on simple premises that point to a potential new limb of disease vector control. When mosquitoes feed on human blood, people swat mosquitoes and mosquitoes transmit parasites that harm people. However, it is only a very small amount of our blood that mosquitoes are after. We and the mosquitoes would all prefer for them to eat something else. Let's give them something else to eat.

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