

Webinar Q&A

New tools to reach outdoor-biting malaria vectors

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Panelists

Dr Kevin Kobylinski

Principal Investigator, Department of Entomology
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Dr Lina Finda

Research Scientist
Ifakara Health Institute, Republic of Tanzania

Mr Amir Galili

Founder and CEO
Westham Co.

Moderator

Dr. Leo Braack

Technical Lead (APMEN Vector Control Working Group)
Senior Vector Control Specialist (Malaria Consortium)

Question	Mr Amir Galili : Given the differences in the diversity of flowering plants, vegetation ecology and micro-climate between Mali (Sub-Saharan Africa ecosystem) and South East Asia (Tropical and equatorial ecosystem), how would competition for natural plant sugars and ABTS affect the efficacy of ABTS when they are placed in houses or in forested areas with abundant flowering plants in Asia? A recent trial of ATSB in Thailand showed that
Mr Amir Galili	ATSB efficacy relies on the attractiveness of the bait to the target vector. ATSB bait-stations were also tested in sugar rich environments, and although there was some effect of the environment on the feeding rates, the overall efficacy of the bait-stations caused a significant reduction of the vector population numbers even in sugar-rich environments

	Dr Lina Finda : What are the chances of getting PQ-approval of transfluthrin treated materials in the future? what are the next steps regarding safety, public health impact and value, regulatory approvals, scaleup manufacturing and supply-chain pathways? what is the bioassay method would you recommend to test the residual bio-efficacy of transfluthrin-treated materials? Apart from sisal (plant fibre) what other types of materials or surfaces you have tested that showed a high affinity for transfluthrin and a
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	six-month residuality? Using a plastic sheet made of polyethylene terephthalate (PET) (31.3 x 21.6 cm, 676 cm ² surface area) treated with 55 mg of transfluthrin (TFT) AI we only achieved 66% protective efficacy (PE) in SFS enclosure and 20% PE over 30 nights against mosquitoes. Based on your experience I believe that the plastic PET is not an effective treatment platform for delivery of transfluthrin.
Dr Lina Finda	We tried hessian, denim and canvas materials; hessian was the best. The next step for us is to conduct epidemiological assessment as well as more vigorous assessment of safety (AE and SAE) on the users and non-users. We will also conduct cost-effectiveness assessment before we seek approvals for commercial releases.

	is there evidence from the onchocercose prevention campaigns that it has effect on malaria in the regions ?
Dr Kevin Kobylinski	Onchocerciasis MDAs are typically performed in the dry season to clear everyone's blood of microfilariae before the rains come and black fly populations expand. Also, malaria surveys are typically done once per year so would need a before and after survey in control and treated villages to show an effect via onchocerciasis MDAs.

	Dr Kevin: Ivermectin is known for its toxicity. How long one MDA protects human beings from outdoor mosquito bite infections? What should be the frequency of MDAs? Is it cost effective as compared to LLINs ?
Dr Kevin Kobylinski	Mammals lack GluCl target channels found in Anopheles. Ivermectin lacks toxicity in almost all mammal species used in to date with the exception of Collie/Sheepdogs. See Alout et al. 2014 for duration of effect following a single iveremctin MDA. Ivermectin MDAs to humans should ideally be performed once per month during transmission season. No cost effective analysis has been published, but I believe these are underway now

	Dr Kevin: Is MDA an answer to the low transmission areas to fight against malaria to achieve elimination?
Dr Kevin Kobylinski	Lower transmission settings have been modelled to be even more sensitive to ivermectin MDA (Slater et al. 2020)

	Dr Kevin: the human metabolic of ivermectin seems to call for slow release formulation, e g micro encapsulation
Dr Kevin Kobylinski	See Chaccour et al. 2015 for ivermectin implants and Bellinger et al. 2016 for ivermectin expandable pills

	Dr Kevin: Is there any way we can treat macaques with Ivermectin?
Dr Kevin Kobylinski	It is safe to use ivermectin in macaques and it appears that macaques reach much higher concentrations compared to humans (Vanachayangkul et al. 2020). Let me know if you would like to discuss ivermectin bait development further kobylinskikevin@gmail.com

	Dr Kevin: What would be the regularity of retreatment with ivermectin to make it an effective and sustainable alternative intervention? Can ivermectin MDA used in cases where there's no other NTDs thus no dual benefit?
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Dr Kevin Kobylinski	Not sure of any area with malaria without at least one NTD in the same population but if it exists then could still be justified for malaria. Likely once a month is necessary for human MDA to be effective.
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	Dr Kevin: Is there Ivermectin formulation with long lasting effect?
Dr Kevin Kobylinski	Not licensed but expandable pills (Bellinger et al. 2016) and implants (Chaccour et al. 2015) have been developed.

	Dr Kevin: what percentage of coverage during MDA with ivermectin is needed to stop malaria transmission to zero level ?
Dr Kevin Kobylinski	Coverage has been modelled to need >65% (Slater et al. 2020). Combining ivermectin with antimalarial drugs would accelerate time to elimination.

	Dr Kevin: Can Ivermectin use affect milk production? Is there age specific of cattle to be targeted?
Dr Kevin Kobylinski	Ivermectin is not recommended in dairy cattle to avoid consumption by people. Eprinomectin was specifically developed for use in dairy cattle to reduce possibility of milk contamination, eprinomectin is effective against Anopheles. Need to avoid ivermectin use close to slaughter time, called withdrawal period and varies by product. Not sure how well these principles are adhered to in the field. Possible that people ingesting milk or meat with ivermectin could then have sublethal amounts present when fed on by Anopheles. But I think resistance would most likely be driven by longer sublethal tails in treated livestock and exposure to feces in the environment in aquatic habitat.

	Dr Kevin: Have there been any cost-effectiveness analyses for Ivermectin in humans and/or livestock? If so, what are the results?
Dr Kevin Kobylinski	None published to my knowledge but I believe this is underway for the BOHEMIA trial.

	Dr Kevin: with all the publications on Ivermectin the issues are mode of action in mosquito; after half-life of Ivermectin the concentration is very low and what dose is effective against mosquito and finally the experiments done against cows but usually when buffaloes are present, more mosquitoes are found on buffaloes. Ivermectin is well proven drug being used for LF and oncho but the exact mechanism needs to be established
Dr Kevin Kobylinski	Ivermectin targets the glutamate-gated chloride ion channels leading to paralysis of the Anopheles musculature, although I suspect there may be other targets not yet characterized. I recommend use of oral ivermectin at 400 ug/kg in humans. Would be excited to treat buffaloes as well as cattle with ivermectin.

	Dr Kevin: if ivermectin affect to anopheles, does it affect to <i>Aedes</i> ?
Dr Kevin Kobylinski	Unfortunately ivermectin does not affect <i>Aedes</i> at human-relevant concentrations.

	Dr Lina: transfluthrin is a pyrethroid with high vapour pressure providing a repellent effect. Is there a delayed mortality effect that could provide the
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	population effect seems when 60-80 % of houses were protected with treated hessian ?
Dr Lina Finda	Yes. We collected all the mosquitoes that were exposed to the chambers with transfluthrin-treated products. In the semi-field settings, we observed >99% mortality 24 hours later. However, in the field settings the 24-hour mortality was down to 66%. So yes, we have proven that it does provide personal as well as communal protection. With modest improvement this protection should be further improved.

	Dr Lina: What are the resistance profiles of the vectors as pyrethroids resistance is a major issue these days. Also is there any measure on malaria burden or is the evidence all entomology? Thanks.
Dr Lina Finda	So far, the evidence is all entomological. We are still conducting resistance assays on transfluthrin; we had to adapt WHO guidelines for other insecticides as there isn't one specifically for transfluthrin. However, we have tested efficacy of transfluthrin on both resistant and susceptible colonies and they both respond similarly.

	Dr Lina: Is it possible treated the ITN with transfluthrin? and are there any difficulty? e.g. safety?
Dr Lina Finda	Yes. I have been informed by Bayer who manufacture transfluthrin that they have actually tried to impregnate bed nets with transfluthrin and managed to get slow releases that lasted up to five years. However we have not tested these at Ifakara Health Institute.

	Dr Lina: Any reason why there's low protective efficacy of the transfluthrin-treated accessories/products against the non-malaria vectors; Culex, Aedes? Is that a difference vector behavior factor?
Dr Lina Finda	We are not sure the efficacy is consistently low against Culex and Aedes mosquitoes, but we are exploring different options on how to improve the efficacy against non-malaria vectors.

	Dr Lina: Is transfluthrin treated products different from IRS?
Dr Lina Finda	They are different. We are using transfluthrin primarily as a spatial repellent, although it still has killing effects upon contact. Its high volatility means that it vaporises easily especially on higher temperatures, so it can repel and kill mosquitoes without contact. IRS mainly kills mosquitoes through contact.

	Dr Lina: Is it possible treated the ITN with transfluthrin? and are there any difficulty? e.g. safety?
Dr Lina Finda	It is possible. Bed nets impregnated (not coated) with transfluthrin have shown high efficacy and maintained the efficacy for up to 5 years, and the risk assessment was okay, not different than other LLINs. However, we have not tested this at Ifakara Health Institute.

	Dr Lina: How often do we have to impregnate the ribbons and chairs?
Dr Lina Finda	We propose retreatment or replacement every 6 months.

	Dr Lina: Interesting presentation on transfluthrin products, what risk assessments have been done to ensure that the proposed products are safe to use?
Dr Lina Finda	Contact, ingestion and inhalation tests have been done on different products, and the results are not too different from other insecticides in their categories. However, we have designed our products so that we minimize the risks by creating barriers between the treated fabrics and skin, or in terms of ribbons, putting them under the chairs or on top of the walls (below the roof).

	Dr Lina: How/ which transfluthrin-treated product can be applied to forest-going mobile and migrant populations?
Dr Lina Finda	Transfluthrin-treated ribbons would be the best options as these can be used anywhere. Treated shoes could also be good in providing personal protection.

	Dr Lina: what is the cost effective findings of transfluthrin coated strips/ products used in your area ?
Dr Lina Finda	We have not conducted cost-effectiveness analyses yet, but currently the ribbons cost ~7USD to make, and the sandals cost between 2.2 USD and 9.4 USD to make, depending on the quality.

	Dr Lina: Have you tested the safety in regards to inhalation due to prolonged, even if minimal, transfluthrin fume exposure?
Dr Lina Finda	IVCC did conduct safety assessment of transfluthrin (for sandals), and they were considered safe for experimental purposes. Bayer has also conducted safety assessment on different transfluthrin-treated products and they are all okay. We have not assessed the ribbons or strips put in chairs, but that is in the planning.

	Dr Lina: In term of effectiveness and remanence, how much time these products last?
Dr Lina Finda	They maintain >90% efficacy for up to six months, then efficacy starts to gradually decline. Previous studies indicated that the ribbons maintained efficacy of up to 90% for 12 months, depending on the concentration of transfluthrin. However, we recommend retreatment or replacement of the products every 6 months.

	Dr Lina: Do you ever test for Aedes mosquitoes with transfluthrin strips/ ribbon??
Dr Lina Finda	We have, and the efficacy is consistently lower with Aedes mosquitoes. We are investigating different options on improving efficacy on Aedes and other non-malaria vectors.

	Dr Lina: Are hessian/sisal strips the most effective carrier materials for infusing the transfluthrin pyrethroid, have you tested other products as well?
Dr Lina Finda	Yes, we tried canvas and denim materials, but the best substrate was hessian due to its high capacity to absorb and release transfluthrin. It is also of a lower cost and more locally available.

	Dr Lina: Thank u for a wonderful presentation. I have done outdoor transmission study in 2015-2016 in the Philippines and it the investigation of possible controls that i have not had time to look into. Your presentation is an inspiration to pursue this some more as people do tend to forego use of LLIN in transient agriculture areas in the mountains.
Dr Lina Finda	I am happy to hear that. Yes, the products we are making are really designed to provide relief in situations where most other vector control tools cannot work.

	Dr Lina: If effective good idea to try these transfluthrin strips to hammocks which are used by forest goers in the Mekong region.
Dr Lina Finda	I think they would work perfectly in hammocks, I would propose that you put them on the out-side to minimize direct contact with skin. Do let us know if you need any help testing these.

	Dr Lina: Is it repellency or mortality that caused the reduction in the number of mosquitoes collected. Will resistance to other groups of pyrethroid alter the effect.
Dr Lina Finda	Transfluthrin works about the same on mosquitoes that are susceptible or resistant to other pyrethroids. However, we are currently working to establish a resistance profile of transfluthrin to the major mosquito species in our settings. In terms of mortality effects, transfluthrin did cause 100% 24-hour mortality on malaria vectors that were exposed in semi-field settings and ~66% 24-hour mortality in the field settings.

	Dr Lina. Thank you for this very nice presentation.in Kenya we have a lot of mosquitoes biting people especially going about their activities like farming and trading. What would be the options to protect themselves?
Dr Lina Finda	We believe any of the products we have could work well with the migrant communities. We would be more than happy to work with you if you would like to test any of the products we have in your settings.

	Dr Lina: What is the current resistance status of the transfluthrin in malaria vectors? Is there a risk of resulting in high selection pressure for resistance if it is used along LLINs? and how this can be mitigated?
Dr Lina Finda	We are just now testing this.

	Dr. Lina: I have noticed that creating the table/chairs impregnated with transfluthrin, and placed it outdoors. Have you considered transfluthrin being drainages from those impregnated products by rain, and how is its efficacy after 1st/2nd time exposing to rain?
Dr Lina Finda	The products have maintained more than 90% efficacy for over six months of exposure in the sun and rain. Tranfluthrin is not water soluble, so we also anticipate that it does not drain too much in the rain. We also tested wash effects on sandals where we washed and dried them up to seven times, and they maintained 100% of their initial protective efficacy.

	Mr Amir: the ATSB targets are they rain safe ?
Dr Kevin Kobylinski	
Dr Lina Finda	

<i>Derric Nimmo from IVCC and answering for Amir</i>	Derric Nimmo from IVCC and answering for Amir as we are collaborating on this project. Yes, durability studies have been performed over 6 months and even when fully exposed to the elements, rain, sun, wind etc., they remain intact and continue to perform well in feeding and killing studies with mosquitoes.
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	Mr Amir: Is there any efficacy loss of ATSB especially spraying bushes during heavy rain fall??
Mr Amir Galili	Although we added adhesive materials to the bait, rainy conditions will definitely have an effect on ATSB spray and would probably necessitate a second application. Rain does not pose a problem when ATSB stations are used as the bait is protected from the environment.

	Mr Amir: Is the efficacy of the ATSB affected by the number of other sugar sources around the home or wherever the ATSB is positioned?
Mr Amir Galili	See my answer above.

	Mr Amir: I am from Kenya and i would be more interested in what you are doing since i have seen u have trials in Kenya. how can i get to know more about your product.
Mr Amir Galili	You are welcome to view our website - www.westhamco.com

	Mr Amir: what is the attractive effect of ATSB in the presence of other bait e.g. Human being? could mosquitoes prefer ATSB even in the presence of human?
Mr Amir Galili	ATSB attracts male and female mosquitoes seeking sugar to supplement their energy requirements. Female mosquitoes looking for blood will prefer blood hosts to sugar.

	Mr Amir: Why not use he baits indoors? This would avoid adverse effects on non-target insects. (a mosquito unable to feed on a host in a net may then feed on sugar if they cannot get blood)?
Mr Amir Galili	Although our current project is aimed to assess outdoor vector control, we also believe that indoor control will be simpler and is suitable for the ATSB method.

	Mr Amir: Amir's presentation is very nice but could you explain the difference on impact on Aedes vs malaria vector both during its use as station bait and as spraying?
Mr Amir Galili	Most of our experience with Aedes mosquitoes is using ATSB spray application (although a limited number of experiments using bait-stations were conducted in the US). The ATSB stations targeting Aedes mosquitoes will have a different geometry and different application strategy, mainly pertaining to the height and locations of deployment

	Mr Amir: Are the sugar baits tested against all species of the major exophilic vectors?
Mr Amir Galili	We tested it against Culex (pipiens and quinquefasciatus), Aedes albopictus and various Anopheles sp. mosquitoes.

	Mr Amir: Do you expect behavior resistance in the way that was observed with cockroaches avoiding the traps?
Mr Amir Galili	We expect behavioral resistance to occur in the same manner as insecticide resistance mosquitoes which are less responsive to the plant-based attractant will be less affected, and may become the prevailing population. We have several types of plant attractants in development, and plan to alternate between different attractants if this becomes a problem.

	Mr Amir : As the ecology and vegetation between Mali and SE Asia are different could you elaborate on competition for natural plant sugars and ABTS which may compromise the efficacy of ABTS?
Mr Amir Galili	See my answer above.

	Dr Kevin: In Papua New Guinea pigs are the main domestic animal. Has Ivermectin been used with pigs?
Dr Kevin Kobylinski	Yes, ivermectin is frequently used in pigs. Pharmacokinetics in pigs is different from cattle, as residence time is much shorter so reduced duration of Anopheles lethal efficacy. For standard ivermectin, pigs are treated with 300 ug/kg while cattle 200 ug/kg. Can also use long-lasting formulations in pigs.

	Mr Amir: Is ATSB safe to other insects attracted by its component? Will it be safe for other sugar eating creatures?
Mr Amir Galili	Bitterx was added to the bait in order to deter mammals from feeding on the station. Only insects with slender piercing mouthparts can feed through the perforated membrane, and as such, is safe for non-target insects and pollinators

	Dr Lina: Have you compared transfluthrin with metafluthrin?
Dr Lina Finda	We have not, but we have a new project coming where we plan to compare a number of other products, metafluthrin is one of them.

	Mr Amir: In the SSA trial for ATSB how will you consider the impact of vegetation as it may compete with the ATSB stations?
Mr Amir Galili	See my answers above.

	Dr Lina: What are the chances of getting PQ-approval of transfluthrin treated materials in the future? what else need to be done?
Dr Lina Finda	I am not sure for now. We are still conducting entomological assessment for most of the products, but they are all quite promising.

	Dr Lina: thanks for the fascinating presentation. Have you tested the boots and slippers with the forest goers or night time workers in the forest? How relevant are they, and how long will it take to protect individuals wearing them?
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Dr Lina Finda	We have not tried with forest workers but we have tested them in communities with migrant rice farmers. They provide protection right away, though not as high as the transfluthrin-treated ribbons. I suppose due to the small size and amount of transfluthrin in sandals, they are best at providing personal than communal protection. Like all the other products we have, they maintain more than 90% of their initial protective efficacy for at least six months.
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	Mr Amir: How to keep a bait not dry for long time?
Mr Amir Galili	High sugar content prevents complete desiccation of the bait formulation. Mosquitoes continue feeding on the bait even after reaching lowest water content, without significant reductions in feeding rates

	Dr Lina: Answers directed to Lina about whether any of the products are already registered and ready for commercialization. All products are yet to be commercialized. But, discussion and process toward that is ongoing.
Dr Lina Finda	The products are still under investigation, none are commercially available for now.

	Dr Lina: How did you assess the efficacy of the transfluthrin on the sandals
Dr Lina Finda	In the semi-field settings, we had one volunteer wearing transfluthrin-treated sandals sit in one chamber and another wearing untreated sandals (control) sit in a separate but identical chamber and we released lab-reared mosquitoes, and assessed how many were collected using human landing catches method. In the field settings we had volunteers wearing treated or untreated sandals sit inside exposure-free double net traps, and we collected mosquitoes that were trapped.

	Dr Lina: Since malaria transmission is expected to be higher in the rainy season, how does exposure to rains affect the strips? Has you evaluated this?
Dr Lina Finda	We have tried to wash the strips up to seven times (exposing them to water, sun and detergent) and they have maintained 100% their initial protective efficacy. Also we maintained their protective efficacy for six months during which three were rainy season, and they maintained over 90% of the initial protective efficacy.

	Mr Amir: honey bee go for flowers as visual stimuli, but other insects that pick sugar from aphids and excludes from plants, how will they be affected ?
Mr Amir Galili	Only insects with slender piercing mouthparts can feed through the perforated membrane, and as such, is safe for non-target insects and pollinators

	Dr Kevin: Your research shows that intervention using Ivermectin effectively reduce mosquitoes' longevity, an important factor in vectorial capacity. Can these results be generalized to malaria vectors in other countries? Thank you.
Dr Kevin Kobylinski	Yes, hopefully! All Anopheles evaluated to date are susceptible to ivermectin at human and animal- relevant concentrations so this should

	translate to effectiveness with mass treatment in most settings assuming vector preference and treated host matches correctly.
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	Dr Kevin. Considering the half-life of ivermectin in human and cattle and also the acceptability, do u suggest use of ivermectin in cattle than human for vector population control
Dr Kevin Kobylinski	I urge people to use ivermectin in both humans and livestock or humans alone. The main concern using ivermectin in livestock alone is that we may select for mosquitoes that are more likely to feed on people.

	Dr Lina: Some of the products that you show in your presentation, are in very close contact to the skin, are there any chance of the control agent would be absorbed through the skin?; have you see any allergy reaction?
Dr Lina Finda	Only sandals are products that are worn by people, and there's a layer of leather between the skin and the treated fabric. In terms of chairs, the treated fabric is put under a chair where there's no contact with skin. The ribbons or decorations are also placed where there's no direct contact with people.

	Dr Lina: What is the impact of transluthrin against ticks, mites and fleas?
Dr Lina Finda	We have not investigated their impact on other insects. We are also using such low dosage that we have only tested on mosquitoes.

APMEN would like to thank all of our panelists for their time and sharing their knowledge.

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