Vector Control Product Development Pathway:

Phase-Dependent Evidence Gathering

A Workshop Organized by the
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases/National Institutes of Health
June 24-25, 2019

Meeting Report

NIH National Institute of Allergy and Infectious Diseases

Table of Contents

Executive Summary

Background

As global progress toward malaria eradication stalls and other vector-borne disease outbreaks continue to pose substantial public health threats, there is an urgent need for new and improved vector control tools. At the same time, the evidence base for evaluating vector control tools is extremely limited. Many developers rely on the World Health Organization (WHO) to evaluate and recommend vector control interventions. This workshop was organized to address the need to better understand the data requirements for each phase of product testing, including laboratory and pre-field studies (Phase I), small-scale field studies (Phase II), and large-scale field studies (Phase III). The workshop goals were to:

- Gather perspectives from industry, regulators, and academia on the process for gathering the evidence required to drive novel vector control product development and use.
- Gain a better understanding of and identify gaps and challenges related to the safety, efficacy, quality, and regulatory evidence required to move novel vector control products through the different phases of development.
- Stimulate an ongoing dialogue among different stakeholders involved in vector control product development.

Stakeholder Environment & Regulatory Requirements

During the final session of the workshop, participants discussed gaps, challenges, and lessons learned for each phase of the product development pathway. The following were the main themes from these discussions.

Overall:

- There is a need to better define the stages of vector control product development and to harmonize terminology across agencies and institutions.
- Building understanding and use of Target Product Profiles (TPPs) and Preferred Product Characteristics (PPCs) is a critical need.
- Better understanding within the research community of WHO's prequalification process is a need and a gap.
- Engagement with regulators should span the product development process, starting prior to Phase I (lab studies) through Phase III (large field trials).
- It is beneficial to engage local government agencies early and at multiple levels (Ministry of Health and local officials).
- It was noted that the academic mindset is different from the corporate mindset with respect to the decision process. In industry, design criteria are used to determine what is working; in academia there is a more open-ended mindset. For example, having a TPP is routine in industry but could also be important in academia.

Laboratory and Pre-Field Studies (Phase I):

- Phase I studies provide confidence that the product has a chance at succeeding in later phases.
- Bioassays should be related to mosquito behavior, use field-relevant mosquitoes, and researchers should take into consideration the effect of the proposed method on other regional vectors.
- In terms of conducting studies that will potentially be in the product's regulatory dossier, it is important to consider the design of the study in the context of the proposed implementation of the intervention.
- With respect to assessing product quality for regulatory approval, there is a need to describe the product by its physical and chemical characteristics in the laboratory and to consider the methods by which these characteristics will be verified by field testing.
- Basic research investigators need more resources and information on the factors that they should consider before moving forward with the development of a vector control product.
- In terms of field-relevant mosquitoes, there is concern about how representative laboratory colonies are of the situation in the field as some unexpected genetic drifts may take place in colonized species.
- Methods for control and evaluation of other vectors (sand flies, tsetse flies, etc.) may not be as developed as those for mosquitoes.
- Risk assessment and risk management are considerations needed before the in-country regulatory agencies will allow field testing of an intervention. These factors typically are part of the dossier required by regulatory agencies.

Small-Scale Field Studies (Phase II):

- The Phase II stage is the assessment under real world, but contained, environments. It involves collaboration with stakeholders, regulatory agencies, and local expertise. It is important to identify challenges early and to address them quickly. The design should be robust, but not so defined as to prevent flexibility.
- Resistance monitoring is crucial for defining susceptibility and must take into account the mechanism involved. In designing trials, there is an opportunity to learn from other industries, e.g., pharmaceutical, agricultural and others. Phenotypic markers and bioassays may not always translate to functional resistance and/or product failure or success. Diagnostic doses are intended to serve as an early warning of resistance.
- The design of semi-field and Phase II studies should consider long-term public health impacts and opportunities to inform future studies.
- It is important to think about the mechanistic basis for a failure in Phase I as there can be a disconnect between Phase I and Phase II, in that work on a product may have been discontinued based on results in the laboratory that might work in the field. For example, a product that is sub-lethal in the laboratory may be functionally lethal in the field. In considering the experiments and experimental design, it is important to consider how the evidence obtained from the work would contribute to the overall approval package.

Large-Scale Field Studies (Phase III):

- A Phase III trial is more likely to be successful when there is high community acceptance, early engagement with the Ministry of Health and regulatory authorities, and knowledge of the entomology and epidemiology of the local area.
- In terms of selecting field sites, it is best to focus on hotspots for prevention approaches; however, for outbreaks, flexibility is necessary. Consideration should be given to complementary activities at sites that could be built upon for the proposed study.
- Assembly of a multidisciplinary team is very important for success and should include a range of expertise, including areas such as epidemiology, modeling, clinical medicine, entomology, and social sciences.
- There is a need for more emphasis on the value of clinical evaluation in the context of Phase III trials for vector products.
- It is important to consider how a new intervention can be integrated into an existing control program and work with other interventions. In some local contexts, the emphasis is on incorporating new interventions into ongoing work rather than sticking with a single intervention.
- It is important and sometimes a challenge to select both appropriate entomological and epidemiological endpoints of public health significance.
- Regarding WHO prequalification, it is important to keep in mind the target market, as this informs the requirements. For example, WHO prequalification is required if the product is procured by Global Fund. In other cases, WHO prequalification may not be required, but many Ministries of Health find it desirable.

Meeting Summary

Introduction

The purpose of this workshop was to bring together experts in vector control product development to discuss the data and evidence requirements along the translational pathway for laboratory/pre-field (Phase I), semi-field and small-scale (Phase II), and field/large-scale (Phase III) trials. National Institute of Allergy and Infectious Diseases (NIAID) program officers, Drs. Adriana Costero-Saint Denis and Ghiorghis Ghenbot, opened the meeting by describing the need to specify the evidence base required for novel vector control interventions to move forward through the different phases. The goals of the workshop were to:

- Gather perspectives from industry, regulators, and academia on the process for gathering the evidence required to drive novel vector control product development.
- Gain better understanding and identify gaps and challenges on the safety, efficacy, quality. and regulatory evidence required to move novel vector control products through the different phases of development.
- Stimulate an ongoing dialogue among different stakeholders involved in vector control product development.

Vector Control Product Development Landscape

Stakeholder Environment

Dr. Helen Jamet of the Bill and Melinda Gates Foundation (BMGF) provided an overview of the product development pipeline and stakeholder environment to emphasize the need for considering market segmentation before beginning to develop a product. The product development process differs for private market products and those intended for a public/country market. For the private market, one would start with user-centered market research to determine what is available and what is needed, followed by country registration, consideration of available distribution networks, and marketing. For community-based interventions, one would assess the policy evidence for the intervention and work with WHO for product evaluation and listing. For country registration, consideration should be given to the developmental stage of the country's system, as some systems are less well developed, especially for new products. After country registration, public health organizations often work with WHO on scale-up and procurement. In this sense, WHO is a doorway to the country market.

To illustrate the difference in private vs. country markets, Dr. Jamet offered the following example: The 2018, global private retail market for mosquito control products was approximately $10 billion, including products for disease control and nuisance biting mosquitoes. By contrast, the 2017 public health market for mosquito control products was $3.1 billion – much lower than the private retail market – and was mostly for malaria control. Major funders included The Global Fund, the President's Malaria Initiative (PMI), endemic country governments, and other country governments. In the 2014-2017 Global Fund budget cycle, 83 percent of vector control funding was for long-lasting insecticidal nets (LLIN) and 14 percent was for indoor residual spraying (IRS). Any new category of intervention in this market must therefore compete for a finite amount of funds.

Those involved in vector control product development should aim to: 1) understand the market segment; 2) plan ahead by identifying commercial partners, providing evidence for product claims, providing evidence for appropriate policy, developing assays and having them approved, preparing regulatory dossiers, defining the product's pathway through WHO, and addressing the economics of acceptable cost-of-goods (COGs) from the donor and user perspective; and 3) achieve good communication in terms of donor awareness, driving country demand and creating an enabling environment. The latter should include ensuring that the prospective country knows how or why the product is to be used and knows the groups that may specifically benefit from the product or be at risk from it.

Regulation in the U.S.

Dr. Susan Jennings of the U.S. Environmental Protection Agency (EPA) provided an overview of the regulation of vector control products in the United States. The specific roles of the U.S. Food and Drug Administration (FDA) and the EPA in regulating vector control are defined in "The Final Guidance for Industry #236 – Clarification of FDA and EPA Jurisdiction over Mosquito-Related Products", October 2017 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-236-clarification-fda-and-epa-jurisdiction-over-mosquito-related-products).

The guidance states that mosquito-related products intended to function as pesticides by preventing, destroying, repelling, or mitigating mosquitoes for population control purposes are not "drugs" under the Federal Food, Drug, and Cosmetic Act, and are regulated by the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act. By contrast, the FDA has jurisdiction over mosquito-related products that are intended to prevent, treat, mitigate, or cure a disease (including by an intent to reduce the level, replication, or transmissibility of a pathogen within mosquitoes). However, since the release of this guidance, new methods of vector control have been developed that do not easily fit into one of these distinct categories, and, in those circumstances, decisions are currently being made on a case-by-case basis.

There are several unique data considerations related to mosquitoes: 1) dissemination is mosquito-dependent in that the application rate needs to be defined and the release point does not equal the treatment area; 2) the health of the released mosquitoes will depend on several factors including their age at time of release, handling conditions during shipping, and fitness costs of the new trait; 3) the density of the existing wild mosquito population will affect the release numbers needed; 4) the potential for accidental female release needs to be addressed by its likelihood, species of mosquito, and potential human health and ecological implications.

Risk assessment and risk management should be considered and addressed. While not all studies are required for all submissions, issues that need to be considered include: 1) toxicity for terrestrial and aquatic organisms; 2) exposure to workers, bystanders, and ecological species through oral, dermal, or inhalation routes; and 3) environmental fate of the product (e.g., degradation in soil, water, or air).

In terms of satisfying data requirements, there are several approaches. If a study is needed, it should be conducted in accordance with EPA guidelines. However, it may be possible to cite existing data from similar active ingredients/products, in which case "bridging" rationale or studies may be needed. Submitters can provide a scientific rationale to address the requirement, such as citing scientific literature or providing physical and/or biological characterization of the active ingredient and product formulation. Submitters can request a data waiver based on lack of exposure or on the relevance of the study to the use patterns of the pesticide. The basis for this request must be scientifically defensible.

With respect to efficacy data for public health pests, Pesticide Registration Notice (PRN) (https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year) 2002-1 includes a list of pests of significant public health importance, defined broadly to include pests that "pose a widely recognized risk to significant numbers of people" (https://www.epa.gov/pesticide-registration/prn-2002-1-lists-pests-significant-public-health-importance). The purpose of such data is to promote the control of invertebrate pests of concern and to ensure that labeling provides consumers with accurate information concerning how long and how quickly the product works.

WHO Prequalification Process

Dr. Marion Law (WHO) described the steps in the WHO evaluation process for vector control products. She noted that the WHO is undergoing a major transformation from the WHO Pesticide Evaluation Scheme (WHOPES) system to the WHO Prequalification Team (PQT)-Vector Control

(VC) framework for registration (https://apps.who.int/iris/bitstream/handle/10665/255644/WHO-HTM-GMP-2017.13-eng.pdf).

The first step is the determination of the relevant pathway. This process enables the WHO to provide manufacturers with the most applicable guidance regarding the data requirements and specific process to reach prequalification. The two outcomes are the Prequalification Pathway or the New Intervention Pathway.

The Prequalification Pathway involves assessment of the quality, safety, and efficacy of the product, as well as the inspection of manufacturing facilities. These issues continue throughout the lifetime of the product. The responsibility of the manufacturer involves the development and submission of the dossier. The dossier format has six modules:

- Module 1: Administrative information and labelling
- Module 2: Discipline summaries
- Module 3: Quality dossier- Physical/Chemical Data; Declaration of Product Formulation; Description of Manufacturing Process; Declaration of Manufacturing Sites; Confidential Appendices
- Module 4: Safety dossier- Acute Toxicology (Acute Inhalation, Acute Oral, Acute Dermal, Primary Eye Irritation, Primary Skin Irritation, Dermal Sensitization); Product Risk Assessment (Occupational and Residential Exposure); A.I. Specific Hazard Assessment (or summary of publicly available information)
- Module 5: Efficacy dossier- Laboratory Studies (Characterize the efficacy, residual activity, and cross-resistance of the active ingredient, and analyze in a controlled environment using well-characterized colonies; assess endpoints measuring efficacy; conduct testing to estimate efficacy); Semi-Field Studies (Integrate mosquito behavior and human dwelling into a more realistic assessment of efficacy in a still relatively controlled experimental settings to assess endpoints measuring efficacy; conduct testing to estimate efficacy); Field studies (Assess the effectiveness of vector control products in variable environments and communities; measure endpoints such as vector longevity, infectivity rate, entomological inoculation rate and vector capacity; conduct field studies testing households in communities)
- Module 6: Inspection dossier- Site Master File(s), and an inspection report following the manufacturing site inspection. This process involves back-and-forth interaction with the manufacturer for information and assessment to reach a decision point.

Dr. Law indicated that the prequalification format is no longer divided into Phase I, Phase II and Phase III. All information is received at one time and the evaluation integrates all factors, with an emphasis on the labeling claims of the product. The process ends with a Decision Document addressing the approval or disapproval of the submission.

WHO Evaluation Pathway for New Products

Dr. Anna Bowman of WHO's Vector Control Advisory Group (VCAG) (https://www.who.int/groups/vector-control-advisory-group) described the WHO's process for evaluating new interventions. WHO's guidance document, "The Evaluation Process for Vector Control Products," describes the revised evaluation process following the 2017 transition from the

WHOPES to the WHO Prequalification Team (PQT), details the role of the VCAG as part of this process, and outlines the two pathways and their associated components. It is meant to guide interactions between product developers/manufacturers and WHO (https://apps.who.int/iris/bitstream/handle/10665/255644/WHO-HTM-GMP-2017.13-eng.pdf).

Both the prequalification pathway and new intervention pathway involve the VCAG confirming the public health value of the proposed product, with the public health value defined as proven protective efficacy to reduce or prevent infection and/or disease in humans. VCAG is a cross-departmental collaboration of the WHO Global Malaria Program (GMP), the Department of Control of Neglected Tropical Diseases (NTDs), and the WHO Prequalification Team (PQT) for vector control products. For any new vector control tools in new product classes, the WHO requires evidence from at least two well conducted, randomized controlled trials (RCT) with epidemiological outcomes, and follow-up over at least two transmission seasons.

Perspectives from Disease-Endemic Countries

Researchers from local institutions in Mexico, Kenya, and Peru discussed the challenges for product development and implementation in their countries. **Dr. Pablo Manrique-Saide** of the Universidad Autónoma de Yucatán described that in Mexico the regulatory framework for vector control products is overseen by COFEPRIS (Federal Commission for the Protection against Sanitary Risk), through which companies can apply to register products for public health use. The Ministry of Health through CENAPRECE (the National Center of Preventive Programs and Disease Control) issues an annual call for registered products for use in public health programs.

Dr. Eric Ochomo of the Kenya Medical Research Institute stated that public health insecticides are regulated by the Pest Control Products Board (PCPB) in Kenya. The challenges to registration in Kenya include: the process of obtaining funding for the evaluation of vector control products; the lack of infrastructure and intellectual capacity; the effect of political influence versus scientific evidence on decisions; and the lack of transparency and clarity in the evaluation process.

Dr. Gissella Vazquez of the U.S. Naval Medical Research Unit No. 6 (NAMRU-6) stated that in Peru vector control is focused on malaria and dengue vectors. Each state has its own public health directorate which reports to the national Ministry of Health. Peru adheres to the WHO vector control guidelines. If a product is not listed by WHO, then permits are required from three different local level agencies. One challenge for new products in Peru is the lack of a clear communication channel between local public health directorates and the national Ministry of Health.

Generating Evidence at Each Phase

Laboratory and Pre-Field Studies (Phase I)

Phase I studies take place in the laboratory and can include pre-field studies of prototypes on a small scale. These studies generate crucial data required to proceed with product development.

Phase I evaluation of LLINs – **Dr. Philip McCall** of the Liverpool School of Tropical Medicine noted the need for new insecticides and control methods to deal with the rapid spread of pyrethroid

resistance in Africa. The assays currently used to evaluate new insecticides are often carried out under artificial conditions that that have little similarity to natural exposure, focus on short-term knockdown, are not always representative of true LLIN action, and provide limited insight into slow-acting chemicals or to sub-lethal effects.

Dr. McCall described three new tests to evaluate active ingredients (AIs) in LLINs. All tests use mosquito strains with appropriate insecticide-resistant phenotypes and all are repeated by two operators. Rapid impact product measures include: excito-repellency (i.e., behavioral avoidance), knockdown, and mortality. Delayed/sub-lethal effects can be measured by follow-up of survivors and include longevity, blood-meal inhibition, blood-meal volume, egg batch size, and egg hatch rate.

1. The Video Cone Test Analyzer (ViCTA) is a rapid screen done at close range to assess interaction at a treated surface and measures repellency, irritancy, knockdown, and mortality. This 3-minute simple test is not dependent on responsive mosquitoes. Its disadvantages are 1) that it is forced; 2) net contact is assumed, which can be potentially misleading if the netting has repellent or irritant properties which result in reduced contact, and thus an underestimation of net efficacy; 3) if no host is present, there may be no attraction for some mosquito species and the repellency estimate could be inflated; and 4) minimal data are developed from the test. The two main behaviors assessed are flying or resting on the net. Resting on the cone is rare.

2. The Thumb-Test or Baited-box Test is a 20-minute test that details behavior during final net approach, landing, contact and exit. The test provides for quantifying net repellency/irritancy and other immediate effects; assesses mosquito probing, blood-feeding, persistence, success, and duration; and, through follow-up, allows measurement of sub-lethal impacts on individual mosquitoes.

3. Room-scale video tracking is a technology that maps how/where nets alter basic responses and the location and duration of net contact. It also has the potential to capture effects of LLIN over eight hours (i.e., one night). It uses a scan at five seconds and assigns each mosquito to one behavior. Dr. McCall showed examples of the kind of data and visuals that can be obtained.

Increasing the value of Phase I testing – **Dr. Matthew Thomas** of Pennsylvania State University described research on the development of a fungal biopesticide for control of adult mosquitoes to illustrate three points related to Phase I testing: 1) the need for defining a clear use case; that is, why a particular product is needed and what it brings to the table; 2) the need to consider the full TPP to guide evaluation and key decision points; and 3) the value of being creative in the design of Phase I studies to answer as many questions as possible with respect to an ultimate product.

Semi-Field and Small-Scale Studies (Phase II)

Phase II is the transition of an intervention into a semi-field or small-scale field study. The following are examples of data needs and considerations for these studies.

Assessing Insecticide Resistance – Insecticide resistance is a major challenge in the fight against vector-borne diseases. **Dr. Audrey Lenhart** of the U.S. Centers for Disease Control and Prevention (CDC) addressed how insecticide resistance can be assessed along the three phases of the developmental pathway. Either in laboratory or semi-field settings of Phase I studies, there should be a determination of how effective the AIs in the product are against insecticide-susceptible and insecticide-resistant mosquito strains. This includes the need to understand how the mosquito response to the insecticide occurs. The components of such studies include bioassays and characterization of the resistance mechanisms of the strains used (e.g., molecular markers, synergist assays, etc.).

For Phase II studies, the key issue is how effective the product is against wild mosquito strains in field settings. The components of such studies include: 1) longitudinal monitoring of product efficacy against strains of differing resistance phenotypes, including monitoring of residual efficacy and bioavailability of the AIs over time; 2) longitudinal monitoring of changes in resistance phenotypes of local mosquito strains; and 3) monitoring changes in insecticide resistance mechanisms in the mosquitoes (i.e., resistance allele frequencies, gene transcription differences, etc.). Phase III studies consider how effective the product is at preventing disease and/or pathogen transmission in field trials. The same measurement components are needed as for Phase II studies. Data collected on resistance in the field trial settings can allow for the estimation of the effect that insecticide resistance may have on epidemiological endpoints.

For products with multiple AIs, one challenge is disentangling the differential impacts of the AIs on resistance – that is, is one AI primarily responsible for mortality while another continues to select for resistance? For other approaches, challenges include understanding how genetic markers of resistance move through populations; developing assays and identifying molecular markers for behavioral resistance; determining if there are behavioral modifications by vectors to avoid contact with interventions (i.e., exophily/exophagy); and determining the basis for the lack of an excito-repellency response to spatial repellents. With respect to non-chemical interventions, an important issue is determining if there is "resistance' to harboring *Wolbachia* or "resistance" to entomopathogenic fungi.

Autocidal Methods against Aedes Mosquitoes – **Dr. Stephen Dobson** of MosquitoMate, Inc., and the University of Kentucky described two new autocidal vector control tools. The first approach is based on *Wolbachia*, an endosymbiotic bacterium that is common in many invertebrate species. This method uses repeated inundative releases of *Wolbachia*-infected male mosquitoes to cause a form of conditional sterility, as eggs laid by females don't hatch. This approach received EPA approval for use on *Aedes aegypti* and *Aedes albopictus.* The second approach, "Auto-Dissemination Augmented by Males" (ADAM), employs repeated inundative introductions of male *Aedes* mosquitoes to distribute pyriproxyfen as an inhibitor of *Aedes* development.

Dr. Dobson described a small field study in South Miami that used the first approach. The research area was a district with two zones, one treated and one untreated, with each area containing 160 acres and about 460 homes per area and of equal demographics. The choice of the locations was acceptable both to the government officials as well as the regulators. In the treated area, there were 75 release sites, with about 1000 mosquitoes per release event and five events per week. Thus, about 370,000 *Aedes aegypti* per week were released in the treated areas or a total of 6.8 million males released over six months. The study design recognized that female mosquitoes from

adjacent areas could fly into the study areas. Since females are monogamous and after mating carry the sperm with them for life, it was anticipated that there would be some "immigration" from non-treated areas and that such female mosquitoes would be resistant to the *Wolbachia* approach. For this reason, the treated area was studied as containing a core area (which was outside the flight range for female mosquitoes to fly into) and edge areas that were inside the flight range. The results were encouraging. In the untreated areas, Dr. Dobson saw the usual seasonal increase in female mosquitoes and a reduced number of females in the treated areas. The "immigration" effect was seen along the edges. Overall, there was a 75% reduction of female mosquitoes in the treated areas.

Large-Scale Studies (Phase III)

Testing Ivermectin for Malaria Control – Ivermectin is an endectocide that is used in animals and humans for helminth and ectoparasite control, but researchers are also investigating ivermectin's potential as a malaria intervention. **Dr. Brian Foy** of Colorado State University summarized a Phase III RCT testing ivermectin for malaria control in Burkina Faso. The goals of Dr. Foy's research are to target adult malaria vectors through blood meals, to primarily affect their daily probability of survival, but also to affect other variables of vectorial capacity if possible.

Dr. Foy summarized some of the studies that laid the groundwork for the Phase III trial. For observational field data studies, Dr. Foy's group followed a single ivermectin mass drug administration (MDA) that was given by health authorities during the rainy season for the control of onchocerciasis or lymphatic filariasis in West Africa. Participants were given pills based on a minimum height of ≥90 cm as a surrogate for weight over 15kg. It was estimated that about 75% of the population of a "treatment" village's mosquitoes were collected from homes and measurements were done for mortality, parity, and sporozoite rate before and after the MDA and compared with control villages that did not participate in the MDA. The results demonstrated that the number of older mosquitoes was reduced, and that there were more young mosquitoes and fewer sporozoites.

The Phase III trial in Burkina Faso led by Dr. Foy's team was a cluster-randomized controlled trial with four villages in each arm. The primary outcome of the intervention was a reduced incidence of malaria in children in the treatment arm. Assessing a salivary marker in blood as a measure of exposure to *Anopheles* found that children in the ivermectin MDA group received fewer bites overall (https://www.sciencedirect.com/science/article/pii/S0140673618323213?via%3Dihub).

Dr. Foy currently has an NIH-funded cooperative agreement (U01AI138910) to support a double-blind cluster randomized clinical trial for integrated malaria control using ivermectin. The study will integrate repeated high dose ivermectin MDA into the existing monthly seasonal malaria chemoprevention (SMC) delivery plan in Burkina Faso, combined with LLIN distribution. The broad goal is to develop an evidence base that ivermectin MDA can be easily and safely integrated with current measures to significantly enhance malaria control, as well as to preserve the efficacy of current tools by adding another synergistic product that targets both vectors and parasites in unique ways. The three aims of his study are to: 1) assess the impact of a combined approach of repeated ivermectin MDA and SMC on malaria; 2) characterize the entomological, pharmacokinetic, and parasitological indices associated with the primary outcome; and 3) define the trial's impact on markers of insecticide and drug resistance in both vectors and parasites.

Dr. Foy noted that challenges for this kind of study include safety, resistance development, product and regimen development, feasibility, and regulatory issues. He stated that the key lessons are embracing the risk, convincing others (reviewers, funders) to do so too, and being open to inviting others into your research area, as the Phase III stage and beyond is too big for one research group. A product concept is more likely to be embraced by others if more than one group shows positive results.

Targeted Indoor Residual Spraying (TIRS) for Control of Aedes aegypti – **Dr. Gonzalo Vazquez-Prokopec** of Emory University described his experience testing targeted indoor residual spraying (TIRS) for dengue control. The underlying behavior related to the dengue vector *Ae. aegypti* is that the vector spends most of its time resting, is a lazy flyer, preferentially a daytime human biter, and seeks blood on an average of every 1.5 days. Prior studies on *Aedes* behavior showed that there was a 17-fold greater chance of finding *Ae. aegypti* resting in areas below 1.5 meters in height, with the mosquitoes resting principally in bedrooms (44%), living rooms (25%), bathrooms (20%), and kitchens (9%).

Studies in Cairns, Australia in 2002 showed that TIRS led to a significant reduction in dengue cases. However, the dengue control environment in Cairns is different from endemic settings in that it is well-resourced and features a compliant human population, as well as a susceptible *Aedes* population. One major hurdle for using TIRS in other endemic environments, such as Latin America, is pyrethroid resistance and the availability of non-pyrethroid formulations. Another issue is whether a modified IRS protocol with the right chemistry would offer a sustainable tool in the medium term. In this regard, there was a need for information about the epidemiological impact of TIRS in endemic settings, ideally generated by randomized trials.

Dr. Vazquez-Prokopec described the design and results of the first Phase II entomological clustered randomized controlled trial (CRCT) in Mexico to evaluate the effectiveness of TIRS against pyrethroid-resistant *Ae. aegypti*. Fourteen clusters of homes were involved with three arms: untreated; IRS with bendiocarb (susceptible population); and IRS with deltamethrin (resistant population). Entomological measurements were done at 15 days, and at one, two, and three months.

Dr. Vazquez-Prokopec described a second Phase II entomological CRCT in Merida to measure the effectiveness of preventive (preseason) TIRS on *Ae. aegypti*. There were 14 clusters of homes in two arms: untreated; and TIRS with pirimiphos-methyl on a susceptible population of mosquitoes. The study showed a significant (60-70%) reduction in entomological indices for up to seven months. Importantly, Dr. Vazquez-Prokopec found that there was community acceptance of the intervention. Additional studies found that a 10 to 20-minute application may protect the home environment for up to four (bendiocarb) or seven (pirimiphos-methyl) months. He is currently evaluating new formulations and modes of action.

Dr. Vazquez-Prokopec described further studies and plans in preparation for a two-armed Phase III CRCT to estimate the epidemiological impact of a TIRS. The trial would evaluate two paradigms: TIRS and prevention control. It would need an international consortium and local Ministry of Health participation. The target population would be children 2-15 years of age at the time of

enrollment living within the assigned clusters in the city of Merida, Yucatan, Mexico. The primary epidemiological endpoint will be laboratory-confirmed *Aedes*-borne disease.

In summary, TIRS appears to be effective at preventing dengue in Australia. Information generated from Phase II semi-field and field trials have paved the way to evaluate the epidemiological impact in endemic settings. Dr. Vazquez-Prokopec hypothesized that performing preemptive control with TIRS will significantly reduce *Aedes*-borne disease burden in comparison to routine reactive vector control strategies. If efficacious, TIRS could drive a paradigm shift in *Aedes* control by incorporating preventive control within the operational toolbox for effective prevention.

Gaps, Challenges, and Lessons Learned

During the final session of the workshop, participants discussed gaps, challenges, and lessons learned for each phase of the product development pathway. The following were the main themes from these discussions.

Overall:

- There is a need to better define the stages of vector control product development and to harmonize terminology across agencies and institutions.
- Building understanding and use of TPPs and PPCs is a critical need.
- Better understanding within the research community of WHO's prequalification process is a need and a gap.
- Engagement with regulators should span the product development process, starting prior to Phase I through Phase III.
- It is beneficial to engage local government agencies early and at multiple levels (Ministry of Health and local officials).
- It was noted that the academic mindset is different from the corporate mindset with respect to the decision process. In industry, design criteria are used to determine what is working; in academia there is a more open-ended mindset. For example, having a TPP is routine in industry but could also be important in academia.

Laboratory and Pre-Field Studies (Phase I):

- Phase I provides confidence that the product has a chance at succeeding in later phases.
- Bioassays used should be related to mosquito behavior, use field-relevant mosquitoes, and researchers should consider the function of the proposed method on other regional vectors.
- In terms of conducting studies that will potentially be in the product's regulatory dossier, it is important to consider the design of the study in the context of the proposed implementation of the intervention.
- With respect to assessing product quality for regulatory approval, there is a need to describe the product by its physical and chemical characteristics in the laboratory and to consider the methods by which these characteristics will be verified by field testing.
- Basic research investigators need more resources and information on the factors that they should consider before moving forward with the development of a vector control product.
- There is a need for laboratory testing to improve consideration of insect behavior.

- In terms of field-relevant mosquitoes, there is concern about how representative laboratory colonies are of the situation in the field as some unexpected genetic drifts may take place in colonized species.
- Methods for control and evaluation of other vectors (sand flies, tsetse flies, etc.) may not be as developed as those for mosquitoes.
- Risk assessment and risk management are considerations normally needed before the in-country regulatory agencies will allow field testing of an intervention. These factors are part of the dossier required by regulatory agencies.

Small-Scale Field Studies (Phase II):

- The Phase II stage is the assessment under real world, but contained, environments. It involves collaboration with stakeholders, regulatory agencies, and local expertise. It is important to identify challenges early and to address them quickly. The design should be robust, but not so defined as to prevent flexibility.
- Resistance monitoring is crucial for defining susceptibility and must take into account the mechanism involved. In designing trials, there is an opportunity to learn from other industries, e.g., pharmaceutical, agricultural and others. Phenotypic markers and bioassays may not always translate to functional resistance and/or product failure or success. Diagnostic doses are intended to serve as an early warning of resistance.
- The design of semi-field and Phase II studies should consider long-term public health impacts and opportunities to inform future studies.
- It is important to think about the mechanistic basis for a failure in Phase I as there can be a disconnect between Phase I and Phase II, in that work on a product may have been discontinued based on results in the laboratory that might work in the field. For example, a product that is sub-lethal in the laboratory may be functionally lethal in the field. In considering the experiments and experimental design, it is important to consider how the evidence obtained from the work would contribute to the overall approval package.

Large-Scale Field Studies (Phase III):

- A Phase III trial is more likely to be successful when there is high community acceptance, early engagement with the Ministry of Health and regulatory authorities, and knowledge of the entomology and epidemiology of the local area.
- In terms of selecting field sites, it is best to focus on hotspots for prevention approaches; however, for outbreaks, flexibility is necessary. Consideration should be given to complementary activities at sites that could be built upon for the proposed study.
- Assembly of a multidisciplinary team is very important for success and should include a range of expertise, including areas such as epidemiology, modeling, clinical medicine, entomology, and social sciences.
- There is a need for more emphasis on the value of clinical evaluation in the context of Phase III trials for vector products.
- It is important to consider how a new intervention can be integrated into an existing control program and work with other interventions. In some local contexts, the emphasis is on incorporating new interventions into ongoing work rather than sticking with a single intervention.

- It is important and sometimes a challenge to select both appropriate entomological and epidemiological endpoints of public health significance.
- Regarding WHO prequalification, it is important to keep in mind the target market, as this informs the requirements. For example, WHO prequalification is required if the product is procured by Global Fund. In other cases, WHO prequalification may not be required, but many ministries of health find it desirable.

APPENDIX 1: Workshop Agenda

Vector Control Product Development Pathway: Phase-Dependent Evidence Gathering
June 24-25, 2019
5601 Fishers Lane, Rockville, MD

Purpose: Bring together experts in vector control product development to discuss the data/evidence requirements along the translational path for laboratory/pre-field (Phase I), semi-field and small-scale field trials (Phase II), and large-scale field (Phase III) trials.

Expected outcomes: 1) Gather perspectives from industry, regulators and academia on the processes for gathering the evidence required for novel vector control product development and use; 2) Gain better understanding and identify gaps and challenges on the safety, efficacy, quality and regulatory evidence required to move novel vector control products through the different phases of development; and 3) Stimulate an ongoing dialogue among different stakeholders involved in vector control product development.

DAY 1 - June 24, 2019			
Date/Time	**Presentation**	**Speaker**	**Topic**
7:45-8:45 AM	Registration		
8:45-9:00 AM	Welcome and Introduction	Ghiorghis Ghenbot and Adriana Costero-Saint Denis (NIAID/NIH)	Background and Expectations
Session 1: Overview - Vector Control Product Development Landscape			
	Chair	Adriana Costero-Saint Denis (NIAID/NIH)	
9:00 – 9:30 AM		Helen Jamet BMGF	Vector Control Product Development and the Stakeholder Environment
9:30 – 10:00 AM		Susan Jennings EPA	Regulation of Vector Control Products for Use in the U.S.
10:00 – 10:30 AM		Marion Law WHO/Evaluation	WHO Prequalification Process for Vector Control Products
10:30 – 11:00 AM		Anna Bowman WHO/Policy	WHO Evaluation Pathway for New Vector Control Interventions
11:00 – 11:15 AM	BREAK		
Perspectives from Disease-Endemic Countries (DEC) on Vector Control Product Development: Panel Discussion			
	Chair	Jennifer Armistead (USAID)	
11:15 – 11:45 AM	Panel members	Pablo Manrique-Saide UADY/Mexico	Challenges for Product Implementation in Mexico
		Eric Ochomo KEMRI/Kenya	Challenges for Product Implementation in Kenya

		Gissella Vazquez NAMRU-6/Peru	Challenges for Product Implementation in Peru
11:45 – 12:00 PM	Discussion	ALL	
12:00 – 1:00 PM	LUNCH		
Session 2: Generating Evidence for Phase I and Phase II Studies			
1:00 – 2:00 PM	Laboratory/ pre-field	Efficacy, Safety and Regulatory Aspects	Process for established product classes (Phase I), challenges for new products and product classes
	Chairs	Dave Malone (Sumitomo) Pablo-Manrique-Saide (UADY)	
1:00 – 1:20 PM		Philip McCall LSTM	Generating an Evidence Base for Evaluating LLINs
1:20 – 1:40 PM		Matthew Thomas Pennsylvania State Univ.	Increasing the Value of Phase 1 Testing
1:40 – 2:00 PM	Discussion	ALL	Gaps and Challenges
2:00 – 2:15 PM	BREAK		
2:15 – 3:15 PM	Semi-field and small-scale field	Efficacy, Safety and Regulatory Aspects	Process for established product classes (Phase II), challenges for new products and product classes
	Chairs	Kurt Vandock (Bayer) and Gissella Vasquez (NAMRU-6)	
2:15 – 2:35 PM		Audrey Lenhart CDC	Assessing Insecticide Resistance Along the Translational Pathway
2:35 – 3:55 PM		Stephen Dobson MosquitoMate, Inc. and University of Kentucky	Autocidal Methods Against *Aedes* Mosquitoes
3:55 – 4:15 PM	Discussion	ALL	Gaps and Challenges
4:15 – 4:30 PM	Wrap up Preparation for Day 2	Adriana Costero-Saint Denis and Ghiorghis Ghenbot NIAID/NIH	
4:30 PM	Adjourn		
DAY 2- June 25, 2019			
Date/Time	**Presentation**	**Speaker**	**Topic**
9:00 – 9:15 PM	Welcome back	Ghiorghis Ghenbot and Adriana Costero-Saint Denis NIAID/NIH	

Session 3: Generating Evidence for Phase III Studies			
	Chairs	Melinda Hadi (Vestergaard) Eric Ochomo (KEMRI)	Process for established product classes (Phase III), challenges for new products and product classes
9:15 – 9:45 AM		Brian Foy Colorado State Univ.	Phase III studies Testing Ivermectin for Malaria Control
9:45 – 10:15 AM		Gonzalo Vazquez-Prokopec Emory University	Targeted Indoor Residual Spraying (TIRS) for the Control of *Aedes aegypti*: Evidence from Phase-I/II to Inform a Phase-III Trial
10:15 – 10:45 AM	Discussion	ALL participants	Gaps and Challenges
10:45 – 11:00 AM	BREAK		
Session 4: Integration and Identification of Gaps and Challenges			
	Chair	Ghiorghis Ghenbot NIH/NIAID	
11:00-11:15 AM		Phase I: Dave and Pablo	
11:15 – 11:30 AM		Phase II: Kurt and Gissella	
11:30 – 11:45 AM		Phase III: Melinda and Eric	
11:45 AM – 12:15 PM	Discussion	ALL participants	What are the gaps/challenges at each phase of development?
			How can these gaps/challenges be addressed?
12:15 – 12:30 PM	Wrap up and Next Steps	Adriana Costero-Saint Denis and Ghiorghis Ghenbot	
12:45 PM	Adjourn		

APPENDIX 2: Participant List

Jennifer Armistead
U.S. Agency for International Development

Roberto Barrera
U.S. Centers for Disease Control and Prevention

John Beier
University of Miami

Eric Bohnenblust
U.S. Environmental Protection Agency

Anna Bowman
World Health Organization

Eric Caragata
Johns Hopkins Bloomberg School of Public Health

Cristina Cassetti
National Institute of Allergy and Infectious Diseases

Adriana Costero-Saint Denis
National Institute of Allergy and Infectious Diseases

Brinda Dass
Foundation for the National Institutes of Health

Gregory Deye
National Institute of Allergy and Infectious Diseases

Stephen Dobson
MosquitoMate, Inc.

Molly Duman Scheel
Indiana University School of Medicine and University of Notre Dame

Sally Eatmon
National Institute of Allergy and Infectious Diseases

Noel Elman
GearJump Technologies

Joseph Fireman
Verily Life Sciences

Brian Foy
Colorado State University

Ghiorghis Ghenbot
National Institute of Allergy and Infectious Diseases

Melinda Hadi
Vestergaard

Catherine Hill
Purdue University

Steve Huang
National Institute of Allergy and Infectious Diseases

Audrey Hutter
Bill and Melinda Gates Foundation

Maliha Ilias
National Institute of Allergy and Infectious Diseases

Stephanie James
Foundation for the National Institutes of Health

Helen Jamet
Bill & Melinda Gates Foundation

Susan Jennings
U.S. Environmental Protection Agency

Chung-Yan Koh
Defense Advanced Research Projects Agency

David Larsen
Syracuse University

Marion Law
World Health Organization

Audrey Lenhart
U.S. Centers for Disease Control and Prevention

Erica Lindroth
Armed Forces Pest Management Board

Michael Macdonald
Innovative Vector Control Consortium

Hannah MacLeod
Johns Hopkins Bloomberg School of Public Health

David Malone
Sumitomo Chemical Co.

Pablo Manrique Saide
Universidad Autónoma de Yucatán

Jeannette Martinez
World Health Organization
martinezjea@who.int

Philip McCall
Liverpool School of Tropical Medicine
philip.mccall@lstmed.ac.uk

Christina McCormick
National Institute of Allergy and Infectious Diseases

Gunter Muller
USTTB Bamako University Mali

Effie Nomicos
National Institute of Allergy and Infectious Diseases

Douglas Norris
Johns Hopkins Bloomberg School of Public Health

Eric Ochomo
Kenya Medical Research Institute

Jean Patterson
National Institute of Allergy and Infectious Diseases

Amanda Pierce
U.S. Environmental Protection Agency

Sarah Rees
Innovative Vector Control Consortium

Alan Reynolds
U.S. Environmental Protection Agency

Jennifer Saunders
U.S. Environmental Protection Agencys

Nicole Scott
Cybele Microbiome Inc.

Colleen Sico
National Institute of Allergy and Infectious Diseases

Nigel Snoad
Verily Life Sciences

Susan Spring
Freelance Science Writer

Dan Stoughton
National Institute of Allergy and Infectious Diseases

Wiebke Striegel
U.S. Environmental Protection Agency

Matthew Thomas
Penn State University

Karen Tountas
Foundation for the National Institutes of Health

Kurt Vandock
Bayer U.S. LLC

Gissella Vasquez
U.S. Naval Medical Research Unit No.6

Gonzalo Vazquez Prokopec
Emory University

Andre Wilke
University of Miami

Gabriela Zollner
Armed Forces Pest Management Board

APPENDIX 3: Resources

National Institute of Allergy and Infectious Diseases (NIAID):

- Resources for Researchers: https://www.niaid.nih.gov/research/resources
- Preclinical Services: https://www.niaid.nih.gov/research/resources
- Reagents: https://www.beiresources.org/Home.aspx
- Live vectors: https://www.beiresources.org/Catalog/VectorResources.aspx

World Health Organization (WHO):

- Vector Control Advisory Group: https://www.who.int/groups/vector-control-advisory-group

U.S. Environmental Protection Agency (EPA):

Product Registration:

- https://www.epa.gov/ingredients-used-pesticide-products
- https://www.epa.gov/pesticide-registration/registration-requirements-and-guidance
- https://www.epa.gov/pesticide-registration
- Pesticide Registration Manual: Chapter 12 - Applying for an Experimental Use Permit (EUP)

Pesticides and Biotechnology:

- https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/epas-regulation-biotechnology-use-pest-management
- https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/modernizing-regulatory-system-biotechnology-products

U.S. Food and Drug Administration (FDA):

- Regulation of Mosquito-Related Products (GFI #236) (January 2017)
- Regulation of Intentionally Altered Genomic DNA in Animals (GFI #187) (January 2017)

Environmental Assessment Explained:

- EPA: Testing Requirements to Assess Risks to Human Health and the Environment
- Guidance on the environmental risk assessment of genetically modified animals

Modernizing the Regulatory System for Biotechnology Products:
Final Version of the 2017 Update to the Coordinated Framework for the Regulation of Biotechnology - 2017_coordinated_framework_update

U.S. Agency for International Development (USAID):

- Combating Zika and Future Threats: A Grand Challenge for Development https://www.usaid.gov/grandchallenges/zika

U.S. Centers for Disease Control and Prevention (CDC):

- Preparing the Nation to Address Vector-Borne Disease Threats
  https://www.cdc.gov/ncezid/dvbd/about/prepare-nation.html
- Vector-Borne Disease Regional Centers of Excellence
  https://www.cdc.gov/ncezid/dvbd/about/prepare-nation/coe.html
- Division of Vector-Borne Diseases
  https://www.cdc.gov/ncezid/dvbd/index.html

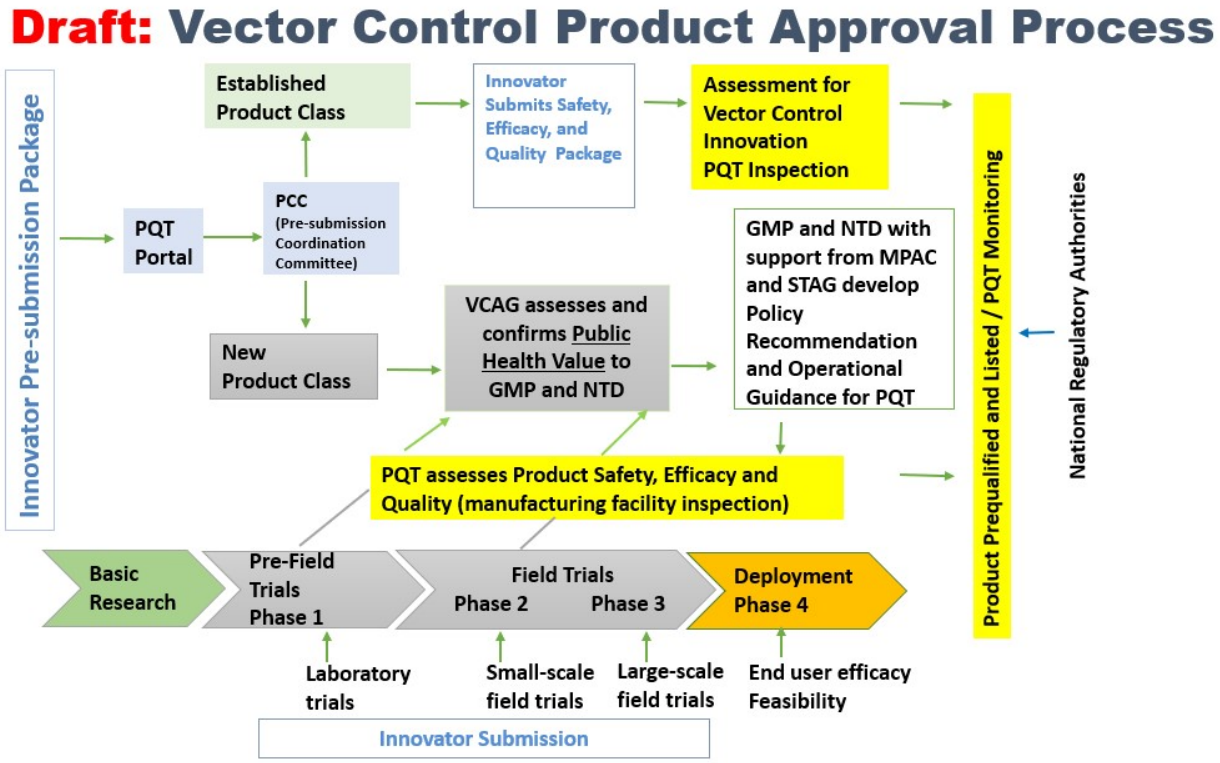
Armed Forces Pest Management Board (DoD): https://www.acq.osd.mil/eie/afpmb/

Publications of Interest:

- Global Vector Control Guidelines – The Need for Co-Creation (2019)
  https://www.sciencedirect.com/science/article/pii/S1471492218302708?via%3Dihub
- Intersectoral Collaboration for the prevention and control of vector-borne diseases to support the implementation of a global strategy: A systematic review (2018)
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6179246/pdf/pone.0204659.pdf
- Developing multi-sectoral approaches to prevent and control vector-borne diseases (2017)
  https://www.who.int/tdr/news/2017/multi-sectoral-approaches-to-prevent-vbd/en/
- Evidence-based vector control? Improving the quality of vector control trials (2015)
  https://reader.elsevier.com/reader/sd/pii/S1471492215000975?token=021ACBF1513AE30D343B13087F6BFD0B2977381ED575BCA393A0B8176730AB5C68C287DBE35574127DF28C9F9FC65CF9
- Framework for rapid assessment and adoption of new vector control tools (2014)
  https://reader.elsevier.com/reader/sd/pii/S1471492214000348?token=7A2CB3CC6AC35B340D2DD1190E428F54FF72431FA2C03807068AA17E4946E36D50A33CBE5A7C0105F433808E355AEB41

APPENDIX 4: Vector Control Product Development Pathways Draft Diagram

PQT: Prequalification Team, VCAG: Vector Control Advisory Group, GMP: Global Malaria Program, NTD: Neglected tropical diseases,



References: (1). Devine et.al. (2019). Global Vector Control Guidelines – The need for Co-Creation. Trends in Parasitology. Vol. 35: 267 – 270

(2) How to design vector control efficacy trials: Guidance on phase III vector control field trial design provided by the Vector Control Advisory Group. WHO/HTM/NTD/VEM/2017.03

(3) Wilson et. al. (2015). Evidence-based vector control? Improving the quality of vector control trials. Trends in Parasitology. Vol. 31: 380-390.

(4) EPA Product Performance Test Guidelines OPPTS 810.1000 (Overview, Definitions, and General Considerations), OCSPP 810.200 (General considerations for Uses of Antimicrobial Agents) , and OPPTS 810.3400 (Mosquito, Black Fly, and Biting Midge (Sand Fly) Treatments

MPAC: Malaria Policy Advisory Committee, STAG: Strategic and Technical Advisory Group