Brussels, 23 June 2017

COST 038/17

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Investigation and Mathematical Analysis of Avant-garde Disease Control via Mosquito Nano-Tech-Repellents" (IMAAC) CA16227**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Investigation and Mathematical Analysis of Avant-garde Disease Control via Mosquito Nano-Tech-Repellents approved by the Committee of Senior Officials through written procedure on 23 June 2017.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16227
INVESTIGATION AND MATHEMATICAL ANALYSIS OF AVANT-GARDE DISEASE CONTROL VIA MOSQUITO NANO-TECH-REPELLENTS (IMAAC)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to address the quantitative and mathematical investigation of the effect of employing avant-garde mosquito control measures as part of the technological processes in the textile and paint industries. The measurement of these effects in population to improve the new generation of control measures is the core of this challenge. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 32 million in 2016.

The MoU will enter into force once at least five (5) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14.

TECHNICAL ANNEX

OVERVIEW

Summary

IMAAC aims at investigation and mathematical analysis of the effect of avant-garde control measures in vector-borne diseases involving day-time active mosquitos transmitting diseases like dengue, Zika, chikungunya and yellow fever. The control measures involve new technologies in textile and paint products based on nano- and micro-particles releasing repellents or pesticides in well portioned dosage. The study will also be expanded to scenarios using vaccines in combination with mentioned control techniques. The main focus will be on dengue fever transmitted via *Aedes aegypti* and *Aedes albopictus* mosquitoes in synergy with existing EU-projects, but the application will have also positive effects on other vector-borne diseases.

Nano- and micro-particles are used in textile production for various purposes, and can be used to release chemicals like repellents and insecticides in a well-controlled rate. First attempts in this direction have been made, but no efficacy studies could be performed yet. The spectrum of combinations of nano- or micro-particles, repellents, insecticides and types of textiles (or paint) has not been well studied. Especially, efficacy studies in cases using these control measures in combination with vaccines are unchartered territories and mathematical modelling has to be developed.

This Action aims to bring together experts from epidemiology, biostatistics, mathematics, biology, nano-technology, chemical and textile engineering to implement new techniques to combat mosquito transmitted vector-borne diseases. The key question remains, in how far such avant-garde measures can help to reduce the disease burden, eventually in collaboration with existing vaccines which turned out to have only limited efficacy on their own.

Areas of Expertise Relevant for the Action	Keywords
● Mathematics: Statistics ● Biological sciences: Biostatistics ● Chemical engineering: Medicinal chemistry, drug synthesis ● Materials engineering: Nanophysics for materials engineering applications ● Nano-technology: Nano-materials and nano-structures	● Epidemiology and Modelling ● Disease Control Measures ● Vector-borne Diseases ● Mosquito ● Dengue Fever

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination

● Investigation of the effect of employing avant-garde mosquito control measures as part of the technological processes in the textile and paint industries. Nano- and micro-particles release repellents or pesticides in well-controlled dosage. The Action would measure these effects in population to improve the new generation of control measures.

● The development of structure, coordination, and maintenance of a long-term European Network between Industry and Research Institutes pursuing the goal of a new generation of mosquito control measures with the long-term vision of field studies and cumulating licensing of the products.

● This Action will not only have an immense impact on healthcare in relation to mosquito transmitted diseases but has economic benefits for the industry by producing new kind of textiles, paints (and other products i.e. tiles).

● Dissemination of research results to general public to improve life quality in endemic countries and

research efforts towards new generation of control measures.
● Input for future market application of these new generation of control measures in coordination with private or public enterprises.

Capacity Building
● The core capacity objective remains, to assess how new avant-garde technologies against mosquito-disease spreading can help to combat the vector-borne disease burden. This objective will be fundamentally based on mathematical analysis of the acquired data during the pilot project.
● Gain expert knowledge from: 1) textile and paint research 2) related new material industries including nano-technology 3) research in mathematical epidemiology and biology. Combining this information with state of the art knowledge in mosquitoes and vector-borne disease spreading, to formulate strategies for their control.
● Knowledge exchange and development of a joint research agenda to join forces for theoretically, experimentally, and industrially tackling problems applying new techniques in combating mosquito-transmitted diseases. This information sharing will be fostered by various activities such as collaboration with existing EU projects and/or organizing new events.
● Initiating some pilot field study projects in the medium range future through the gained knowledge. Some advances have already been achieved in the development of repellents or insecticides. These will help us to reach the set targets with the help of mathematical tools developed by the theoreticians in this consortium.
● This Action will also help in long run to apply for EU or National grants to fund more costly research such as extended chemical and mathematical studies and field studies.

1) S&T EXCELLENCE

A) CHALLENGE

I) DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Zika, dengue fever, chikungunya and yellow fever are examples of vector-borne diseases (VBD) transmitted by day-time active mosquitoes. In 128 countries, in particular in tropical and sub-tropical regions of Asia and Latin America (notably highly populated countries, such as Thailand, Brazil, India and Pakistan) these diseases are a major health risk and a negative economic factor [see Fig1].

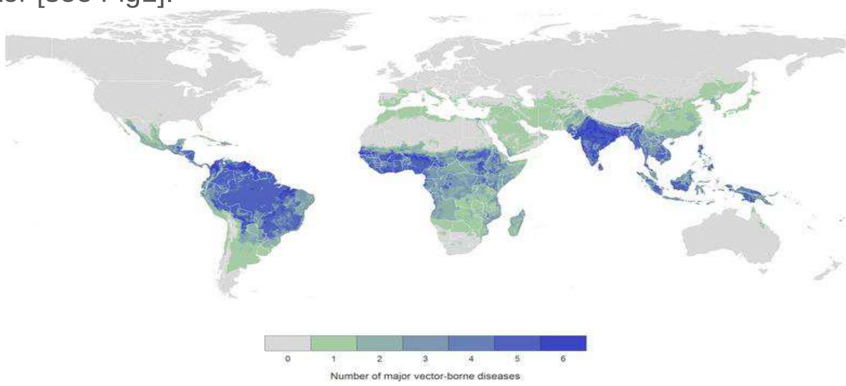

Fig.1: Combined global distribution of seven major vector-borne diseases for which integration of vector control programmes may be beneficial: malaria, lymphatic filariasis, leishmaniasis, dengue, Japanese encephalitis, yellow fever, and Chagas disease.

In 2010, infections with the dengue virus were registered in Croatia, France and Italy. In 2012 and 2013, patients having dengue fever were found on the isle of Madeira/Portugal transmitted by *Ae. aegypti*. Chikungunya infections occurred in Italy (2007) and Spain/France (2015). Eggs, larvae, pupae and adult mosquitoes of *Aedes albopictus* were repeatedly detected in the south of Germany in autumn 2014 and in 2015. Researchers assume from these findings that Asian tiger mosquitoes can survive the winter and settle in Germany. Over the past few decades, the incidence of dengue has grown dramatically. Recent studies indicate the existence of approximately 390 million dengue infections per year and that 3,9 billion people, in 128 countries are at risk of being infected with the dengue virus. The WHO has set the goal to constrain and control the spreading of dengue fever by 2020, however there are major obstacles in achieving this goal. Some vaccines are in advanced trial stages, but not effective against all serotypes (phase 3 results of the Sanofi Pasteur vaccine as front runner just concluded), and have negative effects in some age classes. WHO guidelines for vaccine trials are very detailed and specific in their requirements of scientific investigation before licensing (phase 1, 2, 2b and 3, finally phase 4 after licensing).

As previously mentioned, for dengue fever preliminary vaccine trials are running, but the results are not satisfactory. In general, regarding mosquito vector-borne diseases, vaccines are either quite imperfect, like DengVaxia for dengue fever (recently licenced by Sanofi-Pasteur), or do not yet exist as is the case for the Zika virus. In relation to yellow fever, the vaccine is even in some cases lethal. Classical mosquito control measures, such as bed-nets and municipal spraying in the streets, have proven to be of little effectiveness in combating disease cases. In mosquito control, some activities in demonstration of efficacy using bed-nets via the WHO are performed. One reason that the nets are not fully effective is that vectors of dengue, the species *Aedes aegypti* and *Aedes albopictus* are active in the morning and evening, but not very active at night. Another important aspect in eliminating mosquitoes by classical pesticides and insecticides, beside the danger to human health, is that the elimination of mosquitoes would also deprive many fish, birds, and reptiles of a food source and even destroy critical pollinator for plants. It is well-known that the emergence of insecticides resistance in *Ae. aegypti* and *Ae. albopictus* is described in the literature, which adds to the challenge.

Technological Challenge

The above issues regarding combating mosquito VBD are major challenges worldwide. The main focus of this Action is to develop a quantitative understanding by using mathematical modelling and techniques for the effect of introducing a new mosquito repellent technique usable for textiles, paints and other applications to combat VBD. The deduced data will help to improve the repellent technology and their specific applications but also trigger a proper understanding of transmission ways. Herein modified nano- and micro-particles applicable to many carrier substances are investigated, which continuously release mosquito repellents or insecticides, as an effective tool to suppress mosquito-transmitted diseases.

The main aim is the disease burden reduction of vector-borne diseases such as dengue fever with its 4 distinct serotypes and secondary infection as main risk factor of severe disease. Major problems and challenges, especially in dengue fever are:

1. In the present generation of vaccines: a) only limited vaccine efficacy of around 60% b) and further reduced efficacy against some of the dengue serotypes c) and finally even negative efficacy in seronegative persons, putting them at higher risk of severe disease than without vaccination. This especially of importance in young age classes with high numbers of seronegative susceptible and in travellers from non-endemic countries. The scientific community has spent that last 40 to 50 years in the attempt to develop vaccines against dengue fever.

2. Present mosquito control measures, mainly via insecticides, have shown limited to no effect on disease transmission (besides their health risks for humans and the appearance of resistance in mosquitoes). The main problem in this case is not that the total number of mosquitoes is decisive for present huge inter-annual fluctuations of dengue fever cases, but the long-time scales of human susceptibility against the different serotypes.

From the analysis of the problems and challenges 1. and 2. follows that new ways should be explored to block disease transmission, and not so much combat mosquitoes as a whole.
Repellents could be a way forward and now in combination with new technologies for smart dosages, i.e. micro- and nanoparticles applied to a variety of products including textiles, wall colours, tiles etc. The aim is also to protect relevant groups of people left out by other control measures like vaccines, essentially these are children, pregnant women and travellers. This poses significant new technological, socio-epidemiological and mathematical questions. Technical, because of the interaction between nanoparticles, repellents and fabrics or colours; socio-epidemiological, because of questions about where to protect first, what logistics is needed, which resources should be deployed for which control measure, like for imperfect vaccines, repellents and insecticides; and hence mathematical questions as follows:

1. Given the present understanding of complex diseases, like dengue fever with secondary infection as a major risk factor of severe disease (versus subclinical asymptomatic cases in primary and if at all relevant tertiary and quaternary infections), or with serotype competition as major driver for large fluctuations in severe disease epidemiological data (as exemplified in Thailand data over 30 years and all provinces), how much disease transmission reduction is needed to significantly reduce severe disease cases?

2. Given the at present available vaccine efficacies (of e.g. DengVaxia, licensed recently by Sanofi-Pasteur in several endemic countries, where the just concluded phase 3 trials gave empirical data via vaccine groups and placebo groups), what efficacies would be needed from additionally applied control measures, like conventional mosquito control via insecticides, what efficacies would new control measures like repellents in nano-particles need to have for significant impact in reducing the overall disease burden?

3. What evidence empirically is there on efficacies of mosquito control measures in terms of mosquito to human transmission reduction (like the mentioned repellents or even more microbiological blockings in mosquitoes, besides Wolbachia, this could be eventually simpler in mosquitoes than in humans since mosquitoes do not have complex immune responses and occasional side effects killing some mosquitoes would not matter too much)? What laboratory data are available (we are well aware that such data mainly exist on numbers of mosquito bites, not on disease transmission impacts)? What studies have already been conducted in the field, especially in terms of impact on disease burden, i.e. with mosquito control groups versus placebo groups (if any).Such trials are difficult for some control measures, not so for e.g. repellents like IR3535 which is colourless, and to humans as well odourless.

4. With present evidence of efficacies, what is the optimal strategy to deploy resources in combining vaccine campaigns and other disease reduction measures (repellents etc.)? This is a classical question of optimal control, just this time with economically feasible linear cost functions (which tend to give bang-bang controls and are therefore in mathematics often neglected against quadratic cost functions originating from physics problems with energy functional). Here is mathematically new territory to be explored in combination between complex non-linear disease models (as originating from question 1) and linear versus quadratic cost functions.

From these mathematical questions and literature data gathering, follow further empirical socio-epidemiological and technological questions as:

5. Socio-epidemiological: How can the database of efficacies be improved quickly to guide further mathematical modelling and political decision making (on the basis of complex models and optimal control)? Here a repellent like IR3535 can help to design trials with disease control and placebo groups, due to its physical and chemical properties being colourless and to humans odourless. The Action suggests (and have the logistics at hand) small pilot trials organized and conducted by motivated industry partners, and analysed independently by statistical evaluation in terms of efficacy and ultimately predicted impact in disease reduction. Connections with public health entities in endemic countries will support these first pilot studies, which later can be scaled-up depending on their initial results to larger trials in separate additional funding schemes.

6. Technological further questions: when efficacies turn out to be not yet sufficient to have the desired impact in disease burden reduction how can the interaction between repellents, nano- or micro-particles and carrier materials be quickly improved?

With this set of questions, an active and vivid interaction loop between industries (on technical questions), public health epidemiology (on efficacy trials), and mathematicians (on information collection, modelling the interplay between different information and decision guidance via prediction of intervention impact and optimal strategy combinations), is established to guide the activities of the proposed COST Action.

It is of course clear that NOT all questions can be answered in a satisfactory manner in 4 years of this Action, but an enormous step will be taken towards improvement of the understanding. New developments in mathematical models and tools describing the dynamics of VBD and mosquitos introducing avant-garde control measures. Theories already exist in produced papers by [W1] improvement of the already existing ready-to-use products like T-shirts, tiles etc. treated with nano-micro-particles with repellents with the help of [W2] and [W3].
Working on a plan to engineer a field study using the new control measures in an endemic country already in our network by distributing for instance T-shirts in several schools or using wall-paints

II) RELEVANCE AND TIMELINESS

Changing climate, worldwide trade, and travelling, lead to an increase of vector borne diseases and their occurrence in European countries as described. In recent years, mosquitoes that can transfer viruses causing vector-borne diseases, like dengue fever or chikungunya, were found in European countries, too. Additionally, the current flow of migrants from Africa and Asia into European countries bears the risk of spreading of diseases. The knowledge on the spreading of rare diseases and on the control measures of their prevention are the basis of the fight against them. The exchange of knowledge on these subjects within the consortium of partners from several countries, including some countries from Southern Europe where the occurrence of these diseases is more likely than in Northern European countries, will lead to higher awareness of the problem and to the development of measures of prevention. Therefore, the urgent need for translation of knowledge of nano- and micro-capsule technologies in combating mosquitos is of immense interest. It should also be emphasised that an EU Call (in Horizon 2020) tackling the mentioned problems is lacking until now. This Action will create a platform and necessary network to apply in future for national or EU research fund to finance the costly field studies and research on avant-garde mosquito control techniques.

B) SPECIFIC OBJECTIVES

I) RESEARCH COORDINATION OBJECTIVES

This Action aims at quantitative and mathematical investigation of the effect of employing avant-garde mosquito control measures as part of the technological processes in the textile and paint industries. Nano- and micro-particles release repellents or pesticides in well-controlled dosage. The Action would measure these effects in population to improve the new generation of control measures. The core of this Action is the development of structure, coordination and maintenance of a long-term European Network between Industry and Research Institutes pursuing this goal with the long-term vision of field studies and cumulating licensing of the products.
The main focus in the Action initially will be on dengue fever transmitted via *Aedes aegypti* and *Aedes albopictus* mosquitoes in synergy with existing EU-projects specific on dengue (Denfree, Idams, Dengue Tools), but the application will have positive effects on other vector-borne diseases transmitted by the Aedes species, like yellow fever, Zika and chikungunya. Depending on the use of relatively unspecific repellents or insecticides, other mosquito species will be hindered in spreading disease, such as Anopheles mosquitos spreading malaria. Nano- and micro-particles are used in textile production for various purposes, and can be used to slowly release chemicals like mosquito repellents and insecticides in a well-controlled rate, which can be more efficient than spraying on skin or other classical ways of application. Other applications could be the inclusion of nano-particles and micro-particles in wall painting

colours. First attempts in this direction have been made (as an example, the first mosquito repellent T-shirts have already been distributed in Brazil by one of the partners participating in this Action). However, so far, no serious efficacy studies could be performed and the spectrum of combinations of nano- or micro-particles, repellents, insecticides and types of textiles or paint has not been well studied to this point. In particular the application of these kind of measures combined with vaccines are totally unknown. The key question remains, in how far such new avant-garde technologies against mosquito- disease spreading can help to combat the vector borne disease burden, eventually in collaboration with (certainly in the case of dengue fever) existing vaccines and other measures which turned out to only have limited efficacy.

Unfortunately, researchers from different fields are not always aware of new developments in other research areas. This Action aims to bring together experts from the technological side from textile and paint research and related new material industries, from nano- and micro-technology, from repellent and insecticide industry and research in mathematical epidemiology and biology with expert knowledge in mosquitoes. Notably, in the case of dengue fever, as a multi-strain disease, good knowledge of different aspects of the disease have turned out to be crucial in understanding the large fluctuations in disease cases with years of very high burden followed by extremely low years etc., which make any efficacy tests challenging, independent of the control measures to be tested in the field. Addressing these open questions requires an interdisciplinary approach in order to bridge the involved fields in this Action.

II) CAPACITY-BUILDING OBJECTIVES

The core capacity objective remains how far based on mathematical analysis of the achieved data regarding new avant-garde technologies against mosquito- disease spreading can help to combat the vector-borne disease burden. The Action involves expert knowledge from textile and paint research and related new material industries, from nano- and micro- technology, from repellent and insecticide industry and research in mathematical epidemiology and biology, combined with state of the art knowledge in mosquitoes and vector-borne disease spreading and control. Knowledge is generated daily and available in research and industry, particularly in the face of the new occurring challenges presented by the presence of Zika in Brazil and USA, but the knowledge is fairly fragmented. This Action will provide help by various activities such as collaborating with existing EU projects, organizing new events to join forces tackling problems applying new techniques in combating mosquito transmitted diseases: theoretically, experimentally, and industrially. Since countries already struggling with dengue and malaria are connected to IMAAC, the Action will have good capacities to initiate some pilot field-study projects in future through the gained knowledge. Already some advances have been achieved in development of repellents or insecticides. This will help us to realize the set targets in the period of this project. The mathematical tools developed by the theoreticians in this consortium help us to define the set objectives in a measurable manner. This Action will not only have immense impact on healthcare in relation to mosquito-transmitted diseases, but has economic benefits for industry by producing new kind of textiles, paints, and other products, i.e. tiles. This would strengthen competitiveness in this field. This Action will also help in the long run to apply for EU or National grants to fund more costly research such as field studies.

C) PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

I) DESCRIPTION OF THE STATE-OF-THE-ART

Most of the products used in industry, in contrast to products developed by some of the industrial partners in this Action (hereinafter called Mosquito-Repel-Action-Product (MRAP) in this proposal), are insecticides, i.e., cause the death of invertebrate beings. Others mask the odour of humans, such as products containing Citronella oil, an essential oil that has a strong characteristic and very unpleasant flavour. MRAP consists on the repellences of mosquitoes without killing them or by disguising odours. One possible product which can be used as MRAP has a compound named 3- (N-acetyl-N-butyl) aminopropionic acid ethyl ester (or IR3535), which is a synthetic insect repellent and whose structure is related to beta-alanine. Through innovative nano particles, the repellent IR3535 can be fixed to various substrates (see figure 2), originating a highly effective product for the prevention through mosquito-repellency and combating diseases caused by insect bites, particularly those carrying the dengue virus.

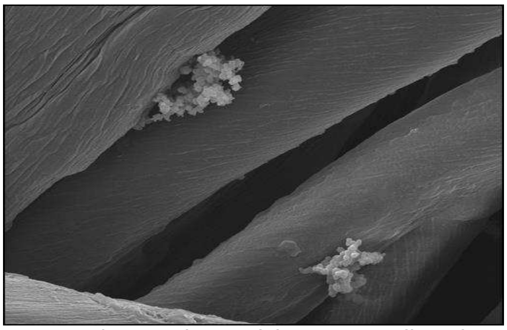

Fig.2: Repel Mosquito particles on a textile substrate

The mentioned product has revealed a high repellence efficacy rate against the mosquito species *Aedes aegypti*, as shown in various international laboratory test results. Through this Action additional types of MRAPs are planned with the final goal to explore the possibilities of performing field studies. Some of these products as T-shirts and tiles, are already produced and used in Brazil by one of the partners in this Action. The safety of anti-mosquito products for human health is another very important factor. Some active ingredients have started causing some concerns among scientists, such as Citronella oil, synthetic N,N-diethyl-meta-toluamide (DEET) and permethrin. In the case of Citronella oil, its effects are not yet proven within the EU and its use as an insect repellent, for humans and animals, is prohibited under the Commission Directive[1]. Health Canada is in the process of phasing out Citronella entirely as an insect repellent, because there is not enough data to prove the oil is safe when used in bug repellents. Regarding DEET, the United States Environmental Protection Agency (EPA) reported in the document Reregistration Eligibility Decision (RED) 14 seizures potentially related to exposure to DEET, including 4 deaths, from 1960 to 1998. Briassoulis, et al. (2001) tested the toxicity of repellents that contain DEET on children and concluded that they are not safe when applied on the skin and that its use should be avoided. Permethrin was classified by the EPA as ”Likely to be Carcinogenic to Humans”, based on studies in rats fed with permethrin, where they developed liver and lung tumours. Furthermore, this synthetic chemical can cause irritation and itching when in contact with the human skin. Eye exposure can induce a burning feeling and ingestion can lead to throat pain, abdominal pain, nausea and vomiting. When inhaled, Permethrin may cause headaches, respiratory irritation, breathing problems, dizziness, nausea and vomiting.

The active ingredient used in MRAP, like IR3535, has no toxic or irritation effect on the human skin and is well tolerated. This substance is also not likely to be toxic if inhaled or ingested. By demonstrating an excellent safety profile, its use is advisable in children and also pregnant women. The French Ministry recommended, in 2006, repellents containing IR3535 for children and pregnant women, during epidemics of Chikungunya. In addition, this active ingredient is used in Europe for over 20 years and is licensed for sale in the EPA since 1999. In the skin sensibility tests conducted by Pharmaceutical Research, the product has been classified as non- irritating. Regarding ecotoxicity, the repellent is safe for the environment because it has no toxic effect on other insects, or on aquatic organisms, unlike Citronella oil, DEET and Permethrin. It has to be emphasized that control measures using repellents are in general advisable for children and pregnant women, whereas measures should be taken for

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[1] 2006/50/EC of 29 May 2006 (amending Annexes IVA and IVB to Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal product on the market)

insecticides and pesticides in adults and not sensitive health cases. Using MRAPs is maybe a powerful tool advisable in cases like dengue, where vaccines are not recommended for children less than 9 years old and pregnant women. The other aspect is encapsulating MRAPs in nano- or micro-particles and the treatment of textile and paints. This is already done in the laboratory, but not on industrial scale (but a lot of research is needed to improve the specifications). And finally, the epidemiological mathematical tools needed to explore the efficacy based on data extracted from possible field studies using the avant-garde MRAP is at the core of this Action and the consortium of mathematicians and physicists have years of experience dealing with this kind of problems. In this relation, new mathematical methods and tools have to be developed to mimic the effects of MRAPs used in the field studies.

II) PROGRESS BEYOND THE STATE-OF-THE-ART

The MRAP used by members in this Action can be applied to new products or through tumblers (spraying and drying) on new or used products. Some of the applications, which already exist, are on curtains, sheets, towels, table bases, clothing or even additive for paints and varnishes. This could improve the mosquito-repellency in housing or working spaces. Unfortunately, little information has been published on the results of introduction of these avant-garde products in combatting mosquitos and related disease reduction. This gap can be closed in this Action through the better understanding of epidemiological data analysed by new mathematical tools developed and contribute to the understanding of the duration of the effectiveness of repellency which is not very well understood. Some other applications are in development through one of the participants, which leads to new generation of MRAPs and are the vision to be addressed by this Action. These new applications include ceramic materials that produce a mosquito repellent effect. This could be achieved by attaching chemically new generation of MRAPs developed in the framework of this Action or by plasma pre-treatment of the surface structure to attach these MRAPs. Domestic wash additive: an application for domestic wash of cloths that works by inserting the product into a bowl of clean water and stirring, are also being produced. When the cloth dries after washing, a mosquito repellent effect will be created that will last for a small number of washes. Laundry washing machine additive: an application for domestic use that works by inserting the product into the softener container of the washing machine. Spray for textile: an application to be use on any textile product that is intended to be sprayed at that same piece of clothing or textile before wearing/using. When dry, a mosquito repellent effect is created and will last until washed. Skin wipes: an application to be used on the skin, that produces a mosquito repellent effect. Bracelets: a product to be used on the wrists and ankles that produces a mosquito repellent effect and will last over 2 weeks. Synthetic grass: to be used in the production of synthetic grass, which after application produces a mosquito repellent effect and will last years. The mentioned products do exist or are in development. The mathematically measured efficacy of these products can be easily improved through this Action, since textile engineers, chemists and surface engineers are participants in this Action.

III) INNOVATION IN TACKLING THE CHALLENGE

Through the knowledge transfer between members of this Action, more advanced mosquito-repellent materials can be developed and new ways of applying these products on textiles and paints could be found. The new generation of repellents can be also applied to new materials like ceramics or washing additives (see also 1.3.2). The communication between industry and innovative research in this Action could be the key to achieve this goal.

Another aspect is, of course, the better understanding of the analytical methods to quantify parameters like efficacy in case of using these products in the society. In particular in combination of using possible vaccines. Many new theoretical tools are achieved by applying new theories (as in Control Theory) to make these kinds of quantifications more achievable through the real data. These new mathematical innovations will be more visible through the knowledge transfer expected in this project.

D) ADDED VALUE OF NETWORKING

I) IN RELATION TO THE CHALLENGE

Mosquito transmitted diseases are a major health concern and a pan-European interdisciplinary approach is needed to tackle the problem. The experts included in this Action come from many different scientific fields, industrial areas and countries. The Network includes textile-chemists, engineers, chemical-engineers, biologists, mathematicians, physicists, industrial managers and data-analysts, scattered in various systems (i.e. Research, Education and Industry). The networking will include both vertical and horizontal activities within and across the different groups, and gathers experts from textile, nano-technology, paint industry, epidemiology, biology and bio-statistics.

This COST Action has the great potential of reducing mosquito-transmitted diseases significantly, and produce new kind of materials and products combatting mosquitos without damaging the environment or the human health. This COST Action in this field is timely in face of the threats from Zika and various other mosquito-transmitted diseases in regions such as Latin America. One of the critical concerns regarding VBD is the possible connection between the Zika virus and microcephaly in newborn babies. Climate change and other factors facilitate the increase of such diseases even in countries that never had this problem.

II) IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

This Cost Action will provide synergies that will enhance the development of collaborative studies theoretically and practically. Some of the centres participating in the Action have expertise in certain subjects of which may not be available to other centres, yet they can contribute ideas, laboratory work and personnel to support such activity. Results can be used from EU-projects like EPIWORK, on modelling and data analysis of epidemiological systems or DENFREE, specific on modelling dengue fever, descriptive and predictive, including modelling control measures and invasion scenarios into new world regions like Europe due to Global Warming. Synergy effects are expected with other National, European or international level on research topics comprising textile functional finishing (FP7-NMP project NanoBond) or insecticide treatment of textiles (FP6-Integrated project FlexiFunBar; FP5-GROWTH project Green Mothproofing).

2) IMPACT

A) EXPECTED IMPACT

I) SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

This COST Action will have an impact first on the scientific knowledge of how much the vector-borne disease burden can be reduced by using new avant-garde mosquito control measures via e.g. nano-technology. Secondly, it will have impact in technological advances of improving the already existing mosquito-control by developing further the repellent nano- or -micro particle combination/treatment and the carrier material combination (textiles, colours etc.). Thirdly, advances in the understanding of mosquito infestation and its reduction and the effect on related disease burden will be investigated further so that efficient reductions of mosquito exposure can really reduce disease cases. This Action will ultimately have the desired socioeconomic impact on reduction on vector-borne diseases resulting in social and economic advances.

The Aim of this COST Action is to collect information on the existing and newly developed methods to combat vector-borne diseases, in particular dengue fever, and establish a database, which will be made public. The main approaches will deal with: the mathematical analysis of the spreading of mosquitoes and dengue fever cases; the analysis of the existing technologies to treat textiles; paints and other materials containing insect repellents or insecticides in the surroundings of human beings; and the analysis of newly developed technologies based on nano- and micro-particles or micro-capsules as carriers for the active agents. The final aim of the Action is the improvement of the existing technologies in mosquito control and the design of large field studies in future projects of this network. Since some of the participants are coming from vector-borne disease countries pilot field studies can be performed in cooperation with existing funded projects. Even if a small effect of the proposed techniques were demonstrated, its impact on Zika, dengue fever, and other mosquito related diseases worldwide would be immense.

The short-term impact of the Action is the exchange of knowledge on the subject within the consortium, which should lead to increased alertness on the problem and activities with regard to the prevention of vector-borne diseases by the development of special chemical/physical treatments of textiles and paints. The evaluation of different procedures to finish textiles or to apply insect repellents to paints or walls aims at the establishment of the optimum process with regard to effectivity, permanence and compatibility with the health of human beings.

On the long-term, the Action will lead to the reduction of vector borne diseases in hazardous areas leading to improved health and safe live. The socioeconomic impacts of the COST Action result from the mentioned targets of the Action. The generation of knowledge on the fluctuation of vector borne diseases in Europe and in the whole world will be the basis for the uptake of measures of prevention. The treatment of textiles and materials in the surroundings with insect repellents are easy ways to protect human beings from attack by mosquitoes and contamination with vector-borne diseases. This will lead to improved health and living standards without killing mosquitos and damaging the eco-system.

Further outcomes of this COST Action will include:

- The creation of a “road map” to address improved techniques in treatment outcome of textiles, paints and other materials with nano- or micro- particles encapsulating mosquito repellent/insecticides;
- The enabling of specific scientific and clinical trial challenges in order to move towards first and never performed field-studies and understanding the efficacy of used techniques based on data analysis and mathematical simulations as outlined above;
- The sustainable application of these developed avant-garde techniques in combination with possible vaccines in healthcare;
- The reduction of healthcare cost compared to classical control measures.

B) MEASURES TO MAXIMISE IMPACT

I) PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

Besides meeting between the Action’s participants, the Action includes dissemination activities, primarily by organizing special sessions at international scientific conferences, but also by providing public lectures and events to address the wider community, as well as scientific presentations in industry, including both the consortium industry partners and new to-be-addressed industrial enterprises. Secondly, existing contacts with local authorities in endemic countries will be intensified during small pilot field trials of the nano- and in comparison micro-treatment of materials used in mosquito control. Finally, one main aspect in stakeholder approach lies in creating online platforms (website, social media).

The network of this COST Action is composed of mathematicians, epidemiologists, biologists, chemists, climate scientist, physicists, textile and chemical engineers from both the research and industrial areas. Each participant is willing to contribute to the Action on basis of its knowledge and specific expertise. The Main Proposer will be in charge of the Action coordination beside the mathematical analysis of the spreading of vector-borne diseases in combination with the new materials.

II) DISSEMINATION AND/OR EXPLOITATION PLAN

Dissemination in the scientific community, in industry and to the wider public is planned. The implementation of D&E will be executed and organized within WG5 with proper communication tools and will make the connection between the WGs to support maximum exploitation of results. In this collaboration the results, ideas and recommendation of the network plays the crucial part. The idea of the Action and the obtained results will be disseminated in lectures, poster presentations, and publications in conference proceedings and in peer-reviewed journals to the interested public from the areas of academia, associations, industry, international press and the civil society. The Action will be presented at various public events, conferences etc. Furthermore, an Action's specific website with public and private areas will be established and the Action's participants will make links to this web site on their individual internet sites. Information on the Action will be disseminated to representatives from industry, healthcare groups, hospitals, associations, public authorities, academia, the civil society and the European Commission.
One major element will be the development of a website to include all the above information. For potential participants, particularly those from industry interested in participating in this Action, a small "Public Conference" is scheduled every 2 years inviting all the participants to present their latest works and publications. Annual Reports will be written at the end of each year and will be made public in the mutual Action Website. The developed and improved mosquito controls that could be brought to market, would go through quality and economic viability thanks to the industry participants involved in the Action.

C) POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

I) POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

The final breakthrough of the IMAAC Action is a substantial and measurable reduction of mosquito vector-borne diseases. The direct impact of these avant-garde mosquito repellent materials on disease burden needs to be scientifically investigated and demonstrated especially in combination with possible vaccines. However, it is already clear that the results will lead to new innovations in the fields of mosquito transmitted diseases, and creation of new repellents working with nano- or micro-particles in combination with carrier materials.

A breakthrough in reducing disease burden will also lead to considerable reduction in health care costs, which specifically is an immense issue in developing countries. Beside these positive effects, an increased competitiveness of European industries in innovative mosquito combating materials and products can be expected.

3) IMPLEMENTATION

A) DESCRIPTION OF THE WORK PLAN

I) DESCRIPTION OF WORKING GROUPS

Five WGs will be organized initially:

WG1: Mathematical Analysis, Data-Analysis and Statistics

Objectives: This working group, equipped with cutting-edge knowledge in new mathematical methods in epidemiology and understanding of diverse EU related projects, is responsible for modelling and including control measures and invasion scenarios into new world regions like Europe:

- Data-analysis of mobility patterns is a core research area of this group;
- Another aspect is to define theoretical tools to measure the efficacy gained from the real data related to disease cases, in case of discussed application of avant-garde mosquito repellents combating diseases using nano-micro-particles on textiles, paints and other materials. Action participants from other Working Partners (WPs) are ready to invest in pilot studies. In this connection, already existing data will be sought.
- Another research line discussed in this group is the crossing between applied mathematics, statistical physics and epidemiology in relation to spreading of mosquito transmitted infectious diseases on large geographical areas including the complexity and stochastic effects in disease dynamics;
- Some analytical methods include Optimal Control Theory. The basic properties of the solutions to structure nonlinear population dynamics with emphasis on existence, uniqueness, positivity, comparison results and large-time behaviour of the solution, will be investigated;
- Another subject related to the topic of the proposed project is the controllability of age-structured population dynamics. In this framework, some stabilization and controllability problems for models describing the dynamics of some diffusive populations must be partially studied.

Tasks:

- To meet in formal COST Action Workshop yearly to discuss the delivery of the objectives;
- To inform other Workgroups about the progress and implement their experimental, industrial and practical results in the mathematical framework;
- To organise formal COST Action training for members within the WG where necessary;
- Centre Visits combined with workshop and training to maximise learning new techniques.

Deliverables/Milestones:

- Development of mathematical tools for analysing data in a possible field study within 12-24 months
- Publication of results in high impact peer reviewed journals.

WG2: Biological and Epidemiological Research on Vector-Borne Diseases focusing on Avant-garde Control Measures

Objectives:

The working group WG2 will investigate the effect of described avant-garde mosquito control measures on vector-borne disease burden, and bring scientific knowledge from laboratories and field studies together, incentivising new pilot studies in the patricipants' institutions:

- The applied controls using nano- and micro-technology will be investigated
- The possible combination of the control measures with imperfect vaccines due to come soon to the market for some diseases, which on their own will not have the power to reduce disease burden significantly to the extent at which it is needed to achieve herd immunity, i.e. disease do not find enough susceptible to sustain large disease outbreaks.

Tasks:

- To meet in formal COST Action Workshop yearly to discuss the delivery of the objectives;
- To ensure close contact with WG3 and WG4 to translate results for mathematical parameters modelled in WG1
- The translation of results achieved in other WGs in biological terms
- Generation of biological models which can be used in WG1

Deliverables/Milestones:

- Development of models implementing the new control measures

- Publication of results in high impact peer reviewed journals

WG3: Avant-garde control measures in combination with textile and paints using industrial applications R&D

Objectives:
This group will be responsible for the implication of the Action gained knowledge towards the control measures combining mosquito repellent drugs applied to nano- or micro-particles and their treatment on textile and wall paints. Some participants have previous experience in the development of chemicals for the functionalization of textiles, polymers or other materials. The development of textiles with activity against microbes and insects are actual research issues in the area of textile chemistry. The expertise on the finishing of textiles against degradation by the larvae of moths or carpet beetles also exists. From this, comprehensive knowledge on insecticides (natural and synthetic insecticides and repellents), the finishing of textiles with insecticides and the analysis of insecticides and textiles treated with insecticides is available. In recent years, the research has expanded to the development of functional finishes for textiles or other materials against mosquitoes. The development of several approaches aiming at the protection of textiles from degradation by insect foraging and the protection of humans against mosquito bites, and thus contamination with vectors is also of interest in this consortium.

- Nano- or micro-scale polymer gels containing cyclodextrins as hydrophobic pockets for the complexation of insecticides, repellents or other hydrophobic active agents and their application onto textile surfaces;
- Possible Silicium dioxide based nano-capsules which could be used as carriers for insecticides or repellents after application and binding to textile surfaces;
- Within the frame of the IMAAC Action, the participants in this WG will contribute in the development of mosquito repellent technologies by textile and paint functionalization;
- The focus of this group will be also to develop new repellents, insecticides or pesticides through gained knowledge in IMAAC and help the application of these products to industrial use.

Tasks:

- To meet in formal COST Action Workshop yearly primarily to discuss the delivery of the objectives and inform other groups on developments;
- Contribute to the Action by overtaking the evaluation of the known and newly developed procedures to treat textiles or paints (or new materials like tiles etc.) with insect repellents and insecticides. This task will be performed in close co-operation with industry and research groups in the network.
- The partners in this WG will evaluate the mentioned finishing procedures from the industrial aspect.

Deliverables/Milestones:

- Development of new materials with the mosquito repellent nano- or micro-particles
- Publication of results in relevant journals

WG4: Pilot Field Studies and their Management

Objectives:
The final challenge will be the contribution to implement the new materials (textile, paint etc.) in the real environment and study the effect on mosquitos and spreading of diseases. The results from this group will help to improve the products.

Tasks:

- Using the developed results and products in field studies;
- Collecting data from the field studies.

Milestones:

- Finding the right environment to perform the field studies by month 24; the results needed for analysis in WP1 for modelling and statistics

Deliverables:

- Development of models implementing the new control measures in actual field studies;
- Publication of results in high impact peer reviewed journals.

WG5: Data-collection, communication and dissemination

Objectives:

Communication between Action participants and other stakeholders is crucial for the network. The collected data and results in different WGs is of high importance for achieving the goals of the Action. This network is highly interdisciplinary, ranging from theoretical modellers to practitioners pursuing field studies. Computer technology will be used to support this communication on various levels:

- Mobile devices can be used to collect data in the field studies
- Data bases provide collected data for further analysis
- Interactive simulators help to understand properties of the derived models
- Visualisation techniques help to communicate results to scientific journals and to the public.

Tasks:

- To create and maintain expert network
- To create databases for the field studies and gathering data from endemic countries where possible the collected data will be analysed for migration patterns and climate variability
- Information exchange between different groups within this Action

Deliverables/Milestones:

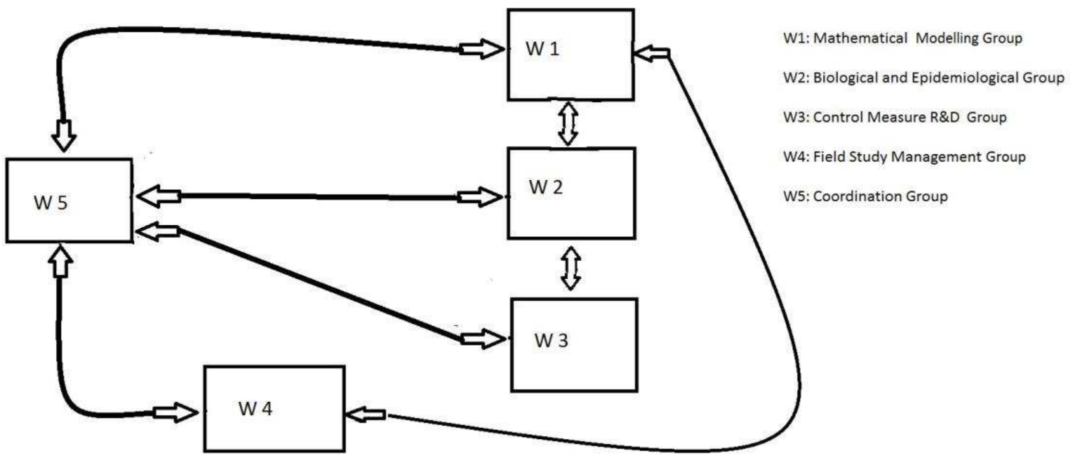
- Implementing a website
- Creating a database of the collected results
- Publication of results in high impact peer reviewed journals

II) GANTT DIAGRAM

Quarter / WGs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
WG 1:																
WG 2:																
WG 3:																
WG 4:																
WG 5:																
Deliverable																
Milestone																
Conference or Academic Meeting																
Teaching or Workshops																

Red: describes the Meetings (Conferences and Internal Meetings); Yellow: describes the Reports; Blue: describes the Workshops and Specific Seminars; Green: describes the Milestones defined.

I) PERT CHART (OPTIONAL)



II) RISK AND CONTINGENCY PLANS

Risk: The main risk the Action is facing is that the chemicals to combat mosquitos are not effective for significant disease reduction. Alternatively, the chemicals are effective, but can not be combined with textiles or paint for dosages needed to have disease reduction effects. **Contingency Plan:** In this case the Action will have definitely results to improve the chemicals, and more data how to improve the combination with nano-particles or micro-capsules. The theoretical work performed in WG1 will not be affected by this risk, since the theory remains the same, but the parameters have to be tuned.
Risk: As in many large-scale projects, participants are often unable to commit to their delivery deadlines. **Contingency Plan:** Increase the frequency of meetings or workshops (to monthly or weekly) if necessary. A lack of coordination should be addressed by WG leaders and adjusted accordingly. The MC will monitor this process.

B) MANAGEMENT STRUCTURES AND PROCEDURES

The coordination and organization of the Action will strictly follow the regulations of COST. The only administrative body of the network responsible for implementing the Action will be the MC. The MC will keep close collaboration with the COST office and will be the only body communicating with this office.

The Management Committee (MC) will be responsible of the organisation and planning, including budgeting, of all activities in coordination with the WGs leaders. The MC meeting will be organized within the “kick-off” meeting. Here a very brief description of the duties of this core body:

- Defining and managing the Action strategy , structure and monitoring their implementation
- Election of Action Chair, Vice-Chair and Grant Holder
- Organizing the Assessment Committee (AC), Editorial Board (EB) including a Dissemination Group and a Webmaster
- Set-up of the WGs and election of the Coordinators and Deputy Coordinators
- Defining the Milestones and relevant deadlines for deliverables
- Decision on date and location of the meetings
- General budgeting

The present Action will last for 4 years after the initial "kick-off" meeting. The main meetings will be held annually at the same time as the Annual Workshop in February of each year. Meetings between Working Group Leaders will be held twice a year close as possible to the possible Workshops/Conferences. In order to share the responsibilities meetings will be held in different COST Countries. Meeting between Working Group leaders will take 1-2 days. The meetings between each Working Group will take 2-3 days. The exact dates and schedule of the Seminars/Workshops will be decided during the "kick-off" gathering. Reports of meetings/Workshops will be published in the Action-Website. In this “kick-off” meeting the Work Group Leaders (WGLs) who will be elected, are responsible to report about the state of the art of technical/theoretical works. The progress will be monitored by WG5 and the status of deliverables will be closely internally communicated with the WGLs. All the efforts will be made in order to have a direct and smooth communication between the Action participants and the Administrative Board and the Grant Holder Institution. This will help to ease the claims and paperwork. Rules and relevant information will be provided in the intra-net and the website. Inclusiveness committee/Equality Agent will be also in charge to overlook the fulfilment of policies to ensure equality at the gender, academic age and geography balance. A Business Committee will also ensure a smooth contact and relation with the industrial partners within this Action.

In general: the MC meeting will take place once per year, WG meetings will be held twice yearly (periodic teleconferences are scheduled), Dissemination meetings will be held once per year and can be performed during the MCs. Workshops (Training) is planned every year. For potential participants, particularly from Industry interested to participate in the Action, a small “Public Conference” is scheduled every 2 years inviting all the participants to present their latest works and publications. Annual Reports will be written at the end of each year and will be made public in the Action Website. For duties like reporting the monitoring and assessment of the Action within WGs, the preference is to appoint Early Career investigators (ECIs).

C) NETWORK AS A WHOLE

This Action consists of 19 academic/research institutes, 5 SMEs and Manufacturing companies/partners, from 8 European countries and 5 COST International Partner-countries, representing a network of expertise in epidemiology, biostatistics, textile & paint-research, nano- and micro-technology, mosquito research, vector-borne diseases and mathematics. It is expected that at least 2 other European countries will join in. One major European company showed interest and is expecting to join in the future. The Action also expects that, as the network grows, more SMEs will cooperate with the Action, due to its interdisciplinary nature. This will also attract a higher number of Early Career Investigators (ECI). At this initial stage already 11 ECIs are included. This network will tackle the lack of interaction and coordination between sectors of mentioned expertise, to provide new solutions for combating vector-borne diseases. The available knowledge generated by this network will also be beneficial for other sectors within vector-borne diseases research, and will create a positive environment for fruitful collaborations and synergies in this research area.