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Opinion

Insecticide-treated livestock: a potential One Health approach to malaria control in Africa

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New vector-control tools are urgently needed to reduce malaria in areas where there is significant transmission after deployment of indoor residual spraying (IRS) and insecticide treated nets. Insecticide-treated livestock (ITL) is a potential novel strategy by which zoophagic mosquitos are killed after feeding upon animals treated with an insecticide. Although there are several insecticide candidates in the pipeline with a wide efficacy range against mosquitos, additional field studies with epidemiological outcomes are required to test the impact of this intervention on malaria transmission. Insecticides under consideration have long been used in livestock to improve animal health and productivity, but each has food and environmental safety considerations. Therefore, moving ITL from a concept to implementation will require a One Health framework.

Highlights

Malaria elimination with current vector-control strategies is hindered by residual transmission; hence, new tools are required to cover this protection gap.

Feeding upon animals is an often overlooked vector trait that can, in some circumstances, contribute to residual transmission.

Strategies that involve treating livestock with insecticides in areas of zoophagic mosquitos offer a new approach by which the mosquitos die after feeding on treated animals.

A One Health framework recognizes the interconnection between people, animals, and their environment, offering a comprehensive approach to investigating insecticide-treated livestock for malaria control.

Several insecticide candidates are in the pipeline, although field trials are needed to demonstrate their effectiveness.

Combinations of human and livestock mass administration of insecticides could maximize impact on mosquito populations.

The problem of residual malaria transmission

Despite significant progress against malaria in the past decades, recent trends show that advancements in reducing the worldwide burden have slowed[i]. Improvement resulted from scale-up of better diagnosis, treatment, and prevention strategies, particularly vector control [1]. The data indicate that new challenges have emerged, and the malaria community is off-track to reach the WHO Global Technical Strategy for Malaria (GTS) goals by 2030[ii], which is being updated accordingly[iii]. Regarding vector control, the efficacy of the current frontline interventions insecticide-treated nets (ITNs) and indoor residual spraying (IRS) is limited partly by increasing insecticide resistance in mosquitos and **residual transmission** (see Glossary) [2,3]. Therefore, innovative, complementary strategies are required urgently to broaden the malaria toolbox [4].

Residual transmission results from certain variant behaviors that allow mosquitos to evade current home-centered vector-control tools by biting outdoors (**exophilic**), having crepuscular activity, and/or feeding upon animals [5]. Even though malaria transmission occurs due to the **anthropophagic** behavior of mosquitos, feeding **plasticity** can lead to anthropophilic mosquitos seeking part of their blood meals from animals [6]. This way, partial **zoophagic** behavior contributes to maintaining vector population densities even though animals are not a parasite reservoir for the disease. Although in certain settings no changes in mosquito behavior have been reported after the introduction of vector control [7], many studies show a proportional increase in zoophagy after broad implementation of IRS and/or ITNs [8–10], possibly due to selective pressure on vectors feeding indoors and upon humans.

ITL – a potential solution

In settings with moderate to high zoophilic *Anopheles*, interventions targeting animals to take advantage of mosquito–animal contacts might be an option. ITL involves treating livestock living in close proximity to humans with an insecticide. Zoophagic malaria vectors may die or have reduced reproductive success after feeding on ITL, which could protect humans by driving

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down the vector population responsible for malaria transmission. Alternatively, there have been successful attempts to address the issue by spraying livestock enclosures and livestock pens [11]; however, this approach has shown limitations linked to structure availability or the stability of insecticide formulations outdoors.

A One Health framework for ITL

The concept of One Health consists of a collaborative approach to health challenges which recognizes the intersection of the human medicine, veterinary, and environmental science fields [12,13]. In the case of ITL, although the primary public health outcome of interest is a reduction in malaria, the insecticides used in livestock can also impact animal health and productivity (Box 1), food safety, and local ecosystems. Partly, this is due to the way in which ITL must be implemented, which is through veterinary mass drug administration (vet-MDA) or dipping campaigns in order to maximize the contact rate between mosquitos and treated animals. The complex system of interactions among humans, animal health, and the environment necessarily influences research, evaluation, and eventual implementation strategies for ITL (Figure 1, Key figure). Here, we summarize the evidence available about ITL candidates and discuss, from a One Health perspective, key issues that need addressing before the potential deployment of ITL.

ITL candidate considerations

A variety of products have been studied, ranging from topical insecticides to antiparasitic drugs with different administration routes. Topically applied insecticides undergo transcuticular absorption by the mosquito, whereas **systemic insecticides** are ingested and delivered to the mosquito midgut along with a blood meal.

The efficacy of systemic insecticides will depend on their pharmacokinetic (PK) profile within the mammal, mainly on the duration of the drug concentration above mosquito-killing levels in the blood. Both drug-related factors (i.e., administration route, formulation) and animal-related factors (i.e., species, age, metabolic rate) may affect the PK of the insecticide and impact its efficacy against mosquitos.

The PK profile also affects the distribution of insecticides within animal tissues (i.e., muscle and internal organs) and animal products (e.g., milk). This becomes important when animals are slaughtered or milk is consumed before the recommended **withdrawal time**, allowing potentially unsafe drug levels to enter the human food chain. Investigating higher doses, unique

Box 1. Livestock health and productivity: the potential for ITL

In many malaria-endemic regions where ITL strategies might be implemented, livestock contribute to household nutrition and economic productivity in multiple ways (e.g., being sold or consumed, or used for draught power or transportation), leaving the burden of livestock parasitism to fall on households already encumbered by malaria and other infectious diseases of human health concern [62]. Endoparasites and ectoparasites affect livestock health and productivity through a variety of mechanisms, ultimately reducing the number of animals and animal products available for sale and household consumption. For example, gastrointestinal roundworm infections in cattle affect feed intake and nutrient absorption, leading to reduced milk production, slowed growth rates, loss of body condition, and changes in fertility [63]. Ectoparasites, including ticks, mites, and lice, can cause direct health impacts or may serve as vectors for diseases that cause significant morbidity and mortality in various livestock species. Sarcoptic mange infestation in pigs (caused by *Sarcoptes scabiei* var. *suis*) has worldwide distribution, causing a severe itching in affected animals that results in skin lesions with secondary infections and subsequent productivity losses related to lower feed conversion ratios, decreased growth rates, and decreased fertility [64]. In Tanzania, the tick-borne diseases anaplasmosis, babesiosis, heartwater, and theileriosis in cattle are estimated to cause 1.3 million cattle deaths and US$364 million in economic losses each year [65].

Most of the insecticides under consideration for use in livestock for malaria vector control are already licensed for use in livestock species to treat or prevent the health and productivity losses caused by endoparasites and ectoparasites, and are therefore critical to the practice of veterinary medicine and economic and food security.

Glossary

Anthropophilic/anthropophagic: refers to mosquitos that show a preference for feeding on humans, even when non-human hosts are available.
Endectocide: a drug with activity against endoparasites (mainly intestinal nematodes) and ectoparasites. Endectocides are systemic insecticides and thus they kill mosquitos that feed on a treated subject, including the malaria vector *Anopheles*.
Exophilic: refers to mosquitos that show a preference to rest outdoors during the period between the end of feeding and the onset of the search for an oviposition site.
Human blood index: the proportion of mosquitos that have fed on humans out of total fed. This term is used to indicate the extent to which mosquitos prefer human versus animal blood.
Mosquito repellency: behavioral avoidance responses of mosquitos exhibited in the presence of an insecticide-treated host. When insecticides are applied to an animal host, this may divert mosquitos to humans, thereby increasing malaria transmission.
Plasticity: the ability to alter behavior in response to different environmental conditions. For example, *Anopheles* mosquitos might exhibit a range of variant behaviors such as indoor versus outdoor biting, or feeding on humans versus animals.
Residual malaria transmission: persistence of malaria transmission following the implementation in time and space of a widely effective malaria program. More specifically, residual malaria transmission is any component of ongoing transmission that can persist after scaling up ITNs and IRS, with active ingredients to which local vectors are fully physiologically susceptible, to universal coverage targets. Such transmission might occur due to variant mosquito behaviors that avoid vector-control interventions by biting early and/or outdoors, or by feeding on animals.
Systemic insecticide: a drug given to a blood host to kill mosquitos that feed on the host and ingest the toxic drug in a blood meal. This includes endectocides and non-endectocide drugs with antiparasitic effects that further benefit the blood host.
Withdrawal time: the period of time between the last administration of a drug

formulations, or novel insecticides will incur additional research related to food safety before widespread use is acceptable.

Similar to the issue of food safety, many regulatory agencies require that companies show that their drug is safe for the environment during the approval process (e.g., FDA and European Medicines Agency, EMA)[iv]. Veterinary parasiticides are often excreted through the feces, releasing drug residues into the environment and potentially affecting animal and/or human health [14,15]. Concerns about such ecotoxic effects even led to revisions of the registration requirements of veterinary products in some countries [14].

Potential candidates

Among existing candidates for ITL we provide examples of topical and systemic insecticides that represent the diversity of products in the pipeline. We distinguish systemic insecticides by their ability to control either endoparasites and ectoparasites (i.e., endectocides), or ectoparasites alone (i.e., ectoparaciticides).

Topical insecticides

Pyrethroids

Pyrethroids are used in livestock topically against ectoparasites (i.e., fleas, mites, lice). Deltamethrin emerged as the early candidate for ITL as it killed most mosquitos even before they fed on livestock [16]. A community-level randomized controlled trial was conducted in Pakistan, where mosquitos were highly zoophilic, and the incidence of malaria decreased significantly [17]. Importantly, this is the only ITL field study to date in which a direct malaria outcome has been reported. Topical deltamethrin has been assessed in experimental studies against *Anopheles arabiensis* in Ethiopia [18], Tanzania [19], and Kenya [20], where it showed a short effective life (i.e., approximately 1 week) and a moderate initial mortality effect. Despite these potential positive findings, the use of pyrethroids in livestock for ITL raises concerns, including the potential acceleration of mosquito resistance and the risk of **mosquito repellency** [21]. Pyrethroids used in livestock have a wide range of slaughter and milk withdrawal times, ranging from 0 to 60 days; and there is well documented evidence of toxicity in aquatic organisms [22].

Systemic insecticides – endectocides

Endectocides represent a promising alternative to pyrethroids as they have a different mode of action and molecular target in the mosquito, thereby reducing the risk of cross-resistance to current vector-control strategies [23]. In addition, no evidence of endectocide-induced repellency has been reported from field studies to date.

Ivermectin

Seminal work by Fritz *et al.* showed that 90% of *Anopheles gambiae* s.s. mosquitos which fed on cattle in the first 2 weeks after ivermectin treatment, died within 10 days postfeeding [24]. Since then, the mosquitocidal and fertility-reducing properties of ivermectin have been tested against *An. arabiensis,* both *in vitro* [25] and under semi-field conditions in Kenya [26] and Tanzania [27], as well as against the important West Africa vector, *Anopheles coluzzii* [28]. Outside sub-Saharan Africa (SSA), zoophagic vectors such as *Anopheles stephensi* and *Anopheles culicifacies* showed reduced survival after feeding on ivermectin-treated cattle in a study carried out in Pakistan [29]. In Papua New Guinea, ITL was adapted to the local fauna by administering ivermectin to pigs, which are more abundant than cattle [30]. *Anopheles farauti* mosquitos feeding on high-dose ivermectin-treated pigs (i.e., 600 μg/kg) died within 2–4 days up to 8 days posttreatment, and lethal effects remained for 2 weeks.

and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug.

Zoonoses/zoonotic diseases: any infection (bacterial, viral, parasitic, or involving unconventional agents) that is naturally transmissible from animals to humans. An example of a parasite that causes zoonotic malaria is *Plasmodium knowlesi*, which is transmitted between primates and humans in Southeast Asia.

Zoophilic/zoophagic: refers to mosquitos that show a preference for feeding on animals.

Zoopotentiation: increasing malaria transmission in humans by having livestock in close proximity, which attracts mosquitos.

Zooprophylaxis: diverting insect blood feeding from humans to animals. For malaria, it involves the strategic placement of livestock sheds or pens close to humans in order to attract mosquitos to the animals, which are a dead-end host for the infection.

Key figure

One Health framework for insecticide-treated livestock (ITL) research, implementation, and evaluation

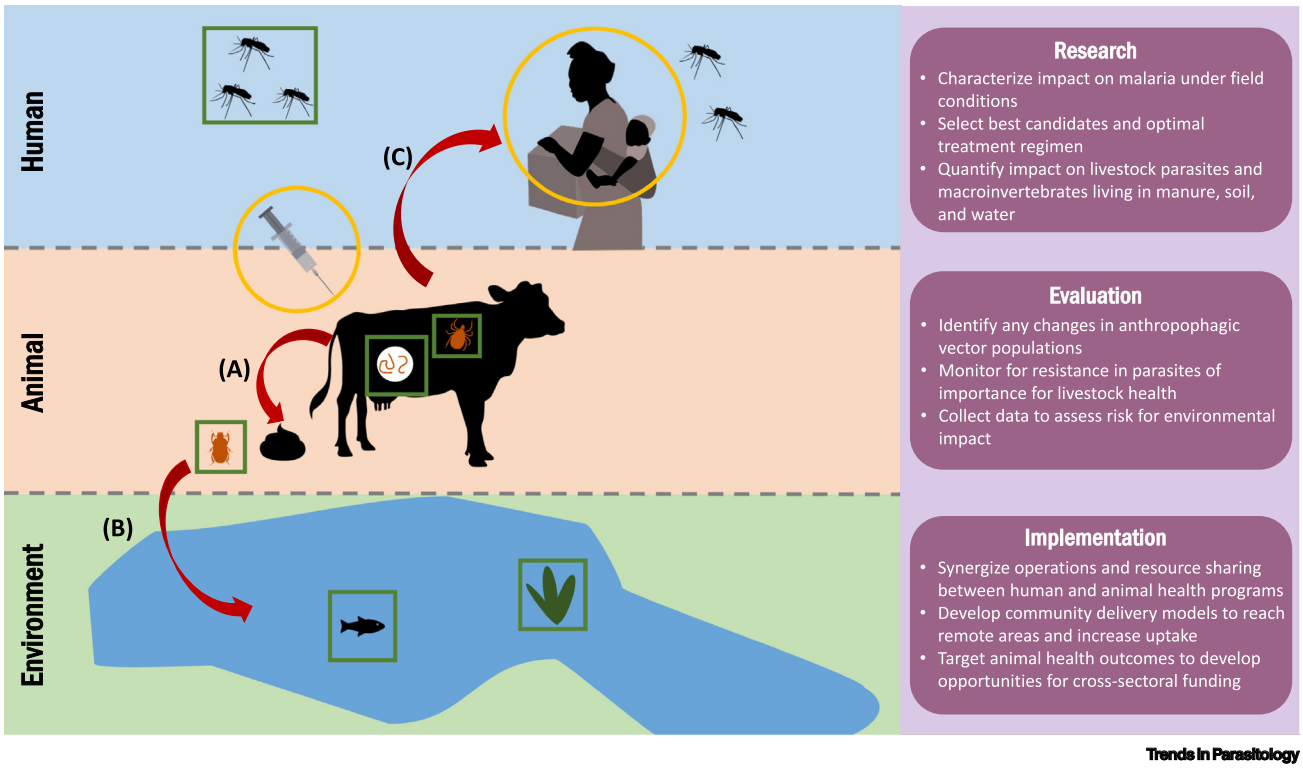

Figure 1. This figure shows a hypothetical injectable insecticide that kills external and internal parasites as the example for an ITL intervention. Red arrows show the potential ways that the insecticide moves though the human–animal–environmental interface after being given to livestock. (A) Some portion of the insecticide and its metabolites are excreted into manure. (B) From manure, the insecticide and its metabolites may migrate into environmental compartments such as soil or water. (C) The insecticide is absorbed into the animal's body, concentrating in milk and meat, which can expose humans when they ingest animal-sourced foods produced without adherence to drug withdrawal times. Green squares indicate where the insecticide has the potential to affect invertebrate and aquatic organisms. In some cases, when the targets are mosquitos or livestock parasites, we anticipate a benefit to human and animal health. However, the insecticide's potential to affect, for instance dung beetle populations and aquatic species, raises the concern for a negative environmental impact, particularly within the context of vet-MDA necessary for an ITL program. Yellow circles identify areas of social and economic impact. Examples include the acceptability of ITL in communities, cost and logistics of drug administration, and the resulting nutritional and economic benefits to the household following increased livestock productivity. By framing ITL in this way we can highlight priority areas for research, identify potential risks for evaluation, and identify barriers/facilitators for implementation.

Withdrawal times associated with the use of ivermectin-labeled doses vary by species and intended use[v]. In cattle and pigs there is a slaughter withdrawal time of 35 days and 18 days, respectively, when using the 1% injectable solution. The same formulation is not approved for use in dairy cattle; however, there is a recommended withdrawal time of 47 days for milk when used off-label [31].

Eprinomectin

In vitro studies of eprinomectin spiked in bovine blood [25] have shown mosquito-killing and sublethal effects comparable with ivermectin when fed to *An. gambiae* s.s. and *An. arabiensis*, respectively. The first semi-field study was carried out in Western Kenya where more than 50% of *An. arabiensis* identified blood meals were from cattle [26]. The action of oral eprinomectin

(experimental formulation) was delayed compared with ivermectin but eprinomectin showed longer-lasting effects attributable to its longer half-life. Another semicontrolled study using extended-release injectable (ERI) LongRange™ (eprinomectin 5%) in Ethiopia found that *An. arabiensis* fed on treated calves died within 7 days [32]. The only field study to examine the impact on zoophagic mosquitos was also performed in Kenya, where cattle received a topical formulation of eprinomectin for two consecutive weeks, but the results were inconclusive [33].

Eprinomectin is available as a topical endectocide for all cattle, including lactating dairy cows, and remarkably, has a zero-day milk withdrawal period [34]. The ERI formulation, LongRange™, is effective for up to 5 months posttreatment [35]; however, the slaughter withdrawal time is 48 days after treatment, and it is not approved for female dairy cattle >20 months of age, thus losing the food safety advantages of the topical formulation[vi].

Environmental studies of avermectins (ivermectin and eprinomectin) [36] have shown that they bind tightly to the feces, undergoing a slow photodegradation to less active compounds, but can have lethal and sublethal effects on dung-dwelling organisms. Negative effects on invertebrates that contribute to dung degradation might further affect soil fertility, nutrient cycles [36], and livestock forage availability [37,38]. Drug residues in livestock feces may also reach aquatic environments, damaging the existing flora and fauna, but thanks to the low affinity of avermectins for water, the chemical residues mostly stay in organic sediments, reducing the risk of toxicity to many aquatic species [14].

Systemic insecticides – ectoparaciticides

Fipronil

Fipronil is commercially available in topical form for the control of ectoparasites in beef cattle, although its use in livestock is not approved in many countries, including the USA and the European Union. Its toxicity has been proven superior to that of ivermectin in *in vitro* studies with *An. arabiensis* mosquitos [26], and in a study with field-collected *Anopheles albimanus* in Belize [39]. The only field study with fipronil was carried out in Western Kenya with an experimental oral formulation given to cattle in which an indoor collection of *An. arabiensis* revealed that resting densities were reduced, and even went down to zero in one of the treatment plots, but fipronil had no effect on the densities of *An. gambiae* s.s. and *Anopheles funestus* s.s. [40]. Although labels on fipronil products used in livestock claim that the product has high efficacy against ticks and horn flies resistant to pyrethroids and organophosphates[vii], cross-resistance to dieldrin and fipronil has been detected in *An. gambiae* [41], suggesting that cross-resistance with other insecticides used for malaria control may emerge.

Approved formulations of topical fipronil have a slaughter withdrawal time of 100 days, and its use is not recommended for pregnant or lactating cows[vii]. Numerous evaluations of the environmental impact of fipronil as a pesticide have shown high toxicity to non-target fauna [42], but studies on its ecological impact after treating animals are lacking.

Isoxazolines

The isoxazolines, fluralaner and afoxolaner, are the latest additions to the pool of systemic insecticide candidates. Used against ectoparasites in companion animals, isoxazolines have demonstrated killing activity against *Anopheles*, *Aedes*, and *Culex* mosquitos. Their different mechanisms of action and long half-lives make them attractive potential alternatives to other ITL candidates [43]. Until recently, isoxazolines were approved only for companion animals so studies on the risk to food safety were lacking. However, an oral product containing fluralaner (Exzolt™) was recently approved for use in poultry with a 14-day slaughter and 0-day egg

withdrawal time. An environmental risk assessment performed by the EMA identified that although fluralaner is toxic to invertebrates, Exzolt™ does not pose a risk to the environment if used as directed[viii].

The ideal candidate

Table 1 shows a summary of the reviewed insecticides compared with characteristics of an ideal insecticide candidate[ix]. Clearly, the ideal candidate for ITL is one that is proven effective under field conditions with an epidemiologically relevant impact on malaria transmission. However, other characteristics that influence acceptability and implementation, and affect food safety, animal health, and the environment, must also be considered.

Table 1. Characteristics of reviewed insecticides

	Ideal	Deltamethrin	Ivermectin	Eprinomectin	Fipronil	Isoxazolines
Efficacy	Proven epidemiological impact considered of public health value by national malaria-control programs	One randomized control trial (RCT) with malaria outcome in Pakistan [17]	Pending results of a small trial with six clusters in Vietnam[xvi] and BOHEMIA clinical trial in Tanzania and Mozambique[xvii]	No studies performed with malaria endpoints	No studies performed with malaria endpoints	No studies performed with malaria endpoints
Formulation	Long lasting, noninvasive (oral or topical)	1% and 7.5% topical (pour-on)	1% and 3.15% injectable solutions; 5 mg/ml topical (pour on); multiple oral formulations	5 mg/ml topical (pour on); 5% injectable solution	1% topical (pour on)	Oral formulations in companion animals
Food safety	No milk or slaughter withdrawal period	1% pour-on: Cattle (meat): 17 days Sheep (meat): 35 days Cattle/sheep (milk): 0 days[xviii] 0.75% pour-on: Cattle (meat/milk): 0 days Sheep (meat): 1 day Sheep (milk): 0 days[xix]	1% injectable[a] Cattle (meat): 35 days Sheep (meat/milk): 11 days Swine: 18 days[xx] 3.15% injectable[a], Cattle (meat): 122 days[xxi] 5 mg/ml pour-on:[a] Cattle (meat): 48 days[xx] 1.5 mg/ml paste (oral):[a] Cattle (meat): 24 days[xx] 0.8 mg/ml drench (oral):[b] Sheep (meat): 11 days[xviii]	5 mg/ml pour-on: Cattle (meat/milk): 0 days 5% injectable:[a] Cattle (meat): 48 days[xxii]	1% pour-on:[a] Cattle (meat): 100 days	Not approved for livestock use
Environmental safety	Limited to no impact on non-target organisms when used in vet-MDA	Toxicity demonstrated in fish, shellfish, non-target invertebrates, and small mammals [70]. Impact in vet-MDA unknown	Toxicity demonstrated in fish, shellfish, and non-target invertebrates; persistence of bound residues in water sediment [71,72]. Impact in vet-MDA unknown	Toxicity demonstrated in fish, shellfish, and non-target invertebrates [73]. Impact in vet-MDA unknown	Toxicity demonstrated in non-target invertebrates, bees, lizards, termites, and certain birds [42]. Impact in vet-MDA unknown	Few studies on non-target organisms. Demonstrated low toxicity to zebrafish [74]. Impact in vet-MDA unknown
Antiparasitic activity	Activity against ecto- and endo-parasites of veterinary importance	Ectoparasites only	Ecto- and endoparasites	Ecto- and endoparasites	Ectoparasites only	Ectoparasites only

A description of example insecticides relative to their efficacy in malaria prevention, food safety, environmental safety, and anti-parasitic activity in livestock as compared with the ideal insecticide candidate (based on the WHO preferred product characteristics: endectocide for malaria transmission control)[x]. Only approved formulations are described; however, this is not an exhaustive list, and formulations listed may not be available in all countries or may have different label restrictions and withdrawal times based on regulatory decisions made by the country in which they have been approved. In addition, for some insecticides, recommended withdrawal times are available when the product is used off-label. For example, although ivermectin is not labeled for use in dairy cows >20 months old, the FARAD database has a recommended milk withdrawal time of 47 days for the 1% injectable formulation.

[a]Not for use in female dairy cattle >20 months of age.

[b]Not for use in sheep producing milk for human consumption.

A product that can be delivered as a single oral or topical dose (versus an injectable formulation) with a long-lasting effect for a whole transmission season would reduce costs and ease implementation of ITL programs. An insecticide without a milk and slaughter withdrawal period would facilitate livestock owner acceptance and prevent human exposure through animal source foods. Finally, limited impact on non-target organisms when delivered through vet-MDA or mass dipping campaigns would avoid unintended consequences to the local ecosystem.

At this time, no candidate meets all desired criteria, and in reality, a perfect candidate may not be found. For example, longer-acting formulations are consistently associated with longer milk and slaughter withdrawal times; whereas shorter-acting formulations may require multiple administrations to demonstrate efficacy during the transmission season. Ultimately, the efficacy of the product for malaria control will have to be balanced with its food and environmental safety profile, cost, and operational feasibility in field conditions.

Addressing potential risks of ITL strategies

Application of a One Health framework in the consideration of ITL malaria-control strategies allows us to identify potential risks across human, animal, and environmental health sectors, and subsequently develop monitoring and risk mitigation efforts to ensure that one problem is not exchanged for another.

Selection of anthropophagic vectors

A risk of ITL is the selection of anthropophagic vectors in the long term, particularly when insecticides are intensively used on livestock only. In this case, there would be a strong selective pressure on vectors feeding predominantly upon livestock. If these vectors were competing for the same ecologic niche with other, more anthropophilic species (or even if there is a genetic polymorphism in these variant behaviors in the local vector population), the net increase in the **human blood index** in the long run could increase malaria transmission. In a similar manner, it would be important to assess whether ITL could have a repellency effect on vectors in the short term, further favoring feeding upon humans. This is all in addition to the baseline risk of **zoopotentiation** when the proximity of livestock may increase malaria transmission in the surrounding households. These risks, although hard to capture, must be evaluated in field studies and further explored through mathematical modeling. Moreover, these risks must be a key factor in the choice among ITL candidates, as well as in determining the ITL implementation strategy (e.g., in conjunction with human MDA).

Resistance in parasites of importance to livestock health

All potential ITL candidates have demonstrated evidence of resistance in primary parasite targets of veterinary importance. For instance, resistance to avermectins in cattle helminths across continents has been well documented in the past decade [44]. Given the economic impacts of livestock diseases caused by endo and ectoparasites (Box 1), the development of resistance and subsequent loss of parasiticides used to maintain and improve animal health should be of critical concern as ITL strategies are developed. Although resistance in relevant livestock parasites could be fostered by a broader, albeit intermittent, use due to a malaria indication, this would be difficult to assess during field trials due to timeframe constraints. However, methods for evaluating resistance exist and could be applied as part of ongoing monitoring in areas where ITL programs are deployed[x] [44]. Luckily, there are well-developed strategies for integrated parasite management that include rotation or co-use of parasiticides, and the practice of selective deworming to maintain refugia, which could be applied as part of ITL programs for prevention, or implemented when resistance is identified.

Environmental impact

Most studies on the adverse effects of veterinary parasiticides on non-target fauna were performed in northern countries (e.g., USA, UK), in the context of their use on individual farms. There is a difference between acknowledging that a particular parasiticide can negatively impact non-target organisms in the environment and the subsequent likelihood that a detrimental effect will be seen when the parasiticide is delivered within a defined animal population. The example of Exzolt™ is illustrative of this as its toxicity to invertebrates was not considered a significant environmental risk when used in poultry production systems as indicated by the label. Therefore, as drugs are being considered for ITL strategies, research should be carried out in malaria-endemic areas and within the context of population-level administration where regional variations (e.g., vegetation, climate, dung fauna) might alter concentrations in soil and water, and subsequent environmental impacts.

Opportunities for One Health synergy in implementation

Recognizing the significant challenges left to be addressed in the process of researching and evaluating potential ITL strategies, it is still important to look ahead and consider how a One Health approach to implementation might offer opportunities for ITL strategies to have greater impact [45].

Coadministration of human and ITL programs

To date, ivermectin is the only candidate approved for human use and the only one that has been widely deployed in a public health context (i.e., for onchocerciasis and lymphatic filariasis[xi]). The mosquitocidal activity of ivermectin in humans has been largely investigated *in vitro* [46] and *in vivo* [47], and the results of a recently-published trial in Burkina Faso point towards a relevant impact on malaria incidence in children [48]. If field studies in humans are successful[xii], there is the potential for ivermectin MDA to be used with a veterinary insecticide in a complementary fashion [49]. For instance, strategies where cattle are treated with eprinomectin and humans with ivermectin, tackling zoophagic and anthropophagic mosquitos simultaneously, could be explored in order to cover more blood sources and would have the potential added benefit of delaying the potential selection of anthropophagic vectors.

Design of ITL programs for livestock health

Additional benefits may be gained if the ITL candidate is selected for its ability to help control vectors other than *Anopheles* mosquitos as well as livestock diseases of public health importance. For example, pour-on eprinomectin demonstrates effectiveness against the tick *Rhipicephalus microplus*, the primary vector of *Babesia* spp. in cattle [50], whereas both deltamethrin and fipronil have demonstrated effectiveness against tsetse flies, the vector of bovine trypanosomiasis [51,52]. Bovine babesiosis and bovine trypanosomiasis are major diseases of economic importance in cattle living in tropical and subtropical regions, causing significant morbidity and mortality in affected populations[xiii,xiv]. The availability of multiple effective insecticides available for use in ITL malaria-control programs would provide the opportunity to tailor use of insecticides based on local livestock diseases, setting the stage for optimizing health outcomes and resource utilization.

Resource optimization and community models

ITL strategies are likely going to be resource intensive due to the added complexity of livestock mapping and migration and the pragmatic challenges of delivering drugs to animals. Moreover, animal health in low-income settings is often deprioritized for funding, and thus veterinary services are frequently under-resourced [53]. Therefore, public health and veterinary program coordination and resource optimization might be especially relevant in contexts of poor access to health

services [54]. For instance, sharing laboratory infrastructure and surveillance databases has been suggested to improve zoonotic outbreak responses [53], and joint vaccination campaigns for nomadic pastoralist groups in Chad and their livestock showed higher coverage than when vaccinating humans only [54].

Community models have been broadly used to reduce morbidity and transmission of human diseases, especially neglected tropical diseases (NTDs) [55]. The figure of the community-based animal health worker (CAHW), who played a key role in rinderpest eradication[xv], and who is still used in many countries [56], might become essential to deliver ITL in remote areas [57]. Besides human resources, strategies such as central point versus house-to-house drug administration should be explored since the delivery point might strongly affect uptake. For instance, one of the barriers reported for low uptake of livestock vaccination in Kenya and Uganda was distance to the intervention central point delivery because some animals are not used to moving long distances [58]. Therefore, in order to ensure effective implementation, operational research will be key to inform about local contexts.

Economic assessment to support cross-sector funding and investment

Traditional cost-effectiveness studies for malaria interventions generate ratios, such as cost per case averted, that account for various costs associated with intervention delivery, malaria treatment, and productivity losses [59]. Economic assessments of malaria interventions that employ ITL must also capture costs associated with the treatment of parasitic infections and productivity losses in livestock. This way, measures of cost-effectiveness account for the additional costs averted by reducing animal disease, which may be significant given the local prevalence of parasitic diseases, the selection of the ITL candidate, and the timing of delivery. Perhaps most importantly, economic analyses that can account for costs and benefits at the sector level (i.e., animal health and human health) can be useful when advocating for funding and buy-in from governments and international organizations, offering opportunities to identify funds under the One Health framework, outside of the already limited resources allocated for malaria control.

Concluding remarks

Although there are several insecticide candidates for ITL in the pipeline, and their efficacy is being investigated, randomized controlled field trials demonstrating a direct impact on malaria are yet to be undertaken. So far, only the deltamethrin study [17] has shown a direct malaria outcome, and only two field studies, using eprinomectin [33] and fipronil [40], have measured direct entomological outcomes. Several studies have modeled the potential impact of ITL and other livestock-based strategies on malaria outcomes with promising results (Box 2), but these need to be validated in the field.

Besides the call for additional studies, research on ITL candidates would benefit from harmonized standards for epidemiological and entomological outcomes. Different metrics of vector lethality are often reported, making direct comparison of compounds under investigation difficult. For instance, a common way to report mosquitocidal activity is the LC_{50} (i.e., concentration needed to kill 50% of mosquitos during a specific follow-up time postfeeding), but this variable can be presented at 24 h, 5 days, 7 days, or 9 days postfeeding, and sometimes the LC_{95} is reported instead. Other metrics used are the percentage mosquito survival during a specific time postfeeding period, or the opposite, the time required to kill a specific percentage of mosquitos. Harmonization of outcome metrics would improve our ability to compare the effectiveness of current and any future novel ITL candidates across the continuum of research from laboratory to field to clinical settings.

Outstanding questions

Of the currently available insecticides for use in livestock, which is the most potent and long-lasting against zoophagic mosquitos?

What are the most appropriate entomological and epidemiological metrics by which to assess the efficacy of ITL against vectors and malaria transmission?

Can novel insecticides or improved formulations ease the operations of administering insecticides to livestock and increase the duration of the mosquito-killing effect?

Which insecticides offer the most acceptable balance between effectiveness against malaria and food and environmental safety?

Which factors (e.g., percentage of zoophagic mosquitos, livestock density, social acceptance) are important in deciding where ITL implementation might be effective?

When and for how long would it be best to implement ITL strategies?

How can we comprehensively evaluate the impact of ITL interventions on mosquito populations, livestock health and productivity, and the surrounding ecosystem?

How can we find synergies between delivery of ITL programs for malaria prevention with other ongoing animal health and public health programs at the community level?

Does combining ITL with endectocide mass drug administration in humans have a measurable effect on malaria transmission?

How can we identify opportunities to deliver ITL programs that also maximize benefit to livestock health so as to improve cost-effectiveness and generate opportunities for cross-sectoral funding?

Box 2. Modeling of livestock-based interventions for malaria

The majority of malaria models used to evaluate impact of vector-control tools on disease transmission have traditionally modeled mosquito behavior as predominantly anthropophagic. New data on mosquitos that are at least partially zoophagic has emerged and has been recently included in models, along with related variables such as relative abundance of host choices (i.e., human versus animal). Models capturing a range of feeding habits show a more realistic picture of vector dynamics in certain areas, and thus they will better demonstrate the impact of context-specific vector-control tools.

Kiware *et al*. developed a model in which malaria transmission was dependent on the human blood index [66], and other modelers have gone one step further by exploring the impact of livestock-based strategies targeting zoophagic mosquitos. Franco *et al.* explored both **zooprophylaxis** and ITL scenarios employing real data from Ethiopia and pyrethroid use in Pakistan respectively [21]. Further work by Yakob *et al.* focused specifically on endectocide-treated cattle models and considered blood availability as a key aspect of mosquito host preference (vector plasticity) [67,68]. A limitation of treating livestock with current endectocides is the short mosquitocidal effect (i.e., weeks), so their use was proposed in areas of seasonal malaria at the peak of transmission [67]. Recently, a study based on published PK and pharmacodynamic (PD) data on various hosts simulated the impact of a broad range of systemic insecticides, including avermectins and isoxazolines, among others [69]. In this case, isoxazolines emerged as better candidates due to their longer-lasting effects under modeled scenarios with varying endemicities.

Despite the significant amount of work still needed to move the concept of ITL from the research stage to implementation as a complementary vector-control tool, there are potential benefits ITL offers that are worth contemplating even at this early stage. The cross-sectoral collaboration required to implement an intervention in livestock to address one of the most important infectious diseases in humans offers enormous potential to synergize resources and operational efforts to achieve better health for all, the true objective of the One Health approach. Finally, ITL strategies open the door to strategies not applicable in humans, which could enhance the effect of the intervention on the final malaria endpoint [60,61].

Going forward, the pathway to assess the potential impact of ITL against malaria and answer the remaining questions (see Outstanding questions) should follow a One Health framework in order to achieve effective, safe, and sustainable ITL programs.

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Declaration of interests

The authors declare no competing interests.

Resources

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