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Endectocide-treated cattle for malaria control: A coupled entomological-epidemiological model

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ABSTRACT

The malaria vector landscape is dynamic and dependence on indoor control tools has drastically affected both species compositions and local mosquito biting behaviours. In the advent of spreading behavioural resilience and physiological resistance to insecticidal nets and house spray, approaches to target more zoophilic, outdoor-biting vectors are being sought with increased urgency. Endectocides are insecticides applied to hosts which are taken up by the vectors during biting, and recent field assessments have demonstrated favourable results of cattle treated with ivermectin, diflubenzuron, eprinomectin and fipronil. Models were constructed to account for the modern, diverse vector feeding behaviours and assess their role in shaping malaria transmission and control with cattle-treated endectocides. Efficacy of this novel approach to malaria control is shown to be strongly dependent not only on intrinsic host preferences of the vector but also on how this preference is augmented by variation in the encounter rates with alternative blood-hosts. Ecological scenarios are presented whereby endectocides used on cattle yield equivalent, and in some cases improved, efficacy over nets and spray in controlling malaria transmission. Interactions between mosquito biting behaviours and relative availabilities of alternative blood-host species have largely been neglected in malaria programmatic strategy but will increasingly underlie sustaining the successes of vector control initiatives.

1. Introduction

Within both control and elimination settings, the primary means of malaria reduction has been through vector management with chemical insecticides (Bhatt et al., 2015). Widespread resistance among numerous disparate populations of vectors has raised serious concern over the sustainability of thus far successful disease control campaigns. Lessons learned during the era of dwindling vector control efficacy include the necessity for optimising control strategy of any new insecticidal approaches to controlling malaria that come to market in order to maximise, and ideally prolong, the benefit achieved with these precious few resources (Mnzava et al., 2015). The current study sought to assess an endectocidal approach to kill malaria vectors and to identify the ecological conditions that would optimise its application.

Endectocides are insecticides applied directly to hosts to kill blood-feeding arthropods. They can either be applied topically, parenterally or they can be ingested by the host resulting in their dissemination through the circulatory system. A forerunner

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chemical for this strategy is ivermectin which antagonises the insect-specific glutamate-gated chloride neuromuscular transmission channels (Kane et al., 2000). Importantly, this mode of action simultaneously impedes any major toxic effects in treated mammals — because they lack this channel (Bloomquist, 2003) - while protecting its efficacy from inadvertent cross-resistance with any of the insecticides currently used as vector control mainstays (Foy et al., 2011). Although its primary application in human disease control is within mass drug administration campaigns for onchocerciasis, empirical evidence is mounting for ivermectin effectively controlling tsetse fly vectors of African trypanosomiasis (Pooda et al., 2013) as well as anopheline malaria vectors (Fritz et al., 2009). However, theoretical studies are comparatively scant and require considerable development for this approach to be strategically assessed in the context of disease control — both as a stand-alone method and as a component of integrated vector management.

Expanding ideas first raised by Wilson (1993), Sylla et al. (2010) developed an age-structured model of *Anopheles gambiae* and assessed treating humans with ivermectin having the dual effect of reducing vector densities (through instantaneous death) while also skewing mosquito demography towards a younger population (through shortened lifespan resulting from sub-lethal dose exposure). Simulations of these authors demonstrated a 90% reduction in the malaria reproduction number, intuitively showing that maximal gains were achieved when treatment coverage and frequency was highest (Sylla et al., 2010). A key disadvantage to this general strategy was the short half-life of typical ivermectin doses in humans resulting in rapidly attenuating effects. However, subsequent to this initial work, higher dose formulations have been optimised for increased longevity in cattle and new chemicals have proven effective additions to the endectocide arsenal.

Diflubenzuron, eprinomectin and fipronil have all shown promise in initial trials in the control of sand fly vectors of leishmaniasis (Ingenloff et al., 2013). Very recently, the first field demonstration was published of the effective treatment of cattle with these chemicals to kill *A. gambiae* sensu lato (Poche et al., 2015). These pose interesting developments in the context of the current malaria vector landscape whereby compositional changes have favoured dominance of exophilic species (Mwangangi et al., 2013) or vectors that have demonstrated increased plasticity in their biting behaviours (Reddy et al., 2011). Understanding the biting behaviour of disease vectors in terms of the distribution of bites among different host species has become a higher priority following these developments; and, in the current study, a novel framework is presented to improve how this behaviour is captured by models to assess the epidemiological impact of applying insecticides to different blood host species.

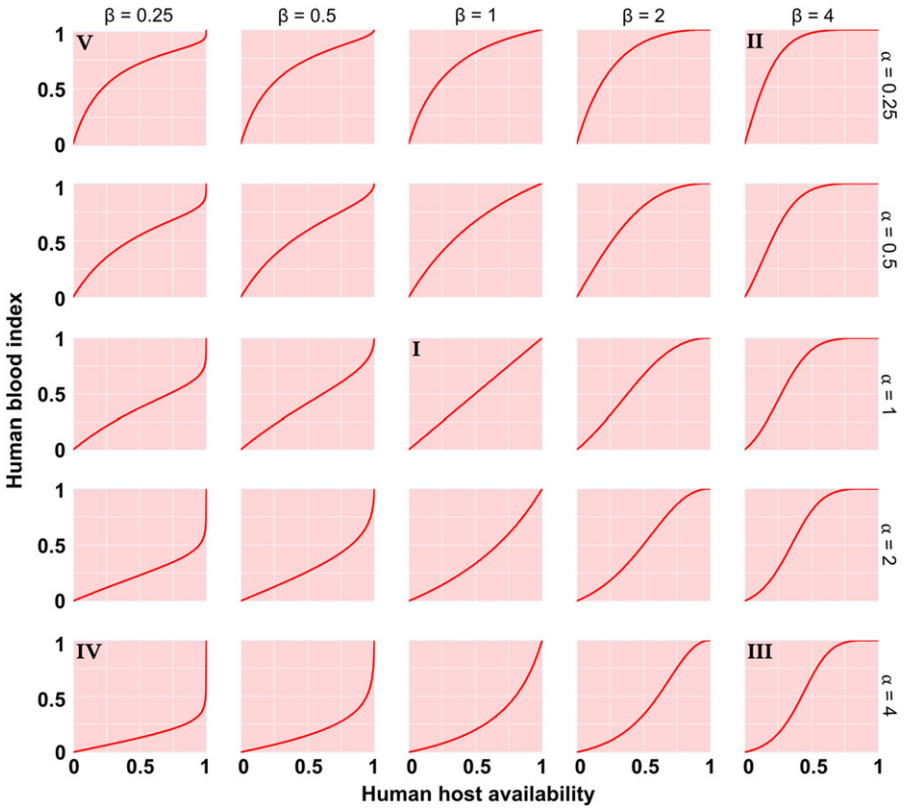

Fig. 1. The human blood index of a disease vector across varying levels of human host availability (relative to all potential blood sources) as augmented by different biting behaviours. Distinct qualitative forms of vector behaviour (denoted 'I' to 'V') are shaped by parameters α and β as described in Eq. 1.