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Current and future opportunities of autodissemination of pyriproxyfen approach for malaria vector control in urban and rural Africa [version 3; peer review: 3 approved]

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Abstract
Despite the progress made in reducing malaria burden, new ways to address the increasing challenges of insecticide resistance and the invasion and spread of exotic malaria vectors such as *Anopheles stephensi* in Africa are urgently needed. While African countries are adopting larviciding as a complementary intervention for malaria vector control, the autodissemination technology has the potential to overcome barriers associated with the identification and treatment of prolific habitats that impede conventional larviciding approaches in rural settings. The autodissemination technology as a “lure and release” strategy works by exploiting the resting behavior of gravid mosquitoes to transfer lethal concentration of biological or chemical insecticide such as pyriproxyfen (PPF), an insect growth regulator (IGRs) to their oviposition sites and result in adult emergence inhibition.

Despite the evidence of the autodissemination approach to control other mosquito-borne diseases, there is growing and promising evidence for its use in controlling malaria vectors in Africa, which highlights the momentous research that needs to be sustained. This article reviews the evidence for efficacy of the autodissemination approach using PPF and discusses its potential as efficient and affordable complementary malaria vector control intervention in Africa. In the previous studies that were done in controlled semi-field environments, autodissemination with PPF demonstrated its potential in reducing densities of captive population of malaria vectors such as

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Anopheles gambiae and *Anopheles arabiensis.* Of importance, empirical evidence and biology-informed mathematical models to demonstrate the utility of the autodissemination approach to control wild populations of malaria vectors under field environment either alone or in combination with other tools are underway. Among others, the key determining factors for future introduction of this approach at scale is having scalable autodissemination devices, optimized PPF formulations, assess its integration/complementarity to existing conventional larviciding, and community perception and acceptance of the autodissemination approach.

Keywords
Autodissemination, Pyriproxyfen, Malaria, Larval source management

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REVISED **Amendments from Version 2**

The revised version addresses both typographical and technical comments raised by the reviewers. In line with the comments received, we discussed the evidence supporting the effectiveness of PPF in controlling insecticide-resistant mosquitoes. Additionally, we also highlighted the importance of exploring an alternative insect growth regulator (IGR), such as novaluron, that could help control other malaria vectors, such as *An. quadrimaculatus*, of which PPF has been reported to be less effective in their control and can be used in rotation with PPF to mitigate the development of PPF resistance in mosquitoes. We have also provided clarification to sentences that were pointed out by the reviewers; for example, we clarified the concern that PPF use in both larviciding and PPF-treated LLINs might enhance the development of resistance.

Any further responses from the reviewers can be found at the end of the article

Introduction

Wide coverage and use of control interventions such as Insecticide treated bed nets (ITNs) and indoor residual spraying (IRS) have accelerated the gains in malaria burden reduction[1,2]. These core interventions are threatened by increasing insecticide resistance development mainly to pyrethroid class in targeted mosquito species[3,4], shift to mosquitoes biting behavior to earlier hours of the evening and morning[5–7], and outdoor mosquito biting when people aren't protected[8].

To sustain these gains, WHO recommended larval source management (LSM) as a supplementary intervention to the core interventions[9]. LSM, particularly larviciding, has proved to be the potential in accelerating vector density reduction in areas where mosquitoes' breeding habitats are few, fixed, and findable[10]. Larviciding as an ecological method can reduce densities of both endophilic and exophilic vector populations[11] as well as malaria incidence and prevalence in selected settings[12,13]. Despite these notable progress and its historical success in malaria control, its wider application in rural African settings to cover productive cryptic breeding habitats requires different innovative strategies for its deployment[14].

The major malaria vectors in Sub Saharan Africa are *An. gambiae, An. arabiensis, Anopheles coluzzii* and *Anopheles funestus*[15]. Studies have shown that the majority of residual malaria transmission is mainly mediated by *An. funestus*[16–18] and *An. arabiensis*[8,19], which exhibit flexible behaviors including exophily[20] exophagy, and zoophagy[21,22]. Despite the efforts placed in controlling mosquitoes indoor, it is clear from the literature that ability of susceptible *An. funestus* and *An. arabiensis* to penetrate the bednets[23], early indoor biting[7,24], outdoor biting[25] as well as day biting[26] could evade the control efforts and sustain the transmission. Moreover, while continuing to deliver interventions that tackle indoor transmission, significant attention should be focused on mosquito behavior change, including outdoor biting and early indoor biting[7,8]. While investments in developing outdoor-based interventions are urgently required to sustain progress made on malaria control and elimination[27–29], it is also important to consider the pertinent ecological and behavioral adaptations of the dominant malaria vectors[30].

Promisingly, there has been an increase in designing and testing different outdoor mosquito control tools in recent years[31]. This includes the application of insecticides to alternative hosts such as livestock[21]; assessing the potential use of large-scale spatial repellents[11,32,33]; development of outdoors odor-baited traps[34]; attractive targeted sugar baits[35]; topical repellents[36]; use of genetically modified mosquitoes[37]; eave-ribbon technology[38], as well as the autodissemination approach[39]. This review discusses the opportunities and challenges of autodissemination approach with pyriproxyfen for controlling malaria vectors in urban and rural Africa.

The autodissemination approach

Autodissemination approach is the management method that involves co-opting host seeking, ovipositing and resting adult female gravid mosquitoes' behavior to transfer a lethal concentration of chemical insecticide such as pyriproxyfen to the breeding habitats and consequently results to adult emergence inhibition[40,41]. Limited evidence suggests that adult *Aedes albopictus* male could directly deliver PPF to the breeding habitats or cross contaminate the females that will eventually deliver it to breeding habitat[42]. However, this strategy is likely to be hampered with mass rearing and release of male mosquitoes[42].

The impetus for testing autodissemination approach for malaria vector control was inspired by Itoh and others who first showed that *Aedes aegypti* mosquitoes can be co-opted to autodisseminate insecticide[43]. Later on, in Peru, Devine and others convincingly demonstrated a 98% larval mortality and 42–98% adult emergence inhibition, with only 4% coverage of *Aedes aegypti* resting sites with pyriproxyfen[40]. Similar empirical benefits were also documented for Asian tiger mosquito, *Aedes albopictus*[41,44]. The successful demonstration of this novel mosquito assisted-larviciding approach in controlling non-malaria disease vectors has paved the way for investigating its utility for controlling malaria vectors.

The autodissemination technology for malaria control

Large semi-field cage studies have proven the efficacy of autodissemination with pyriproxyfen approach in controlling malaria vectors; *An. gambiae*[45] *An. quadrimaculatus*[46] and *An. arabiensis*[39]. These studies demonstrated that captive population of malaria vectors can successfully pick up the pyriproxyfen particles from contaminated surfaces and retain it until reaching a breeding habitat, where during the oviposition process, they contaminated the breeding habitat and render it unproductive. Using captive and stable self-sustaining populations of *An. arabiensis*, Lwetoijera and others demonstrated that only two clay pots that has been treated once with 10% active ingredient of pyriproxyfen were sufficient to crash the entire population within months of exposure[47]. This impact, that was recorded in a relatively small surface area of approximately 184 m^2 covered by 800 L of water in readily available breeding habitats is likely to have been delivered by a relatively small proportion of blood fed *An. arabiensis* that prefer to rest in clay pots[47]. Under expansive real-life settings, clay pots might compete with other nearby vegetations for resting mosquitoes. To that end, it becomes critical to ensure that purpose-built or contamination stations/devices treated with pyriproxyfen are highly attractive to visiting and resting mosquitoes, and the formulations used are efficacious and optimal to work in ultra-dosage.

There have been concerted efforts to generate highly optimized formulation of pyriproxyfen using microencapsulation technology. Previous analysis has demonstrated that microencapsulation is feasible for formulating insecticides for autodissemination and direct application into the aquatic habitats[48,49]. Some of the advantages offered by this innovative formulation include increased percentage of active ingredient (AI) within the formulation, thus reducing the number of mosquitoes that must be recruited to disseminate effective amounts of the formulation to the breeding habitats. In this way, microencapsulation has potential to increase formulation longevity in the field by protecting the AI from degradation by ultraviolet light, and reduce amount of insecticide and frequency of treating the autodissemination stations.

Moreover, electrostatic coating technology can be employed in the dissemination devices to increase the proportion of particles adhered to a mosquito's body[50]. The technology has already been used in pest control, for example in controlling sweet potato whitefly (*Bemisia tabaci*)[51]. In addition, electrostatic technology has been proved to increase the amount of insecticides particles taken by a single mosquito, enhancing bioavailability, and therefore a lower dose can be effective against mosquito consequently breaking resistance[50].

Furthermore, numerous prototypes of autodissemination devices are being developed and tested for their efficacy in controlling vector population. Performance of a novel autodissemination station/device might depend on the attractiveness of the station to mosquitoes; pick-up rate of chemical by the mosquitoes as well as dissemination of picked chemicals to targeted breeding habitats[41]. It will also be worth considering device design with no/or minimal maintenance requirements, low cost and low risk to people who might come in contact with it[41]. Consideration has been made with regard to the mentioned factors for a good autodissemination device; for example the development of In2Care® trap[52], and promising results from the assessment of its efficacy in controlling *Aedes aegypti* and *Aedes albopticus* population in both semi-field and field evaluation settings[53–55]. Most of the autodissemination devices have been designed and tested for mosquito species other than *Anopheles* species[56,57].

With good performance in controlling *Aedes* mosquitoes, it's important to test the effectiveness of these available autodissemination devices in controlling malaria vectors. Lwetoijera and others used the clay pots as the autodissemination devices in semi-field settings for *An. arabiensis*[39]. Worryingly, the clay pots are fragile and impractical for large-scale deployment, but also faces competition from other resting sites in the field environment, which necessitate a new design that is more attractive to resting mosquitoes.

Owing to the paucity of breeding habitats during dry season, the application of autodissemination approach at this time point is likely to deliver desired impact[58–60]. Because mosquito abundance during dry season is low[59,61], the effectiveness of autodissemination approach, items of delivering lethal dosage of pyriproxyfen to breeding habitats, is likely to be achieved *via* multiple visits of gravid mosquitoes to the breeding habitats during sequential egg laying cycles by targeted *Anopheles* species[62]. In addition, *Culex* mosquitoes that often share breeding habitats with Anopheles have potential to improve coverage of the target breeding habitats with pyriproxyfen[59,63].

Despite high mosquito densities associated with rainy season, application of autodissemination is likely to be impractical due to plethora and expansive nature of the breeding habitats in which the lethal concentration of pyriproxyfen cannot be achieved[62,64]. Failure to achieve lethal concentrations at the habitats might amplify pyrethroid resistance in mosquito population exposed to sub-lethal dosage of pyriproxyfen[65]. Table 1 summarizes studies on use of autodissemination with different IGR for malaria vector control.

The autodissemination technology over conventional larviciding

Conventional larviciding with biological larvicides has worked best as a complementary malaria control intervention[60]. Implementation of the larviciding program in several sub-Saharan African countries has greatly reduced the malaria burden[12]. For effective larviciding, WHO recommends, application to be done in areas where larval habitats are fixed, few, and findable, often found in urban settings[9]. Hence, numerous breeding habitats that are often scattered and hard to locate have remained as major challenges for larviciding programs in peri-urban and rural settings[14,66]. Even with strong political will, effective community engagement and participation, some of these operational challenges might not be fully addressed. As solution options, the use of unmanned aerial vehicles (UAVs) to identify breeding habitats for larviciding at wider scales is increasingly proposed[67–69]. However, long processing time and technical skills required to operate UAV and handle generated data, and the need to map all the targeted breeding habitats may hamper the scale-up of this approach[68,70].

Alternatively, autodissemination with pyriproxyfen has the potential to complement conventional larviciding through coverage amplification of cryptic, myriad and hard to reach breeding habitats[71,72]. As promising as it may sound, significant and cost-effective contribution of combining the two approaches, its impact on entomological and epidemiological disease outcomes highlights the gaps that needs to be explored.

Pyriproxyfen as the biorational pesticides for autodissemination approach

Pyriproxyfen is a juvenile hormone analog, that interferes with the metamorphosis of mosquitoes and therefore prevents

Table 1. List of studies on autodissemination technology with different insect growth regulator (IGR) for controlling different malaria vectors.

SN	Study	Country	Method details	Year	Target mosquito Species	Insect growth regulator	Conclusion	References
1	Autodissemination of pyriproxyfen suppresses stable populations of *Anopheles arabiensis* under semi-controlled settings	Tanzania	Semi field experiment	2019	*An. arabiensis*	Pyriproxyfen	Suppression of stable populations of malaria vectors using a small number of simple autodissemination devices.	47
2	Effective autodissemination of pyriproxyfen to breeding sites by the exophilic malaria vector *Anopheles arabiensis* in semi-field settings in Tanzania	Tanzania	Semi field experiment	2014	*An. arabiensis*	Pyriproxyfen	*Anopheles arabiensis* effectively autodisseminated PPF to breeding habitats	39
3	Predicting Scenarios for Successful Autodissemination of Pyriproxyfen by Malaria Vectors from Their Resting Sites to Aquatic Habitats; Description and Simulation Analysis of a Field-Parameterizable Model	Tanzania	Mathematical Modelling	2015	Not assessed	Pyriproxyfen	Autodissemination technology can effectively eliminate malaria transmission s during the dry season with effective contamination of aquatic habitats and retain PPF activity for one week	64
4	Testing a pyriproxyfen auto-dissemination station attractive to gravid *Anopheles gambiae* sensu stricto for the development of a novel attract-release-and-kill strategy for malaria vector control	Kenya	Semi field experiment	2019	*Anopheles gambiae s.s*	Pyriproxyfen	Designed bait stations successfully attracted gravid females which were subsequently dusted with effective levels of PPF.	45
5	Development of an autodissemination strategy for the deployment of novel control agents targeting the common malaria mosquito, *Anopheles quadrimaculatus say* (Diptera: Culicidae)	USA	Semi field experiment	2018	*Anopheles quadrimaculatus*	Pyriproxyfen, Triflumuron and Novaluron	Autodissemination approaches with novaluron may be a suitable tool to manage *Anopheles* populations	46

adult emergence[73] with an additional benefit of sterilizing female mosquitoes[74–76]. A miniscule PPF amount of 50 ppb has been approved for mosquito control. This amount is six times below the maximum recommended limit of 300 ppb in drinking water[77]. Among other factors, low mammalian toxicity, safety to aquatic organisms[78,79] and a long-term persistency up to 6 months in the field breeding habitats[80], makes the use of PPF in larviciding programs advantageous.

Pyrethroid resistance to malaria vectors has been reported to be mostly of metabolic origin[3,4]. Despite that PPF is being metabolized in a same way as pyrethroids[81,82], and no evidence of resistance development in malaria vectors against PPF has been documented[83]. However, there is a need to closely monitor resistance of this novel larvicide[82].

Potential integration to current malaria interventions

Autodissemination (mosquito-assisted larviciding) has the potential to complement the existing frontline malaria interventions in rural and urban settings. LLINs and IRS have contributed nearly 40% of the 57% reduction in incidence of clinical diseases, representing over 81% relative contribution to the success in malaria control for the past two decades[1] and 23% reduction in child mortality across most endemic sub-Saharan countries[84]. These assuring progresses has further fueled the development of next generation LLINs and chemistries for IRS to ensure its usefulness against resistant mosquito populations[85–87].

The use of autodissemination with pyriproxyfen has potential to complement these tools by controlling mosquitoes at its breeding habitats. Convincingly, the use of pyriproxyfen *via* conventional larviciding has already demonstrated effectiveness in preventing emergence of *An. arabiensis* and *An. funestus* at experimental scale in the field settings[88,89]. Pyriproxyfen can also sterilize adult malaria vectors through contact with treated nets, such as Olyset Duo nets[90–92], offering a promising opportunity to control insecticide resistant mosquitoes[92,93].

Of importance, it has been demonstrated that sterilized mosquitoes can still transfer PPF sufficient to prevent adult emergence at the contaminated habitats[94]. This development, highlights the unique complementarity of autodissemination with bednets co-treated with pyriproxyfen. At population level, mosquito will be sterilized following exposure to LLINs treated with PPF, and inhibited from emerging at breeding habitats. A semi field-study by Swale and others demonstrated that *An. quadrimaculatus* can deliver a sufficient novaluron, a chitin synthesis inhibitor, to its breeding habitats via autodissemination approach and cause adult emergence inhibition[46]. Until recent, major malaria vectors *An. arabiensis*, *An. gambiae* and *An. funestus* under semi-field settings have proven to be susceptible to novaluron[95]. Furthermore, it is extremely important that future research should look at the possibility to other explore alternative IGRs that could be used for autodissemination approach in rotation with pyriproxyfen.Habitat-based modelling by Gu and Novak highlighted that in order to combat malaria in Africa, larval interventions should be focused in identifying and targeting prolific habitats[96], a task that might be accomplished with near perfection using autodissemination approach, based on the evidence that gravid mosquitoes know better their most preferred habitats[71,72]. Hence, it is our expectation that eventual deployment of autodissemination with pyriproxyfen might further accelerate these control efforts by amplifying the coverage of pyriproxyfen to the productive breeding habitats. While studies to demonstrate the entomological impact of autodissemination with pyriproxyfen under field settings where LLINs are widely used are ongoing, future trials should also aim to establish the combined impact of autodissemination and LLINs and/or other interventions to understand whether the overall effect would be synergistic, additive, or antagonistic.

Autodissemination technology itself as a novel vector control tool, can be integrated with other malaria intervention in a cost-effective way. Autodissemination with PPF can contribute to tools box for controlling *Anopheles stephensi* in urban settings. Since its first report in Djibouti[97], *An. stephensi* has spread to Ethiopia, Somalia and Sudan and Nigeria[2] and more recently in Kenya (E. Ochomo, unpublished report). Similar to *Aedes* mosquitoes, *An. stephensi* mostly breed in man-made water storage containers and discarded wastes[98]. Successful establishment of this species in urban settings, where discarded wastes are ubiquitous and poorly managed, will pose great challenge to malaria control efforts. The geo-statistical model predicted the "worst case scenario" where by more than 126 million people residing in African cities will be at risk of contracting malaria if no action is taken[99]. Scientists have argued that, instead of addressing the threat as stand alone, it's important to use integrated response that can also target other malaria vectors, and hence proper utilization of resources to fit different contexts[100]. Similar to the successes made in controlling *Aedes* mosquitoes using autodissemination with pyriproxyfen elsewhere[101], this approach is well suited and can be effectively integrated into conventional larviciding programs to specifically target breeding habitats of *An. stephensi*. This approach might be more applicable and cost-effective in urban settings with low transmission and where widespread use of LLINs is unjustified[102].

Impact of community involvement in malaria control should never be underrated. Strong collaboration amongst different experts, including affected communities, is necessary for effective malaria control[103]. The sensitive role of the community in mosquito control is well documented[104,105]. Similar to other malaria interventions, scaling up autodissemination technology shall strongly need community participation, to get the desired impact. However, the evidence of engaging communities with regards to PPF-based studies is limited and therefore needs to be explored[106].

Because the autodissemination stations will be placed outside near human dwellings, raising awareness to the community on the safety of PPF to humans especially children that might come into contact with the stations is critical. Contamination of the environments, including human and animal drinking water with PPF deposited by contaminated mosquitoes, will also necessitate community involvement, approval and ownership of the autodissemination approach in their locality.

The autodissemination technology will be deployed in parallel with environmental cleaning that will not only reduce vegetations exploited by resting mosquitoes, but also maximize mosquito resting time in the provided autodissemination stations. For this reason, it will be important to encourage and empower communities with trainings on household environmental cleaning that will directly reduce mosquito densities and associated bites[107].

Conclusion

Evidences supporting the future use of autodissemination approach with pyriproxyfen for malaria control are increasingly documented but more studies on field validation of this approach to formulate its target product profile are required. Among factors that should be looked at include scalable autodissemination devices with potential to target wide range of *Anopheles* behavior such as mating, host-seeking, resting and oviposition. Moreover, effective PPF formulations that not only can be easily picked and off-loaded with mosquitoes, but also permit extended persistence at different application surfaces of autodissemination devices and in different water quality (polluted/unpolluted) of breeding habitats is critical for the success of autodissemination approach.

Ethical approval
The Institutional Review Board of the Ifakara Health Institute (IHI/IRB/EXT/No: 17-2022) and the Medical Research Coordination Committee of the National Institute for Medical Research in Tanzania (NIMR/HQ/R.8c/Vol.I /2235) approved the study.

Data availability
No data are associated with this article.

Authors' contributions
DWL and ATM conceptualized the idea, curated the reviewed articles, wrote the original review and approved the final review version.

Augustino Thabiti Mmbaga: *Conceptualization, Data Curation, Writing – Original Draft Preparation*

Dickson Wilson Lwetoijera: *Conceptualization, Data Curation, Writing – Original Draft Preparation*

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The article is relevant and important in the current context of malaria elimination goals. A well-written article. There are two technical queries and a few typographical suggestions which have been highlighted.

Technical:

- The authors on page 6 para 2 have mentioned that larviciding with PPF and adult control through PPF-treated LLIN will complement each other. Will exposure at both stages not enhance the development of resistance especially given the fact that pyrethroid resistance will be affected? Please clarify.

- Para 2 on the same page, the authors have commented that larval interventions should be focussed...a task that might be accomplished using autodissemination, please clarify how this will be achieved?

- Conclusion - line 5 - Among factors that should be looked at include scalable autodissemination devices...to target wide range of Anopheles behaviour - can the authors explain which behaviour they are referring to?

Typographical:

The article is well written, however, a few minor typographical corrections are needed. which are as under:

1. Abstract: sentence three needs to be amended with the addition of word inhibition - The autodissemination technology as a lure and release...adult emergence [inhibition].

2. Page 3, Introduction: subheading- "The autodissemination approach" - Please italicize *Aedes albopictus*. Please add ref to the statement that "Limited evidence suggests that adult *Aedes albopictus* males could deliver..."

3. Page 3, Introduction subheading- "The autodissemination technology for malaria control" -

Please amend the sentence, "These studies demonstrated...particles from contaminated..., they contaminate..."

4. Page 4, para 4- last line design that is "more attractive" instead of "attractiveness".
5. Page 4 second column first para - line 7 - "*Anopheles* species" (instead of "specie"); line 8 - "*Anopheles* have" instead of "has"
6. Page 4 second column second para - line 1 delete "of" after despite; delete "below" after Table 1.
7. Page 4 second column third para - line 9 after "remained" delete "to be" and "add as".
8. Page 4 second column fourth para - line 5 "impact of" should be - "impact on".
9. Page 5 second column - line 5 instead of "contribute" it should be "contribution".
10. Page 6 para 2 - line 12 - it should be "highlights" instead of "highlight"; para 3 line 4 - it should be "near perfection" and not "nearly"; line 5 it should be "expectation" and not "expectations"; para 4 line 2 amend can be integrated with other instead of into other; same para line 16 - remove colon after "scientists have argued that".
11. Page 6 second column first para - last line - add "use after widespread"; second para rephrase second sentence to make it more clear - "Malaria control needs..."

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vector borne diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 Oct 2023

Dickson Wilson Lwetoijera

We thank the reviewer for their thoughtful and constructive comments on this manuscript. In the revised version, we have made the following changes and possible clarifications on technical queries and typographical suggestions as per the reviewers' comments.

Technical

Comment 1: The authors on page 6 para 2 have mentioned that larviciding with PPF and adult control through PPF-treated LLIN will complement each other. Will exposure at both stages not enhance the development of resistance especially given the fact that pyrethroid resistance will be affected? Please clarify.

Response: At the population level, mosquitoes will be sterilized following exposure to LLINs treated with PPF and will be inhibited from emerging in breeding habitats. To date, there is limited evidence on the effect of PPF on pyrethroid resistance; a previous study exploring the effect of sub-lethal PPF doses on pyrethroid resistance in *Anopheles arabiensis* was only performed for a single generation, which makes it unclear whether the observable magnification of pyrethroid resistance is just tolerance or actual resistance that can be inherited over multiple generations.

Comment 2: Tilak: Para 2 on the same page, the authors have commented that larval interventions should be focussed a task that might be accomplished using autodissemination, please clarify how this will be achieved?.

Response: A task that might be accomplished with near perfection using autodissemination approach, based on the evidence that gravid mosquitoes know better their most preferred habitats

Comment 3: Conclusion - line 5 - Among factors that should be looked at include scalable autodissemination devices...to target wide range of Anopheles behaviour - can the authors explain which behaviour they are referring to?

Response: In the line 5 of conclusion section, the Anopheles behaviors that the authors referred to were mating, host-seeking, resting, and oviposition.

Typographical

Comment 1: Abstract: sentence three needs to be amended with the addition of word inhibition - The autodissemination technology as a lure and release...adult emergence [inhibition].

Response: The word "inhibition" has been added in sentence three of the abstract, which now reads "The autodissemination technology as a "lure and release" strategy works by exploiting the resting behavior of gravid mosquitoes to transfer lethal concentration of biological or chemical insecticide such as pyriproxyfen (PPF), an insect growth regulator (IGRs) to their oviposition sites and result in adult emergence inhibition".

Comment 2: Page 3, Introduction: subheading- "The autodissemination approach" - Please italicize Aedes albopictus. Please add ref to the statement that "Limited evidence suggests that adult Aedes albopictus males could deliver..."

Response: The Species name *Aedes albopictus* has been italicized. Also, the article by Mains et al., 2015 has been added as a reference for the sentence that reads "Limited evidence suggests that adult *Aedes albopictus* male could directly deliver PPF to the breeding habitats or cross contaminate the females that will eventually deliver it to breeding habitat (Mains et al., 2015).

Comment 3: Page 3, Introduction subheading- "The autodissemination technology for malaria control" - Please amend the sentence, "These studies demonstrated...particles from contaminated..., they contaminate...".

Response: The word "contamination" has been replaced with "contaminated" and "contaminated" replaced with "contaminate" in the introduction subheading section, page 3.

Comment 4: Page 4, para 4- last line design that is "more attractive" instead of "attractiveness".

Response: On page 4, para 4 – last line, the word "attractiveness" has been replaced with "attractive". Now the sentence reads "Worryingly, the clay pots are fragile and impractical for large-scale deployment but also face competition from other resting sites in the field environment, which necessitate a new design that is more attractive to resting mosquitoes.

Comment 5: Page 4 second column first para - line 7 - "Anopheles species" (instead of "specie"); line 8 - "Anopheles have" instead of "has".

Response: The word "specie" has been replaced with "species". Also, the word "has" has been replaced with "have" in page 4 second column fist para – line 7 as suggested by the reviewer.

Comment 6: Page 4 second column second para - line 1 delete "of" after despite; delete "below" after Table 1.

Response: On page 4 second column second para - line 1, the words "of" and "below" have been deleted.

Comment 7: Page 4 second column third para - line 9 after "remained" delete "to be" and "add as".

Response: On page 4 second column third para - line 9, the words "to be" have been replaced with "as"

Comment 8: Page 4 second column fourth para - line 5 "impact of" should be - "impact on".

Response: On Page 4 second column fourth para - line 5, the word "on" has replaced "of"

Comment 9: Page 5 second column - line 5 instead of "contribute" it should be "contribution".

Response: On Page 5 second column - line 5, the word "contribution" has replaced "contribute"

Comment 10: Page 6 para 2 - line 12 - it should be "highlights" instead of "highlight"; para 3 line 4 - it should be "near perfection" and not "nearly"; line 5 it should be "expectation" and not "expectations"; para 4 line 2 amend can be integrated with other instead of into other; same para line 16 - remove colon after "scientists have argued that".

Response: In the Page 6 para 2 - line 12, the word "highlights" has been added to replace "highlight"; para 3 line 4 the word "nearly" has been replaced with "near"; on line 5 the word "expectations" has been replaced by "expectation"; also, on the para 4 line 2 the colon has been removed as suggested.

Comment 11: Page 6 second column first para - last line - add "use after widespread"; second para rephrase second sentence to make it more clear - "Malaria control needs..."

Response: The sentence has been paraphrased to read "Strong collaboration amongst different experts, including affected communities, is necessary for effective malaria control" instead of "Malaria control needs strong collaboration among different expertise including the target communities"

Competing Interests: No competing interests were disclosed.

Reviewer Report 10 July 2023

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The review by Mmbaga and Lwetoijera offers a thorough and impactful overview of the benefits, drawbacks, present and future potential of the autodissemination of pyriproxyfen approach for malaria vector control in both urban and rural regions of Africa. This manuscript is captivating, well-organized, and exemplifies excellent writing with properly referenced statements and a compelling conclusion. The use of autodissemination methods employing insect growth regulators (IGRs) has gained significant interest, demonstrating efficacy in controlling *Aedes* mosquitoes in various field and semi-field settings. However, limited information exists regarding its effectiveness against Anopheline mosquitoes. This review presents updated information on the autodissemination of pyriproxyfen approach for malaria vector control in urban and rural Africa. The authors emphasize the importance of key factors such as the development of scalable autodissemination devices, optimized PPF formulations, assessment of integration with existing conventional larviciding methods, and community perception and acceptance of the autodissemination approach for successful implementation at a larger scale. The manuscript is well written, statements are referenced as required and appropriate conclusion provided.

Minor comments:

1. Please consider italicizing the genus and species names: "Anopheles" on Page 4, line 8, and References 6, 7, and 39; "Aedes" on Page 3, line 16, and Reference 43.

2. Additionally, there is a study by Okazawa *et al.* (1991)[1] that demonstrates the efficacy of PPF in inhibiting adult emergence of *Anopheles punctulatus*.

3. It would be worthwhile to investigate the presence of evidence supporting the effectiveness of PPF in controlling insecticide-resistant mosquitoes.

4. Considering the reported ineffectiveness of PPF for *An. quadrimaculatus* (Swale *et al.* 2018), it would be valuable to explore alternative IGRs as potential options for controlling insecticide-resistant mosquitoes.

References

1. Okazawa T, Bakote'e B, Suzuki H, Kawada H, et al.: Field evaluation of an insect growth regulator, pyriproxyfen, against Anopheles punctulatus on north Guadalcanal, Solomon Islands.*J Am Mosq Control Assoc*. 1991; **7** (4): 604-7 PubMed Abstract
2. Swale DR, Li Z, Kraft JZ, Healy K, et al.: Development of an autodissemination strategy for the deployment of novel control agents targeting the common malaria mosquito, Anopheles quadrimaculatus say (Diptera: Culicidae).*PLoS Negl Trop Dis*. 2018; **12** (4): e0006259 PubMed Abstract | Publisher Full Text

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Vector ecology, malaria epidemiology, molecular biology, and population genetics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 Oct 2023

Dickson Wilson Lwetoijera

We thank the reviewers for their thoughtful and constructive comments on this manuscript. In the revised version, we have made the following changes and possible clarifications on technical queries and typographical suggestions as per the reviewers' comments.

Comment 1: Please consider italicizing the genus and species names: "Anopheles" on Page 4, line 8, and References 6, 7, and 39; "Aedes" on Page 3, line 16, and Reference 43.

Response: The recommended changes has been made in the revised manuscript.

Comment 2: Additionally, there is a study by Okazawa et al. (1991)1 that demonstrates the efficacy of PPF in inhibiting adult emergence of *Anopheles punctulatus*.

Response: We acknowledge the reviewer for the suggestion to add a study by Okazawa et al. (1991) that demonstrated the efficacy of PPF in inhibiting adult emergence of *Anopheles punctulatus*. However, we did not include the study because it did not involve an autodissemination approach, contrary to the central theme of our review work.

Comment 3: It would be worthwhile to investigate the presence of evidence supporting the effectiveness of PPF in controlling insecticide-resistant mosquitoes.

Response: Evidence supporting the effectiveness of PPF in controlling insecticide-resistant mosquitoes has been discussed and two additional citation have been added. In page 8, sub heading titled potential integration to current malaria intervention, the reference for the sentence "Of importance, it has been demonstrated that sterilized mosquitoes can still transfer PPF sufficient to prevent adult emergence at the contaminated habitats" has been added. H. Kunambi personal communication has been replaced with the actual citation (Kunambi et al., 2023).

Comment 4: Considering the reported ineffectiveness of PPF for *An. quadrimaculatus* (Swale et al. 2018), it would be valuable to explore alternative IGRs as potential options for controlling insecticide-resistant mosquitoes.

Response: A semi field-study by Swale and others demonstrated that *An. quadrimaculatus* can deliver a sufficient novaluron, a chitin synthesis inhibitor, to its breeding habitats via autodissemination approach and cause adult emergence inhibition (Swale et al., 2018). Until recent, major malaria vectors *An. arabiensis, An. gambiae* and *An. funestus* under semi-field settings have proven to be susceptible to novaluron (Ngonzi et al., 2022). Furthermore, it is extremely important that future research should look at the possibility to other explore alternative IGRs that could be used for autodissemination approach in rotation with pyriproxyfen.

Competing Interests: No competing interests were disclosed.

Reviewer Report 21 April 2023

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Oscar Mbare
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Accept

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Malaria ecology, vector biology and vector control

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 April 2023

https://doi.org/10.21956/wellcomeopenres.21208.r55603

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This manuscript provides an overview of the current evidence of the potential role of auto-dissemination for malaria vector control including experiments conducted in the laboratory and large semi-field systems. Importantly, the authors have identified the factors that need to be addressed for successful implementation of the auto-dissemination strategy for control of malaria vectors. The manuscript identifies the need to conduct additional studies to increase the evidence on possible role of auto-dissemination strategy as an effective complementary tool for malaria vector control. The manuscript is well written, statements are referenced as required and appropriate conclusion provided.

Minor issues

1. Page 3 (the sub-title "The autodissemination approach") - Can male *Anopheles* also be targeted for transfer of pyriproxyfen? Probably discuss this in this section of the manuscript. See the article Mains *et al.,* (2015)[1].

2. Page 4 (the sub-title "The autodissemination technology over conventional larviciding") – Replace the word 'full' with 'fully'.

3. Add the article by "Swale et al., 2018 Development of an autodissemination strategy for the deployment of novel control agents targeting the common malaria mosquito, *Anopheles quadrimaculatus* say (Diptera: Culicidae)"[2] to Table 1 on the list of studies on autodissemination technology with different insect growth regulators (IGR) for controlling different malaria vectors.

4. Page 4 - Is the difficulty to identify/develop more attractive oviposition-based traps/dissemination stations another limitation in the use of auto-dissemination approach in the control of malaria vectors?

References

1. Mains JW, Brelsfoard CL, Dobson SL: Male mosquitoes as vehicles for insecticide.*PLoS Negl Trop Dis*. 2015; **9** (1): e0003406 PubMed Abstract | Publisher Full Text
2. Swale DR, Li Z, Kraft JZ, Healy K, et al.: Development of an autodissemination strategy for the deployment of novel control agents targeting the common malaria mosquito, Anopheles quadrimaculatus say (Diptera: Culicidae).*PLoS Negl Trop Dis*. 2018; **12** (4): e0006259 PubMed

Abstract | Publisher Full Text

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Malaria ecology, vector biology and vector control

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Apr 2023

Dickson Wilson Lwetoijera

We do thank a reviewer for comments and construction discussion points, and here are point-by-point responses

Comment 1: Page 3 (the sub-title "The autodissemination approach") - Can male *Anopheles* also be targeted for transfer of pyriproxyfen? Probably discuss this in this section of the manuscript. See the article Mains *et al.,* (2015)[1].

Response: In the revised version we have discussed this point, but also acknowledged its practical limitations, by providing a text "Limited evidence suggests that adult *Aedes albopictus* male could directly deliver PPF to the breeding habitats or cross contaminate the females that will eventually deliver it to breeding habitat. However, this strategy is likely to be hampered with mass rearing and release of male mosquitoes"

Comment 2: Page 4 (the sub-title "The autodissemination technology over conventional larviciding") – Replace the word 'full' with 'fully'.

Response: Revision has been made in the revised version of the article.

Comment 3: Add the article by "Swale *et al.,* 2018 Development of an autodissemination strategy for the deployment of novel control agents targeting the common malaria mosquito, *Anopheles quadrimaculatus* say (Diptera: Culicidae)"[2] to Table 1 on the list of studies on autodissemination technology with different insect growth regulators (IGR) for controlling different malaria vectors.

Response: Thank you for this key observation, in the revised article, we have added the suggested article Swale et al 2018 in Table 1.

Comment 4: Page 4 - Is the difficulty to identify/develop more attractive oviposition-based traps/dissemination stations another limitation in the use of auto-dissemination approach in the control of malaria vectors?

Response: We thank the reviewer for this discussion point, while we acknowledge this to be a challenge, we are also convinced that with appropriate funding and time, that highly attractive device that can effectively contaminate malaria vectors can be designed, as it has been for *Aedes* mosquitoes, and this has been discussed in the article. No changes have been made in the revised version

Competing Interests: No competing interests were disclosed.