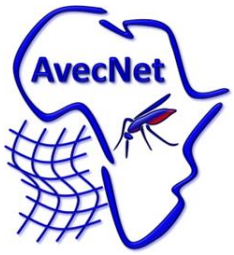

AVECNET

END OF PROJECT REPORT

AVECNET: GRANT AGREEMENT NO HEALTH-F3-2010-265660

EXECUTIVE SUMMARY

Prevention of malaria is best achieved by vector control which, today in Africa, relies almost entirely on the use of residual insecticides in the domestic environment. Wide scale implementation of tools such as indoor residual spraying (IRS) and long lasting insecticidal nets (LLINs) have led to impressive decreases in malaria transmission in some regions and these interventions are the cornerstone of malaria control programmes in most African countries. However these frontline interventions are dependent on a very limited number of available insecticides, whose efficacy is being continuously eroded by the evolution of insecticide resistance in the mosquito vectors. Furthermore, even without the threat of insecticide resistance, the current tools will not be adequate to achieve stable reductions in, or elimination of malaria transmission. Indeed the very success of LLINs and IRS in preventing transmission is highlighting additional challenges and opportunities, including the need to tackle mosquitoes that bite and rest outside the home. It is clear that significant advances are needed in order to secure the future of malaria prevention by vector control.

The vision of the AvecNet consortium was to ensure the sustainability of malaria vector control in Africa by investing in the design and evaluation of new control tools and building capacity to both create and utilise the evidence at global and national level. Our scientific outputs can be grouped into three interrelated areas: mosquito behaviour, insecticide resistance and the impact of both of these on the performance, acceptability and affordability of the portfolio of current and new vector control tools. We developed state of the art new methods for tracking mosquito behaviour that resulted in novel insights on how LLINs function, resulting in a patented new bednet design. New tools for measuring mosquito resting and host seeking behaviour have improved the safety and efficiency of vector control trials. Our studies on insecticide resistance raised the profile of the extent of the threat of this trait on efforts to eliminate malaria, resulting in renewed calls from from the World Health Organisation to incorporate resistance management strategies into national programmes, and directly contributed to the issuance of new guidelines to monitor insecticide resistance.

The AvecNet partners have played a leading role in accelerating the time to market of insecticide resistance breaking products, such as dual action LLINs, new IRS formulations and new delivery methods. Examples of the translational impact of this work have included the registration of new IRS products and the publication of normative guidance on the use of ‘next generation’ LLINs. New approaches to controlling outdoor biting have shown promise and generated follow on funding for further evaluation. Of equal importance, we have also identified critical roadblocks in our evaluation of other products, resulting in timely termination and redirection of resources to alternative products.

In addition to our scientific outputs we have invested heavily in individual and institutional capacity strengthening. We have improved the infrastructure at our field sites, strengthened financial and programme management skills within our African partner institutes and developed a network of scientists providing peer to peer mentorship and support. Our efforts to improve the rigor of vector control trials have been very well received internally and externally and resulted in improved study designs and a greater independence in data analysis within partner organisations. Furthermore, our interdisciplinary approaches and work with policy makers, has helped accelerate research uptake but also identified considerable barriers to the utilisation of evidence to inform national decision making.

SUMMARY OF THE PROJECT CONTEXT AND MAIN OBJECTIVES

CONTEXT OF THE PROJECT

Malaria remains a serious global health problem with half of the world's population at risk. The biggest burden of the disease is borne in sub-Saharan Africa where over 500,000 lives are lost to this disease each year[1]. In recent years, the level of resources and the degree of national and international commitment to malaria control has been scaled up dramatically and the impact of this is now being felt in many malaria endemic regions. For example, there has been a halving of the number of malaria deaths in Africa between the years 2000 and 2015[2]. The majority of these gains have been attributed to the scale up of interventions that target the mosquito vector inside the home: long lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). These interventions are particularly effective in Africa as the major vector species, members of the *Anopheles gambiae* and *Anopheles funestus* complexes, typically feed and rest indoors.

However not all African malaria vectors exhibit such anthropophilic behavioural patterns and are thus not as amenable to control by conventional methods. If we are to successfully scale up malaria control efforts and even move towards elimination, we must recognise the diversity of active malaria vectors in Africa and avoid the tendency to focus future strategies solely on interventions that target the most tractable of vectors. Further challenges to sustainable malaria control are being exposed as coverage with insecticide based interventions in the home increases. There is a danger that high coverage with existing interventions will select for heritable changes in the behaviour of current vectors that reduces their exposure to insecticides (*e.g.* avoiding LLINs by biting earlier or outdoors, avoiding IRS by resting outdoors). However, conclusive data indicating whether behavioural shifts are a common response of African vector populations to interventions are lacking, to a large extent because of limitations in our ability to investigate the topic. Alternative and better tools to study mosquito behaviour, and to explore the epidemiological consequences of such expected behavioural shifts are required. Furthermore, it is important to plan for the changing pattern of malaria transmission that is already being observed in parts of rural Africa by developing effective tools to tackle outdoor transmission.

An additional very serious threat to the future of malaria is caused by the acceleration in the development of insecticide resistance that is currently occurring in many African malaria vector populations. There are currently only four classes of insecticide approved by WHO for use in IRS (organochlorines, carbamates, organophosphates and pyrethroids) and only one class, the pyrethroids, suitable for use on LLINs. Monitoring and evaluation activities are too frequently marginalised in large-scale vector control programmes and this missed opportunity has contributed to the paucity of data on the impact of resistance. However, what is already very clear is that levels of insecticide resistance in malaria vectors are increasing at a very rapid rate throughout sub Saharan Africa and, if left unchecked, could slow or even reverse the recent gains in reducing the malaria burden.

Numerous additional vector control measures have been tested in the laboratory or in field situations but have not yet been translated into field applicable interventions. Further development and research into these novel interventions must proceed down a clear translational pathway towards

demonstration of epidemiological effectiveness and sustainability in the field. This will require a substantial investment in local capacity development to monitor and evaluate these new tools in sub-Saharan Africa. The impetus must be on providing evidence through laboratory based research to develop or optimise tools, and robust controlled field trials, to demonstrate the added benefit of combining these different control measures. We cannot meet the expectations of policy makers, funders and the afflicted populations to scale up malaria control towards elimination without both new tools and new knowledge of their efficacy in different transmission settings.

JUSTIFICATION FOR THE PROJECT

The current methods utilised for malaria vector control are effective but not sufficient and face several emerging threats to their efficacy. They must be supplemented by new tools that can be used in an integrated manner with existing interventions, in a range of different malaria transmission scenarios to target all vector species and must be safe-guarded by investing in evaluating alternative chemicals or delivery mechanisms that will minimise the impact of insecticide resistance. The AvecNet project proposed an exciting portfolio of multi-disciplinary and fully integrated projects, each led by world-recognised experts in their specific disciplines, to contribute both primary research and translational development of pragmatic, urgently required tools and resources. The successful completion of the work has already directly impacted operational malaria control and will continue to do so beyond the life of the project.

PROJECT OBJECTIVES

1. Develop and evaluate new tools, and combinations of existing tools, for mosquito control to enable stakeholders to make informed evidence based decisions on appropriate vector control interventions

2. Expedite the development of new insecticides for malaria control by building capacity for robust laboratory and field trials of new insecticides and formulations provided by industrial associates.

3. Improve the delivery of insecticides to their *in vivo* target sites by identifying and addressing key behavioural and pharmacokinetic parameters that impair insecticide efficacy

4. Exploit knowledge of vector and human behaviour to identify novel opportunities for interrupting mosquito-mediated transmission of malaria and to determine how behavioural plasticity impacts on the efficacy of alternative interventions

5. Determine the impact of the major demographic changes and the large-scale implementation of malaria control tools on vector behaviour and population structure

6. Develop research capacity in malaria vector control in Europe and Africa and strengthen partnerships in Africa

7. Maximise synergies between African, European and global networks and organisations with a commitment to malaria vector control to provide clear guidance on best practices

THE AVECNET APPROACH

The AvecNet work plan recognised the commendable achievements that have been made in malaria vector control in recent years and sought to improve on these by **optimising existing interventions**, **developing new or improved tools** that complement these interventions, increasing the knowledge base on the **biology and behaviour of mosquitoes** and planning for **vector control in a changing environment**.

1. Optimising existing interventions

AvecNet tackled the growing threat of insecticide resistance to malaria vector control by characterising the extent of the problem and developing strategies to mitigate it. In addition the project looked to future-proof malaria vector control, by supporting the development of a pipeline of new insecticides that are suitable for use in proven applications such as LLINs and IRS is required. By characterising and colonising populations of malaria vectors with a range of different resistance phenotypes and by building capacity for laboratory and field screening of new active ingredients or insecticide formulations the project accelerated the development of new public health insecticides.

Improvements to product design will also emerge from studies of mosquito interactions with insecticide treated surfaces using a new, non-lethal mosquito sensor developed by AvecNet partners and by studies at the physiological level, to identify the major attrition points from the point of insecticide contact to binding to the receptors on the target sites in the insect's nervous system which are being utilised by our industrial partners to improve insecticide formulation chemistry.

2. Developing new or improved tools

The project supplemented existing front line interventions by evaluating alternative insecticide delivery systems and developing and optimising tools to tackle outdoor transmission. The latter included new formulations of spatial repellents and optimisation of the application of larval source management (LSM) approaches to reduce the cost and logistics of existing source reduction strategies or indeed identify where spatial targeting would lead to a reduction in effectiveness. Also included in the AvecNet portfolio was a large scale clinical trial to compare the performance of a new combination LLIN, containing a pyrethroid and an insect growth regulator, with conventional, pyrethroid only LLINs.

3. Increasing the knowledge base on the biology and behaviour of mosquitoes

AvecNet developed new tools and knowledge to quantify key behaviours most likely to influence vector susceptibility to control interventions: location of biting (inside versus outside), location of resting (inside versus outside), host species choice, time of biting and vector species composition. These indicators were used to record changes in mosquito behaviour or population structure that resulting from either increasing use of insecticides in the domestic environment or an increasingly urban pattern of malaria transmission.

4. **Planning for vector control in a changing environment**

The opportunity to study behaviour over a five-year period, coupled with the historical samples and data sets that members of the AvecNet consortium had previously collected over the past two decades, provided an opportunity to record the plasticity of the mosquito population.

Research Capacity Strengthening

AvecNet increased the vector control capacity in Europe and Africa by investing in individuals and institutes. We fully supported six PhD candidates and provided technical and mentorship support to a wide network of junior scientists. Multiple on-site training programmes were held including practical courses in improving the quality of vector control trials and workshops on statistical analysis, research ethics and qualitative research. We strengthened infrastructure in our African partner institutes by investing in developing field sites but also in providing support to strengthen financial and project management.

DESCRIPTION OF THE MAIN S & T RESULTS

WP2: CONTROLLING INSECTICIDE RESISTANT POPULATIONS

Objectives: To characterise the causes and extent of insecticide resistance in malaria vectors in the field sites in the work programme, and to use this information to develop new and improved tools to detect insecticide resistance in Africa; to evaluate new insecticides or formulations provided by industrial partners to control these insecticide resistant populations in the laboratory and field.

Major results by task:

Task 1: Identification and validation of genes responsible for insecticide resistance. (**LSTM**, NIMR, CSRS, CNRFP, CNRS) Yr 1-3

Insecticide resistance developed at an alarming rate in the field sites since the onset of the project. The Tanzanian site, which was initially selected as a susceptible field site is now reporting pyrethroid resistance and the intensity of resistance to this class of insecticides has increased dramatically in Burkina Faso over the past five years. Malaria vectors in the Tiassalé site in Cote d'Ivoire were found to be resistant to all four classes of insecticide currently available for controlling adult mosquitoes and are likely to be unresponsive to standard insecticide resistance management practices. Our three PhD candidates, Ako Constant Edi, Toé Kobie Hyacinthe and Theresia Nkya, working in Cote d'Ivoire, Burkina Faso and Tanzania have characterized the status and underlying mechanisms responsible for this resistance. The critical role of agriculture use of insecticides in selecting for resistance in malaria vectors has also been demonstrated.

Task 2: Development of a field applicable tool for vector population and resistance monitoring. (**UoC**) Yr 1-2

Our initial approach to developing a multiplex diagnostic using a Thin-Film Biosensor Chip assay terminated at the end of Year Two due to lack of engagement by our commercial partners. However we did have success in developing an antibody based diagnostic to enzymes involved in cuticular hydrocarbon synthesis; our current data suggests that overexpression of these enzymes is responsible for reducing the rate of penetration of insecticides in some highly resistant populations.

Task 3: Evaluation of new insecticidal compounds against mosquito populations resistant to current insecticides (LSTM, **STPH**, NIMR, CSRS, CNRFP, IVCC). Yr 1-4

Working in close partnership with the 'Liverpool Insecticide Testing Establishment' (LITE) we evaluated new insecticidal products provided by industrial partners. In total over 400,000 mosquitoes from a range of resistant and susceptible colonies maintained by LSTM were screened against chemistries provided by industrial partners including BASF, Bayer CropScience, Syngenta, Dow and AkzoNobel. The results of these bioassays have been utilized by the insecticide manufacturers to optimize the development of their new chemical entities. New mosquito colonies were established from our field sites to aide in the screening process.

Task 4: Experimental Field evaluation of new insecticidal formulations (**NIMR**, CSRS, UG, CNRFP, IVCC, LSHTM) Yr 2-5

Experimental hut stations were built at Tiassale, Cote d'Ivoire and Tengrela, Burkina Faso to increase the capacity to evaluate insecticide resistant populations in the field. A total of seven different products were evaluated under this workpackage

Product	**Site**	**Outcome**
Indoxacarb IRS	Tiassale, Cote d'Ivoire	Terminated due to poor performance of product
Sumishield IRS	Tiassale, Cote d'Ivoire	Proceeding to WHO registration
Malathion IRS	Tiassale, Cote d'Ivoire	Encouraging results, formulation work ongoing
Insecticidal Paint	Tiassale, Cote d'Ivoire	Terminated as non-pyrethroid formulation unavailable
Durable Lining	Tengrela, Burkina Faso	Problems with product stability – further formulation work ongoing
PBO LLINs	Tengrela & VK5, Burkina Faso	Normative guidance on use issued by WHO
Eave Baffles	Kilombero valley, Tanzania	Proof of Principle, further development ongoing

Summary of Important Findings

- Recommendation to WHO on revisions to insecticide resistance monitoring guidelines
- Demonstration of cross resistance (both positive and negative) between insecticide classes caused by elevated levels of mosquito P450 enzymes
- Confirmation that xenobiotics used in agriculture can cause short-term induction, and long term selection for insecticide resistance in mosquitoes
- Over 400,000 mosquitoes from laboratory colonies screened to identify new lead chemistries for the development of new public health insecticides
- Field trials of four alternative IRS chemistries/formulations led to two progressing to next phase
- Field trial of PBO LLINs contributed to guidance on deployment of this product from WHO.

WP3: IMPROVING INSECTICIDE DELIVERY

Objectives: To employ an interdisciplinary systems approach to identify the key behavioural and physiological factors influencing the delivery of pyrethroid insecticides from the impregnated surfaces to the target site in the central nervous system of the mosquito. Key objectives are:

1. To develop state of the art systems for recording single mosquito movement.
2. To determine precise models of mosquito interaction with insecticide treated surfaces.
3. To identify the physio-chemical and biological barriers to insecticide transport in vivo.
4. To develop in vitro assays and structural models to screen novel insecticide preparations.

Major results by task:

Task 1: Development of a non-lethal mosquito tracking system (LSTM, (subcontract: **University of Warwick**)) Yr 1-2

The successful development of the mosquito tracking system, and its deployment under field conditions was one of the major outputs of AvecNet. A collaboration between engineers and entomologists led to the development of a field deployable camera system, consisting of two Fresnel lenses, an illumination source and a camera with an imaging lens. This system generates 2D position information enabling previously unseen mosquito behaviour to be recorded and analysed. A 3D tracking approach using a retro-reflective screen in place of the second Fresnel lens has also been developed.

The 2D system was established at the field site in Mwanza, Tanzania. The hut is located adjacent to large anopheles breeding sites; the large plywood hut structure has open eaves similar to those on local houses, allowing access to mosquitoes; experiments are monitored and all data recorded from the smaller control room adjacent to the expt hut. This second hut functions as the control room from which all mosquito-tracking experiments are recorded; during experiments, all humans (with the exception of the volunteer within the expt. hut acting as bait) remain inside this control room to avoid influencing behaviour of mosquitoes in the expt. hut.

Task 2: To determine precise models of mosquito interaction with insecticide treated surfaces (LSTM, (subcontract: **University of Warwick**)) Yr 3-5

The tracking system enabled details of flight activity of malaria vectors seeking to reach a human bait within an untreated bednet or LLIN to be fully described with unprecedented detail. The results showed that LLINS act incredibly rapidly. Activity at baited nets, both untreated and LLINs, was higher than at unbaited nets. Mosquitoes orientate to the human host as indicated by the higher tortuosity levels in the baited net tests. Furthermore, velocities measured immediately prior to net contact were virtually identical in both untreated nets and LLINs, with no indication that mosquitoes were repelled or deterred by the insecticide at close range. Furthermore, there were no significant differences in the time lag prior to the initial mosquito's response, indicating there was no distant or spatial insecticidal effect on behaviour. Hence we conclude that LLINs act by an "attract and kill" principle.

The importance of the bednet roof was demonstrated by showing that most flight activity is also focussed at or around the roof, regardless of the flight path of the arriving mosquito. This information has been critical to the filing of patent related to an improved design of LLINs to maximise contact with insecticides.

Task 3: Identification of major attrition points in delivery of insecticide to the target site (LSTM, **UoC**). Yr 1-4

Work under this task provided the first evidence for reduced insecticide penetration as a mechanism

contributing to pyrethroid resistance in Anopheles gambiae mosquitoes. Using 14C labelled insecticides, we showed that the rate of penetration of pyrethroids was reduced in resistant mosquitoes and were able to attribute this to both quantitative and qualitative changes in the cuticular hydrocarbon content. Furthermore, we identified two cytochrome P450s, located in the cellular layer under the cuticle, whose expression is elevated in resistant mosquitoes. These P450s catalyse one of the final steps in cuticular hydrocarbon synthesis and we confirmed that ablating these genes, dramatically altered the cuticular structure. Further work under this task also identified a subfamily of ABC transporters, localised in the cuticle. Again, expression of several of these is elevated in resistant mosquitoes and we postulate that these may be involved in modifying the cuticular structure to slow down the rate of insecticide penetration.

Task 4: Development of assays to screen for inhibitors of insecticide metabolism (CNRS, LSTM, UoC). Yrs 1-5.

A panel of mosquito insecticide metabolising enzymes was generated and used for early screening of new active ingredients provided by industrial partners. *In vitro* assays that measure enzyme-insecticide interactions were successfully deployed to provide early warnings of potential cross resistance between existing insecticides widely used in malaria control and new candidate public health insecticides. This screen has provided exceptionally valuable in product development and has been used to inform resistance management strategies.

Summary of Important Findings

- A non lethal tracking system that enables mosquito behavior to be visualized for the first time has been developed.
- The mode of action of insecticidal treated bednets has been characterized with unprecedented detail leading to proposed improvements in bednet design which have generated interest from our industrial partners
- A new pyrethroid resistance mechanism has been described in malaria vectors which has important implications for insecticide design
- A panel of mosquito enzymes have been developed that are being widely used as a pre-screen for potential cross resistance challenges.

WP4: DEVELOPING NEW TOOLS TO TARGET MOSQUITOES OUTSIDE THE HOME

Objectives: To field test a range of interventions to specifically target malaria transmission caused by mosquitoes biting outside the home.

Major results by task:

Task 1: Review of study design (STPH, IHI, **UG**) (Yr 1)

Study designs for all activities in this WP were discussed during the kick off meeting and target product profiles were developed, shared and refined by all partners.

Task 2: Insecticidal treatments for livestock (UG, **IHI**) (Yr1-2)

Anopheles arabiensis is becoming increasingly important as a malaria vector as LLINs and IRS impacts

on *An. gambiae* and *An funestus*. *Anopheles arabiensis* frequently prefers cattle over humans. Small-scale cattle ownership is on the increase as a tool for economic improvement in many parts of Africa. Insecticides are routinely applied to cattle to control ectoparasites. This task set out to determine if this practice could also reduce the risk of malaria to cattle owners. Surveys of cattle owners identified the most common insecticides applied and experimental hut studies were used to measure the efficacy of these in protecting cattle from *An arabiensis.* This was followed by semi field studies to establish whether insecticide treated cattle increased the risk of divergence to nearby humans; results indicated an increased of human exposure if cattle were >15m away from the households. The use of insecticides on cattle was therefore not considered to be a viable malaria prevention tool in these settings.

Task 3: Transfluthrin-treated mats (**IHI**) Yr1-2)

The efficacy of the spatial repellent, transfluthrin, was assessed by application of the chemical to sisal sacking. This delivery format avoids direct contact with the chemical and uses material readily available in rural Tanzania. Initial results showed that a freshly-treated sisal strip reduced mosquito attack rate on human volunteers by >99% and consistently conferred >90% protective efficacy for a period of 6 months. This study was therefore extended beyond the original 2 years. Surprisingly, some level of protection was still evident for 2 years after product treatment. Furthermore the sisal strips provide considerable protection to nearby non-users at distances of up to at least 5m and no evidence of increased risk to non-users beyond that distance was obvious. These results are very encouraging for the development of a low cost, safe and acceptable method to protect against outdoor biting mosquitoes and this approach is being aggressively pursued with follow on funding

Task 4: Odour baited traps (**IHI**) (Yr1-2)

The development of a synthetic odour lure, more attractive than a human being for mosquitoes commonly present in rural Africa, led to the development of locally manufactured traps that dispense the odour lure and can be used to trap mosquitoes. Simulation models suggested that between 20and 125 such traps per 1000 people should be sufficient to achieve malaria transmission control equivalent to 50% community-wide coverage with LLINs. We therefore designed a series of experiments to determine if these prototype odour-baited traps (OBTs) could achieve these encouraging predictions when deployed at the village level Unfortunately, an experiment to determine whether we could replace compressed CO_2 cylinders with alternative, more practical CO_2 sources was not successful, with neither kerosene lamps nor yeast-fermented sugar even approaching the gold standard compressed gas format. It therefore became apparent that it would not be possible to identify a suitable source of CO2 to service the large number of traps needed for the trial and this task had to be terminated early. Unused resources were diverted to Task 3 in WP4.

Summary of Important Findings

- A long lasting, low cost format to dispense the spatial repellent transfluthrin was developed and is being evaluated in a variety of transmission settings to control both Anopheles and Aedes borne disease.

WP5: IDENTIFYING NOVEL OPPORTUNITIES FOR INTEGRATED VECTOR CONTROL

Objectives: To identify new opportunities for integrated approaches to vector control by running

experimental hut trials to test the efficacy of combinations of interventions and/or insecticides compared to current best practice, exploring approaches to improve targeted larviciding and by observing practices utilised by householders to prevent mosquito biting.

Major results by task:

Task 1: Review of study design (STI, IHI, **UG**) (Yr1)

Study designs for all activities in this WP were discussed during the kick off meeting and power analyses were conducted by AvecNet statisticians. These discussions led to the publication of guidelines on power analysis for experimental hut studies.

Task 2: Experimental hut trials to explore alternative delivery systems for insecticides. (**LSHTM**, NIMR, CSRS).

The rapid increase in resistance to pyrethroid insecticides means that new tools are urgently needed that can be used against pyrethroid resistant vectors of malaria. This requires identifying practical means of effectively delivering alternative insecticides either alone, or in combination, inside traditional dwellings. In this task we investigated two new delivery mechanisms, durable lining (DL) and net wall hangings (NWH), to deliver the organophosphate insecticide pirimiphos-methyl. These products were evaluated as single interventions and in combination with LLINs in experimental huts in 3 study sites. P-methyl treated DL and NWH outperformed pyrethroid treated DL and NWH in all study sites demonstrating their potential efficacy against pyrethroid susceptible and resistant populations of malaria vectors.

P-methyl DL and NWH killed almost all pyrethroid resistant *An gambiae* that entered the experimental huts in Vallee du Kou (Burkina Faso) since the population was largely susceptible to this insecticide. Even though this high kill was not observed in Tiassale owing to the presence of organophosphate resistance at this site, the p-methyl wall treatments still performed better than the pyrethroid.

P-methyl NWH were found to be easier to set up on walls compared to p-methyl DL. In this pilot study the bioactivity of the insecticide on the treated materials declined to about 50% by the end of the six week trial. This was not unexpected as the formulation had not been optimised for these delivery formats. Thus, although this study demonstrated the potential of these delivery formats, alternative formulations would be needed before P-methyl treated NWH or DL can be considered as an option for vector control.

Task 3: Rationalizing mosquito larval source management to develop a cost-effective tool for integrated vector management in Africa (KEMRI, **LSHTM**, IHI) (Yr1-2)

Pilot studies of targeted larval source management (LSM) were performed to test the operational feasibility and efficiency. In Western Kenya, application of the larvicide SumiLarv during the high transmission season only (4 months: March to June) had a similar impact on habitat colonisation throughout the year as all-year-round application. However, larval densities were only significantly reduced in the habitats they occurred during the application time. Importantly, significant reductions in immature colonisation and emergence were observed even during the low transmission season indicating that the impact of the Sumilarv applications lasted several months beyond the last date of application. Even though reductions were not as high as those observed in the all-year round

interventions, we consider them sufficiently high to warrant further exploration of this time-targeted strategy for integrated malaria vector control targeting the main transmission season.

In Dar Es Salaam, quarterly mosquito density maps were generated and provided to the National Malaria Control Programme in Dar Es Salaam, in order to enable targeted intervention of larviciding by the government.

Task 4. Understanding householder practices to prevent mosquito biting in the home. (**KEMRI**, LSHTM, CSRS, IHI) (Yr1-2)

Whenever there are large numbers of mosquitoes, householders will use a variety of methods to protect themselves from being bitten within the home. These will not necessarily be related to perceived or actual risk of malaria transmission. Identifying these practices, understanding the factors that influence their use, and determining how this varies in different socio-economic and environmental settings, is essential in order to design effective interventions that will be accepted and used by local communities to prevent mosquito-mediated transmission of malaria. We used focus group discussions, participatory observation via 'photo voice' and structured interviews to collect data on householders perceptions and practices related to prevention of mosquito biting.

In Cote d'Ivoire, participants identified poor sanitation and drainage, and agricultural practices as the key drivers for mosquito numbers. There was general reluctance to use LLINs, despite these being distributed for free by Government programmes. In contrast, in Tanzania, use of bednets was seen as 'part of our culture' and they were the most frequently cited method of mosquito protection. There was good awareness of the importance of outdoor biting and again, environmental management and sanitation was perceived as the best means of reducing this.

The studies in both sites were a reminder of the importance of practicality and credibility in developing new vector control tools. Tools need to be user friendly, affordable, available and effective and, even these criteria are met they will still require time to develop a reputation for reliability and trustworthiness.

Summary of Important Findings

- Proof of principle studies demonstrate effective means to reduce the cost and practical challenges associated with larval source management.

WP6: RANDOMISED CONTROL TRIAL FOR ASSESSING THE PROTECTIVE EFFICACY OF NOVEL TOOLS FOR MALARIA CONTROL

1. To determine whether a new tool or combinations of tools provide better protection against clinical malaria in children compared with long-lasting impregnated nets (LLINs) alone in an area with pyrethroid-resistant vectors
2. To determine if the additional (marginal) benefit of malaria cases averted by the new tools justifies additional cost
3. To determine the acceptability and utility of the new tool(s) over current best practice (LLINs)

Task 1. Decision on which intervention/s to take forward to randomised phase III control trials (Project Management Committee, ETAG).

At the outset of the project it was agreed that we would conduct a large-scale field trial of a malaria vector control tool in an area with high pyrethroid resistance with the primary objective to evaluate an intervention that is expected to be effective at reducing malaria transmission, even in the presence of pyrethroid resistance. We specified that the product had to be sufficiently advanced down the translation pipeline for it to be implemented at scale, if the evidence generated in the trial supports this. A scoping study of potential interventions that would meet the above was conducted with input from all AvecNet partners. This resulted in 8 possible interventions, which was reduced to four following discussion at the Management Committee and advice from our External Technical Advisory Group. The final decision was made to evaluate the new combination net, Olyset Duo, manufactured by Sumitomo Chemical Ltd in a trial to be conducted in Banfora, Burkina Faso.

Task 2 Plan and implement randomised phase III control trials (UDUR, CNRFP, LSTM)

The clinical trial was a two-armed step-wedge, cluster, randomized, controlled efficacy trial. Conventional, pyrethroid only Olyset LLINs were compared with the dual active permethrin and pyriproxifen Olyset Duo nets from Sumitomo Chemical Ltd. Pyriproxifen (PPF) is an insect growth regulator which, in addition to inhibiting metamorphosis or mosquito larvae, sterilises female mosquitoes and reduces their lifespan. Using a computerized algorithm, PPF-LLINs were allocated to 5 clusters and LLINs to 35 clusters at the start of the trial in Burkina Faso. LLINs were exchanged for PPF-LLIN by cluster, selected, in a step-wedge fashion; so 3 months before the end of the 2 year trial all participants had a PPF-LLIN. In each cluster, 50 children, aged 6 months to 5 years, were surveyed at the start of the 2014 transmission season and followed in 2014 and 2015 by passive case detection for clinical malaria. The primary endpoints were clinical malaria incidence measured by passive case detection.

Task 3. Completion of trial and assessment of effectiveness of new tools (UDUR, CNRFP)

A total of 29,084 LLINs were distributed to cover the 30,608 sleeping places identified during the pre study population census with an overall coverage rate of 95.02%. Results show a reduction in clinical incidence of malaria in the Olyset Duo arm in the first year of the study. No difference in malaria prevalence was observed although the number of children with enlarged spleens (a clinical symptom of malaria) was considerably lower in the intervention arm than the control. Further statistical analysis is ongoing

Wild mosquitoes collected in sentinel sites with Olyset Duo showed evident signs of reproductive impairment even after 1 year of deployment indicating that the PPF on the nets was still effective. Insecticide resistance strength was monitored during the trial in several sentinel sites, and time-response data showed an overall reduction of permethrin resistance strength after the distribution of Olyset Duo.

Summary of Important Findings

- The first clinical trial of a new paradigm in bednet design was successfully completed. Results show that the inclusion of a mosquito sterilising agent into LLINs can reduce the incidence of malaria in a site with high malaria burden and vectors that are extremely resistant to

pyrethroids.

WP7: NEW TOOLS FOR MONITORING HETEROGENEITIES IN VECTOR SPECIES COMPOSITION AND BEHAVIOUR, AND THEIR POTENTIAL IMPACT ON CONTROL MEASURES.

Objectives: To apply knowledge of vector behavioural traits and population structure to inform the successful implementation of integrated vector management. Specifically, this WP aims to: 1) develop new cost-effective tools for measuring the outdoor-biting and outdoor-resting behaviour of African malaria vectors; 2) optimize and test these tools against existing methods to identify the best methods for routine vector population surveillance; 3) evaluate the impact of urbanisation and vector control measures on behavioural and genetic heterogeneity in vector populations, and the consequences of this for the effectiveness and sustainability of specific interventions

Major results by task:

Task 1 - Development of new tools to sample mosquito behaviours outside the home (CNRFP, IHI, **UNIROMA1, UG**) (years 1-2)

Most existing front line vector control interventions focus on mosquitoes that bite and rest inside the home. The importance of mosquito populations with alternative behaviours in malaria transmission in Africa, and the pace at which traditional behaviour patterns are being altered as a result of manmade changes, has, until relatively been relatively unexplored, partly due to the lack of suitable monitoring tools. In this work package we developed new tools to assess the extent of outdoor biting (exophagy) and resting (exophily) in African vector populations.

A patented design for a mosquito electrocuting trap (MET) has been developed and shown to be highly effective in collecting outdoor mosquitoes in field evaluations in Tanzania and Burking Faso. The MET has attracted considerable interest from external partners and is now being piloted in studies in Asia, Latin America and Africa.

Two alternative prototypes of resting traps have been now been developed, evaluated and published: the resting bucket and the sticky resting bucket. Trials in Tanzania show the former trap to be superior whilst the opposite was found in Burkina Faso. This may reflect differences in the vector population and/or local climate and ecology.

Task 2 - Assess the impact of urbanization on vector behaviour and population structure (**CNFRP**, UNIROMA1, IHI, UG) (years 1-5)

The availability of 20 years of historical collections of malaria vectors from Oubritenga province, Burkina Faso, provided an unprecedented opportunity to evaluate the impact of environmental changes due to increasing urbanisation on vector population structure. Anopheline vectors were samples along a transect of approximately 50 km, from urban sites in Ouagadougou area to increasingly rural sites including sampling sites from which data/samples from the past collections are available. Microsatellite analysis has been conducted on these samples and the results are still being analysed.

Task 3 - Assess the impact of vector control practices on mosquito behaviour and population structure (**IHI**, UG, UNIROMA1) (years 3-5)

Several studies have anecdotally or qualitatively reported shifts in vector host seeking behaviour and anthrophily following widespread LLIN and IRS use. However, conclusive data indicating whether behavioural shifts are a common response of African vector populations to interventions is lacking, and the epidemiological consequences of such behavioural shifts remain poorly understood. Using tools developed in Task 1, we examined the impact of vector control activities on vector species composition and on the four behavioural traits (i.e. exophagy, exophily, zoophily and biting time) that are most likely to influence vector susceptibility to interventions.

In the city of Dar es Salaam, scale up of LLINs through two campaign rounds of free distribution in 2010 and 2011 had no obvious impact upon the composition or host attack behaviours of the *An. gambiae* species complex beyond normal levels of fluctuation between different experiments. However, LLIN scale up has resulted in decline and the disappearance of *Anopheles gambiae* in the Kilombero Valley, with no specimen of the nominate species caught in the last 3 years, leaving *An. arabiensis* as the only species in the complex present in this setting Furthermore, detailed genetic analysis reveals little if any population structure within *An. arabiensis* in this setting and none that could be associated with specific behavioural phenotypes so the variability in host-seeking behaviour of this species is most probably mediated entirely by phenotypic plasticity.

Similarly, while the host attack behaviours of An. gambiae in Dar es Salaam remain essentially unchanged following LLIN scale up, the remaining *An. arabiensis* population in the Kilombero Valley exhibits dramatically altered feeding behaviours, with less than half of all attacks of residents lacking a bed net occurring indoors. No substantive changes in the host preference of this vector have occurred over recent years in this setting, where *An. arabiensis* appears equally likely to attack humans and cattle.

Task 4 – Model the impact of behavioural heterogeneities on efficacy of alternative vector control interventions (**UG**) (Year 5)

Laboratory observations indicated that insecticide resistant mosquitoes, which survived the immediate toxic effects of insecticides, were less fit than mosquitoes from the same population that had not been exposed to insecticides. The existence of 'sub lethal' effects of insecticide exposure had been proposed previously but there was a paucity of evidence for their existence in malaria vectors. In this task we investigated the impacts of resistance beyond immediate mortality. The existence of previously ignored delayed mortality effects presents a hypothesis for why the presence of pyrethroid resistance in African malaria vectors does not appear to have resulted in widespread reductions in LLIN efficacy. However, the study also highlighted that increasing resistance could erode the ability of LLINs to hold back malaria. As the degree of resistance increases, the magnitude of these delayed mortality impacts diminished and may eventually disappear. This study provided a proof-of-principle for the existence of these delayed mortality effects at a magnitude that could have significant implications for malaria transmission.

Summary of Important Findings

- A new Mosquito Electrocuting Trap, to measure host seeking behaviour, which reduces the risks

associated with these surveys has been developed

- The existence of previously undocumented delayed mortality effects in insecticide resistant populations provides an explanation for the apparent paradox of continued LLIN effectiveness in the presence of high insecticide resistance.

WP8: PROMOTING TRANSLATION AND ENSURING SUSTAINABILITY OF NEW INTERVENTIONS AND TOOLS

Objectives: To ensure that all the experimental tasks are explicitly focused on the translational pathway from the research environment to implementation and demonstrated sustainable effectiveness, and that transparent and independent decision making processes are in place to make the down selection of potential projects required.

Major results by task:

Task 1: Translational research and sustainability workshop **(IVCC)**

An introduction to translation workshop was delivered to all participants at the AvecNet Kick-Off Meeting in 2011. The workshop gave participants an understanding of the stop go approach to product development research which has been fundamental to AvecNet. Each work package team then identified the key translational questions facing their particular interventions or research activities and this was used to set decision milestones and guide research activities throughout the project lifetime. For WPs developing new tools, guidance was provided on the development of Target Product Profiles (TPPs) which clearly define the characteristics being aimed for in a product. TPP were used as the tool or benchmark against which stop go decisions were made for each product. The statistical analysis team ensured that the study designs being finalised had adequate power/sample size to address the question being posed.

Task 2: Ongoing advisory role **(IVCC)**

Work in this task has focussed on keeping industry partners informed and seeking their advice on specific issues, particularly in relation to development of projects under WP4 and WP5. For example Bayer was involved in discussions on the contact toxicity of transfluthrin which influenced the delivery mechanism taken forward, and later on provided funding to support measure the dosage of transfluthrin in the air. Relationships that were initialised by IVCC at the start of the project have continued independently with little direct support from IVCC. However a notable event is the annual IVCC stakeholder day which provides an opportunity for scientists to engage with private sector representatives. AvecNet scientists have been well represented at this event, notably in 2016 where we planned our end of project meeting to coincide with the IVCC stakeholder day.

Task 3: Translational Research Review Workshop and selection of candidate interventions for WP6. **(All)**

The management committee developed a list options for candidate interventions for the WP6 trial. Industrial partners were consulted to establish which products were sufficiently advanced to be included in the product short list. For all of the shortlisted candidate interventions, a full package of evidence was presented to the AvecNet Management Committee and the External Technical Advisory Group (ETAG) and a single product was selected. For the two remaining interventions, a summary of

the next steps on the translational pathway was produced, with the longer-term goal of seeking additional funding to evaluate these products in full field trials.

Task 4: IVCC ESAC 1 Ongoing review of new active ingredients and formulations **(IVCC)**

Throughout the project the IVCC ESAC1 provided on-going evaluation, support and guidance of the candidate ingredients and formulations being evaluated for the development of new public health insecticides. A rigorous stop go approach has been pursued involving laboratory testing of promising molecules on both susceptible and resistant mosquitoes; many of these colonies were established within the framework of AvecNet. Active ingredients that performed well in the laboratory tests are proceeding to lead candidate development. The portfolio of insecticide formulations (and delivery systems) being tested under AvecNet has also been scrutinised by the IVCC ESAC to ensure that unsuitable products are terminated and successful ones proceed rapidly along the developmental pipeline.

Summary of Important Findings

- Translational approach to product development has yielded success and resulted in termination of unsuitable products
- TPPs are a useful tool to guide research and development of new vector control tools
- Portfolio approach, a large consortium with multiple field sites and flexibility to rapidly re-programme resources is essential to efficient translational research

WP9: CAPACITY STRENGTHENING AND DISSEMINATION

Objectives: To enhance skills in disciplines essential to the successful completion of the project by providing specifically tailored short-term training courses; to strengthen research capacities in Africa by providing long-term training and mentorship for students and postdoctoral staff; to promote networking through South-South and North-South exchange programmes and to maximise the dissemination of information generated from AvecNet.

Major results by task:

Task 1: Training in skills essential to the successful completion of AvecNet (**AMANET, STPH**, UG, IVCC, LSHTM)

In the first three years of the project a series of short term training courses were run covering key aspects such as ethics, translational research, quantitative analysis methods, qualitative analysis methods and paper writing for all project scientists. Throughout the project consortium partners were consulted on their needs. As a result of these consultations a statistical support team initiated site visits to all five field sites and provided on-site training and one to one support. This was continued remotely during the life of the programme with additional site visits provided as required. The stats team have also provided support during the paper writing stage to many AvecNet scientists. It is worth noting that at the end of the project, statistical analysis skills were identified as an ongoing critical support requirement in many partners, including European based institutions. The development of statistical techniques for the analysis of vector control trials have been published and the R code has

been made freely and publically available allowing vector biologists outside of the AvecNet consortium to benefit.

Task 2: Quality assurance (STPH, IVCC)

A series of workshops were held covering Good Experimental Practice (GEP: Y1, Y3), Good Laboratory Practice (GLP: Y1) and Quality assurance systems (QA: Y5) with the aim of enabling those with responsibility for the management and conduct of vector control product efficacy trials to develop and implement research quality systems so as to achieve standards equivalent to GEP and GLP. A full set of standard operating procedures (SOP) for experimental hut studies were developed and made freely available via the AvecNet website. In addition, field sites have received on-going mentoring and auditing of research facilities in order to support ongoing quality improvements. Several of the sites are now in the process of applying for GLP accreditation status.

A work plan to identify major sources of variation in phase I (laboratory studies) and phase II (experimental hut studies) was implemented revealing that temperature, nutrition and population density during the larval stage all influence the susceptibility status of adult Anopheles mosquitoes.

Task 3: Long term professional development (All partners)

All six of the AvecNet funded PhD students who started their studies in Period One of AvecNet have now been awarded PhDs and critically are continuing to work in the field of malaria control. In addition the project has supported a further four PhD candidates and five MSc students by enabling them to utilize data from the project in their projects that are funded from other sources.

Four AvecNet scientists have obtained prestigious fellowships to continue research in the field of malaria control including one of the AvecNet funded PhD candidates. A further two scientists have obtained post graduate fellowships to continue working on data or new knowledge generated by AvecNet. Critically the network of scientists that have collaborated on that AvecNet project are continuing to work together and develop further scientific endeavour in this field. This is evidenced by the €23m in multiplier grants that have been awarded to AvecNet collaborators to date.

Task 4: Dissemination activities (AMANET (Yrs 1-2), LSTM (Yrs 3-6))

To date the AvecNet consortium has resulted in 49 peer reviewed publications and up to 40 additional publications are either submitted, in draft or planned. All publications have been published in open access journals are also available to download via the AvecNet website. A major end of project dissemination event was held in the UK in June 2016 where all AvecNet partners shared a summary of their research internally and externally to invited guests from academia, industry, policy fora and other grant funders. Results were demonstrated via scientific poster and oral presentations, but also using interactive exhibit stands, videos and attractive banners. The event was video and posted on the AvecNet website along with all posters, presentations and other materials to create a “virtual meeting”. AvecNet newsletters and the SOPS developed as part of work package 6 and 8 are available on the AvecNet website.

The project outputs have been disseminated extensively via major international conferences, at policy and technical meetings (documented via the participants portal) and via the extensive professional networks of the consortium team. Notably the research institutions in Ivory Coast, Tanzania and Burkina Faso have directly shared scientific findings with the Ministry of Health National Malaria Control Programmes. Community participants in the trial sites have also been sensitised to the results of the trial.

The state of the art mosquito tracking system developed in work package 3 has been demonstrated at a major UK public science event: the Royal Society Summer Science exhibition, London 2016 which was attended by over 14,000 members of public.

Summary of Important Findings

- Robust statistical support to field sites before, during and after field work has led to high quality and robust results reducing wastage and accelerating translation.
- There is an ongoing need for quality statistical support with one-to-one support necessary to supplement group training sessions in both Europe and Africa
- Contribution to new WHO guidelines for efficacy testing of spatial repellents and laboratory and field testing of long-lasting insecticidal nets
- Improvements in data quality for vector control trials have been recognised as a key issue and the AvecNet approaches have been adopted by WHOPES and the Innovation to Impact Initiative
- SOPs to improve experimental hut studies developed and freely disseminated via AvecNet website
- 6 Fully funded PhDs have been awarded, and a further 4 supported indirectly
- 4 AvecNet scientists including one PhD candidate, have been awarded fellowships
- AvecNet results have been disseminated via peer reviewed journals, the project website, conferences, at policy/technical fora and public events

WP10: STAKEHOLDER ANALYSIS OF ACCEPTABILITY ISSUES

Objective: This work package will evaluate the social acceptability of the new tools and interventions developed and/or tested within AvecNet.

Major results by task:

Task 1: Stakeholder assessment (IHI, CSRS, REACH, **LSHTM**)

Standard qualitative research methods (focus group discussion and interviews) and a novel technique involving community use of cameras to document views and perceptions was utilised in this task. Community perceptions and practice studies were conducted in rural and urban areas of Tanzania and Ivory Coast to identify perceptions of mosquito problems, views on responsibility for mosquito control and use of current protection measures. The results revealed that community members had a good knowledge of mosquito breeding and resting places, but were unaware that anyone was playing a leading role in mosquito control. However, they felt that the municipality, national government and community all had a role to play.

The implications for development and uptake of novel vector control methods are that they need to be practical (affordable, convenient, available, accessible, easy to use, adaptable) and credible (effective, safe, durable, govt advice/recommendation and in widespread use by others). The photo voice method was practical and effective and could be used to increase the level of community engagement in policy debates.

Policy level stakeholders and government actors were also widely consulted as part of policy analysis on the use of larval source management in Nigeria, PBO LLINs in Burkina Faso and the global level policy process for adoption of new vector control tools. This work revealed that adoption of new vector control tools at country level is heavily influenced by global policy making and financing decisions that countries have little power to influence. Other policy analysis work revealed a willingness by national governments to domestically finance vector control where it met broad economic development concerns. Critically the studies revealed that price rather than cost effectiveness effects decision making at the national level, and that the standards of evidence required to change policy are not clearly defined or consistently adhered to.

Task 2: Establishment of Local Stakeholder Advisory Groups (IHI, CSRS, **REACH**, KEMRI)

Community and householder perceptions were gathered to inform the development of insecticide treatment of cattle (terminated due to lack of efficacy) and the spatial repellent work conducted in work package 5. Householder/community level stakeholders were influential in informing the development of the format through which the spatial repellent (WP4) would be distributed. Following the rejection of the initial design idea (via a sleeping or prayer mat) due to concerns over contact toxicity, the possibility of using sisal fibres (cheap and readily available in Tanzania) was explored. Although the study identified that sisal was commonly used by householders, it also revealed that they had a preference for other products or found it impractical. This lead to the termination of this idea and ultimately to the development of an alternative approach.

Task 3: Acceptability of combination LLINs among communities in the Banfora Region, Burkina Faso **(CNRFP,** LSHTM**)**

Community acceptability studies were conducted alongside the distribution of the LLINs as part of the WP6 randomised control trial in Burkina Faso. The results revealed that people had a number of criteria for evaluating the nets which included their observable effectiveness at killing mosquitoes, durability, hole (mesh) size, physical appearance (colour) and size as well as other characteristics such as smell and perceived side effects. Respondents were also making clear comparisons between the nets distributed as part of the AvecNet trial (Olyset and Olyset Duo net) versus those distributed in the last national LLIN distribution campaign. The results reinforce those identified in the other tasks in this work package and clearly demonstrate that efficacy against malaria is not the only important factor to consider when developing new vector control tools.

Summary of Important Findings

- Communities and householders have a set of criteria for evaluating vector control products which is broader than efficacy alone
- Opportunities exist to increase domestic financing of malaria or anti-mosquito control if these are more closely linked to domestic priorities

- Global and National level policy and financing decisions are inter-related and must be addressed in tandem to accelerate uptake of new vector control tools
- Decision making and evidence thresholds need to be more clearly defined so that research can more effectively support this process.

IMPACT AND DISSEMINATION

In the initial proposal we identified six areas in which we were committed to make a significant impact. Progress under each of these is briefly described below.

1. **New and improved vector control tools to reduce the malaria disease burden in Africa.** We have completed a clinical trial of a new combination bednet, Olyset Duo, from Sumitomo Chemical Ltd, in Burkina Faso. Our strong partnership with industry, and our investment in resources for laboratory and field evaluation of insecticides, has continued to accelerate the developmental pipeline of new insecticides for malaria control. Insectaries and experimental huts built with AvecNet support have enabled us to expand the number of field sites for evaluating new products. The value of data arising from these trials in making stop go decisions, has been enhanced by detailed characterisation of the mosquito populations in each site.

2. **New tools to aid planning and execution of malaria vector control strategies**. AvecNet has developed a number of tools to facilitate evidence based decision making on the most locally appropriate malaria vector control interventions to employ. These include application of Geographical Information Systems to improve targeting and cost effectiveness of activities to manage mosquito larval populations; development of a panel of recombinant enzymes for screening chemicals for insecticidal properties; application of an ethnographic tool, Photovoice, to explore householders response to mosquitoes and development of a new trap, the mosquito electrocuting trap, to accurately record changes in host seeking behaviour of mosquitoes that would affect the efficacy of control tools. The tracking system, that enables mosquito behaviour to be tracked under natural settings, has generated a great deal of interest from industry partners, and data generated from this device by the AvecNet team has already resulted in a partnership with a major bednet manufacturer for a novel bednet design.

3. **A better understanding of the biology and the population dynamics of mosquito vectors transmitting malaria in Africa**. New tools to monitor mosquito behaviour (including host seeking and resting traps) have been used to observe and quantify the key behavioural traits that impact on malaria transmission. This will directly inform the design of interventions to target mosquitoes exhibiting particular behaviours. The mosquito electrocuting trap is now being employed to study the behaviour of other mosquito vectors, including those responsible for transmission of dengue and zika viruses.

4. **Increase European contribution to on-going global efforts to control and eradicate malaria and strengthening research partnerships and research capacities in Africa**. AvecNet has directly supported six PhD candidates, all of whom are continuing to work in malaria control, and provided mentorship to many other early career African scientists, several of which have secured their own independent funding as a result of data they generated within AvecNet. We have also invested in the infrastructure of our African field sites by building and equipping insectaries and experimental huts. Our focus on Quality Assurance is raising the standard of vector control trials within the community with several sites preparing to apply for international accreditation.

5. **Contribution to Community societal objectives**. Half of the world's population is at risk of malaria and up to 500,000 die from this disease every year. In addition to the devastating impact on human health, malaria also imposes an enormous economic burden, estimated at 1.3 per cent of economic growth per year in sub Saharan Africa. The principle role of AvecNet is to create a portfolio of new or improved vector control tools that are effective against insecticide resistant populations of mosquitoes, and evaluate these for efficacy and acceptability with all key stakeholders within the timeframe of the project. As such the programme has a direct societal impact by planning for a sustainable future for malaria prevention.

6. **Policy impact**. New vector control tools will not be translated into improved malaria control unless we actively engage relevant stakeholders from an early stage and deliver the economic and policy evidence base required to influence key actors. In addition to contributing to this evidence portfolio, AvecNet has conducted studies on the national and global policy frameworks influencing uptake of vector control tools.

Dissemination

The impact of AvecNet will not terminate at the end of the five year funding period. In contrast the deliverables will have their greatest impacts as the new tools and methodologies developed by the Consortium are adopted by control programme managers and policy makers. We will work closely with WHO and WHOPES to seek official recommendations for the new products and incorporate the improvements to methodologies into existing methods into 'best practice'. There is a need for further large scale trials to build upon the results from pilot studies conducted within the AvecNet programme and members of the Consortium will continue to work together to evaluate these interventions.

Attention is also turning to the question of "what next" for AvecNet. We aim to build on the successful partnerships and scientific findings to leverage further research funding to capitalise on AvecNets core strengths of capacity building, developing new tools and translational research. Hence we are actively targeting research funders to disseminate our scientific findings but also make them aware of our successful consortium.