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Veterinary endectocides for malaria control and elimination: prospects and challenges

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Residual transmission is the persistence of malaria transmission after scale-up of appropriate vector control tools and is one of the key challenges for malaria elimination today. Although long associated with outdoor biting, other mosquito behaviours such as partly feeding upon animals contribute greatly to sustaining transmission. Peri-domestic livestock can be used as decoy to protect humans from blood-seeking vectors but this approach often leads to an increased malaria risk in a phenomenon known as zoopotentiation. Treating the said livestock with drugs capable of killing intestinal parasites as well as mosquitoes that feed upon them has the potential to tackle malaria through a previously unexplored mechanism. The advantages and challenges associated with this approach are briefly discussed here. Numerous references are purposely provided.

This article is part of the theme issue 'Novel control strategies for mosquito-borne diseases'.

1. The problem of residual transmission

Residual transmission, defined as 'persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme' [1] is one of the greatest challenges currently faced for eliminating malaria and achieving the 2030 targets proposed by WHO [2].

Residual transmission is the result of evolution [3]. At least two mechanisms could explain this: (i) mosquitoes with pre-existing behavioural traits that favour survival in the presence of scaled-up, home-centred vector control tools such as long-lasting insecticidal nets (LLINs) or indoor residual spraying (IRS) will thrive and eventually replace the vector population with susceptible behaviour, and (ii) the same measures could induce a shift in species composition when two or more vector species coexist. Although strongly associated with outdoor biting [4–6], residual transmission is a complex phenomenon that includes several other behavioural traits of mosquitoes, including crepuscular biting, early exit from houses and intermittently feeding upon animals [7].

2. Zoophagic vectors and residual transmission

Zoophagy, the tendency to feed upon animals, more concretely livestock, is one of such behavioural traits favouring residual transmission [8,9]. The most effective malaria vectors (predominantly feeding upon humans and at night, when humans are most vulnerable) represent a small fraction of all *Anopheles* species, while the number of vectors predominantly feeding upon animals is much larger. Given the vast numbers of predominantly zoophagic vectors, even sporadic feeding upon humans can contribute to sustain malaria transmission [10]. In addition, feeding upon animals is often associated with other traits that fuel residual transmission, such as outdoor biting and crepuscular activity [7,11], which makes evolutionary sense given the availability of livestock blood

outside protected spaces. *Anopheles arabiensis*, opportunistically feeding on animals and humans outdoors and potentially shifting peak biting times to avoid insecticides in LLINs and IRS [12], and shifts in species compositions are good examples of this problem [13].

3. Good decoys and detrimental decoys

Using livestock as a decoy to divert vectors feeding upon humans, a strategy known as zooprophylaxis, has been tried in the past with mixed results [14–16]. Most evidence suggests that while animals can indeed divert some vectors, proximity to the households is critical and short distances between animal pens and human dwellings can actually increase malaria transmission in a phenomenon known as zoopotentiation [17,18]. This phenomenon is not exclusive to malaria as peri-domestic livestock are well known to increase the presence of vectors and risk of Chagas disease in a distance-dependent manner [19,20] and there is a possibility of the same effect regarding Japanese encephalitis virus [21].

4. Veterinary endectocides

Tackling residual transmission will require innovative vector control approaches [22]. Endectocides are drugs capable of killing endo- and ectoparasites and their deployment at the community level has been advocated as a potential complementary strategy to reduce malaria transmission [23–25]. Using endectocides in peri-domestic livestock has the potential to greatly reduce the population of zoophagic vectors and hence opportunistic feeding upon humans [26].

This idea is currently supported by semi-field data [27,28] as well as modelling for malaria [29], which predicts important reductions in transmission with the treatment of pigs [30] or cattle [31,32]. Here again, the models also predict remarkable reduction of transmission for other vector-borne diseases such as Chagas [33] and human African trypanosomiasis [34,35].

5. Additional advantages of using endectocides in livestock

Endectocides are widely deployed in high-income countries. They are used to improve livestock growth and yield by reducing the burden of intestinal parasites [36]. In developing regions, the wider use of endectocides in herds and household-based livestock would have benefits in human health beyond the potential reduction of malaria. This is because the livestock parasites (zoonotic or not) greatly reduce income and food security, and reduce household wealth and capital available for healthcare or house improvement [37].

While human use of endectocides to reduce malaria transmission is limited by a stringent regulatory framework [38], animal use would provide several advantages, allowing for: (i) higher doses of endectocides, which are directly related to their anti-mosquito efficacy [39]; (ii) longer-lasting formulations with the potential to sustain mosquitocidal effects throughout the transmission season [26,40]; (iii) use of endectocides not currently approved for human use such as fipronil [41,42], which opens the possibility of mosaic deployment of different endectocides in herds and humans; (iv) adding a second drug as pharmacokinetic booster to improve the systemic exposure of the endectocide (this could also inhibit metabolic resistance mechanisms in the mosquito to amplify mortality [43] and possibly reverse resistance to endectocides in intestinal helminths of veterinary relevance [44]); (v) potential leverage of agricultural development funds not usually tapped by global health initiatives; and finally, (vi) creative use of endectocides targeting wild birds, as has been proposed to tackle West Nile virus [45], an approach that translated to monkeys, could also to be considered for *Plasmodium knowlesi*.

6. Some challenges

When employing veterinary endectocides to reduce malaria transmission, several challenges need to be overcome. First, the challenge posed by coordinating human and animal authorities—broad deployment of veterinary endectocide would require close interaction between the human and animal health authorities for regulatory and logistic purposes. Another issue to counter are withdrawal times. Endectocides, when used in animals for human consumption, can also pose a risk to human health. This is currently addressed by regulating the admissible drug residues in animal products such as milk or meat. These limits define the withdrawal periods for milking or slaughtering livestock after treatment [46]. As an example, the current guidelines of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) establish withdrawal times of between 14 and 122 days after ivermectin treatment, varying according to the formulation, route of administration and dose. Respecting withdrawal times could be challenging in areas where slaughter and milking are not regulated or supervised by qualified personnel, and will require close surveillance for potential effects on the health of humans that consume animal products in areas where veterinary endectocides are used against malaria. Furthermore, as the transmission is reduced, interventions will need to be tailored to the local bionomics. Targeting the one-health intervention for optimal impact will require defining areas where malaria transmission is driven by zoophagic vectors and where livestock density and malaria burden are above a certain threshold [47]. An additional challenge lies in resistance in veterinary helminths, which is already broadly prevalent (reviewed in [48]). Since the primary indication of most veterinary endectocides is the reduction of the intestinal parasite burden in herds, it will be important to monitor the primary efficacy of these drugs as broader deployment could fuel resistance. The same concern could apply to malaria vectors as broader use in multiple blood sources, particularly with long-lasting formulation, could expose large mosquito populations to sublethal concentrations, potentially selecting for resistance. Concerns about helminth or mosquito resistance can be addressed with refugia, that is, leaving some animals intentionally untreated, which allows for the local parasite/mosquito gene pool to remain heterogeneous and reduces the possibilities of population replacement with resistant phenotypes [49,50]. Moreover, one theoretical risk with scaled-up veterinary endectocides is the disproportionate selective pressure put upon zoophagic vectors. In the presence of multiple vector species competing for the same ecological niche, this pressure could select for vectors feeding predominantly upon humans and increase malaria transmission. It is advisable to manage this risk by either conducting carefully

controlled semi-field experiments or deploying endectocides simultaneously in human and livestock in the field and comparing against human-only use as planned in the BOHEMIA trials (www.bohemiaconsortium.org). Lastly, the effect of endectocide residua in cattle dung and environmental water must be carefully monitored to avoid negative impact on the biodiversity of non-target fauna [51,52].

7. Conclusion

The use of veterinary endectocides to reduce malaria transmission is a relatively unexplored field with enormous potential to tackle residual transmission and help the malaria community to get back on track to achieving the goals proposed in the Global Technical Strategy. Several challenges need to be addressed but none seems unsurmountable. With a stall in progress in reducing annual cases and malaria deaths, it is perhaps time to go beyond *thinking* out of the box and start *acting* out of the box.

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