### Biology and control of vector-borne infections in Europe

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# Table of contents

1 Scientific and technical quality relevant to the topics addressed by the call ........................................... 6

1.1 Concepts and objectives ........................................................................................................................................... 6
   1.1.1 Introduction .......................................................................................................................................................... 6
   1.1.2 EDEN and EDENext ........................................................................................................................................... 7
   1.1.3 Vector point of view ........................................................................................................................................ 7
   1.1.4 Model diseases ................................................................................................................................................ 7
   1.1.5 Rodents beyond rodent-borne diseases ........................................................................................................ 9
   1.1.6 Introduction, emergence and spread of vectors and pathogens .................................................................. 9
   1.1.7 Vector control intervention .......................................................................................................................... 10
   1.1.8 Public health .................................................................................................................................................. 10
   1.1.9 References .................................................................................................................................................. 10

1.2 Progress beyond the state-of-the-art ........................................................................................................... 12
   1.2.1 Tick Group (TBD) ........................................................................................................................................ 12
   1.2.2 Rodent Group (RBD) ................................................................................................................................ 14
   1.2.3 Mosquito Group (MBD) ............................................................................................................................ 15
   1.2.4 Phlebotome Group (PhBD) .......................................................................................................................... 17
   1.2.5 Culicoides Group (CBD) ............................................................................................................................. 19
   1.2.6 Modelling Group (MBD) ............................................................................................................................ 22
   1.2.7 Data Management Group (DMT) ................................................................................................................ 23
   1.2.8 Public Health Group (PH) ................................................................................................................................... 25

1.3 Scientific and technological methodology and associated work plan ................................................. 27
   1.3.1 Overall strategy ............................................................................................................................................. 27
   1.3.2 Project timing ............................................................................................................................................... 45
   1.3.3 Detailed workpackage description .............................................................................................................. 53

2 Implementation ................................................................................................................................................... 131

2.1 Consortium governance and management .......................................................................................... 131
   2.1.1 Governance ............................................................................................................................................... 131
   2.1.2 Management tools .................................................................................................................................... 134
   2.1.3 Management procedures ........................................................................................................................ 134

2.2 Individual participants ........................................................................................................................................ 135
   2.2.1 Partner 1 – Centre de coopération internationale en recherche pour le développement (CIRAD) ...... 135
   2.2.2 Partner 2 – Charles University in Prague (CUNI) ....................................................................................... 136
   2.2.3 Partner 3 – Istituto Superiore de Sanita (ISS) ............................................................................................. 137
   2.2.4 Partner 4 – Institut de Recherche pour le Développement (IRD) ............................................................... 138
   2.2.5 Partner 5 – National Centre for Disease Control (NCDC) .......................................................................... 139
   2.2.6 Partner 6 – University of Crete (UoC) .......................................................................................................... 140
   2.2.7 Partner 7 – Instituto de Higiene e Medicina Tropical (IHMT) ................................................................. 141
   2.2.8 Partner 8 – Instituto de Salud Carlos III (ISCIII) ....................................................................................... 142
   2.2.9 Partner 9 – Hacettepe University, Faculty of Science (HUESRL) .......................................................... 143
   2.2.10 Partner 10 – Ege University Medical School (EUMS) ............................................................................ 144
   2.2.11 Partner 11 – Centre for Ecology and Hydrology (NERC) ....................................................................... 145
   2.2.12 Partner 12 – Institut of Animal Health (IAH) ........................................................................................ 146
   2.2.13 Partner 13 – Institut Senegalais de la Recherche Agricole (ISRA) ......................................................... 147
3.2.1 Partner 22 – The National Institute of Research and Development for Microbiology and Immunology “Cantacuzino” (NIRDMI) ................................................................. 157

2.2.23 Partner 23 – University of Roma “La Sapienza” (UNIROMA1) ..................................................... 158

2.2.24 Partner 24 – University of Zurich (UZH) ................................................................................... 158

2.2.25 Partner 25 – Institute of Public Health Albania (IPH) .................................................................. 159

2.2.26 Partner 26 – Consejo Superior de Investigaciones Científicas (CSIC) ........................................ 160

2.2.27 Partner 27 – Agence Française de Sécurité Sanitaire des Aliments (AFSSA) ............................. 161

2.2.28 Partner 28 – Danube Delta National Institute for Research (DDNI) ......................................... 162

2.2.29 Partner 29 – Finnish Forest Research Institute (METLA) ............................................................ 163

2.2.30 Partner 30 – University of Antwerp (UA) .................................................................................. 164

2.2.31 Partner 31 – Swedish Institute for Infectious Disease Control (SMI) ........................................... 165

2.2.32 Partner 32 – Institut National de Recherche Agronomique (INRA) ............................................ 165

2.2.33 Partner 33 – Slovak Academy of Sciences (SAS) ........................................................................ 167

2.2.34 Partner 34 – Ludwig Maximilians Universität Muenchen (LMU) .................................................. 168

2.2.35 Partner 35 – Fundazione Edmund Mach (FEM) ......................................................................... 169

2.2.36 Partner 36 – Research Centre Borstel (RCB) ............................................................................. 170

2.2.37 Partner 37 – Innovative Diagnostics-VET (ID-VET) ................................................................. 171

2.2.38 Partner 38 – Kafkas Universitesi (KAU) .................................................................................... 171

2.2.39 Partner 39 – Friedrich Loeffler Institute (FLI) ........................................................................... 172

2.2.40 Partner 40 – Süddeutsches Institut für Empirische Sozialforschung (SINE) ............................... 173

2.2.41 Partner 41 – Robert Koch Institute (RKI) ................................................................................... 174

2.2.42 Partner 42 – University of Utrecht (FVM) ............................................................................... 175

2.2.43 Partner 43 – University of Oxford (UOXF) ............................................................................... 176

2.2.44 Partner 44 – Université Catholique de Louvain (UCL) ............................................................... 177

2.2.45 Partner 45 – Université Libre de Bruxelles (ULB) ................................................................. 178

2.2.46 Partner 46 – European Agro-Environmental health GIS associates EEIG (EURO-AEGIS) ...... 179

2.3 Consortium as a whole .................................................................................................................. 181

2.3.1 Sub-contractors ......................................................................................................................... 184

2.4 Resources to be committed ....................................................................................................... 185

2.4.1 Activities ................................................................................................................................... 185

2.4.2 Types of cost ............................................................................................................................... 187

3 Impact ............................................................................................................................................. 188

3.1 Expected impacts listed in the work programme ...................................................................... 188

3.2 Dissemination and/or exploitation of project results, and management of intellectual property .................................................................................................................... 189

3.2.1 Scientific publication ................................................................................................................ 189

3.2.2 Data dissemination .................................................................................................................... 190

3.2.3 PH Risk communication .......................................................................................................... 191
4 Ethical issues .......................................................................................................................... 193
5 Gender issues ....................................................................................................................... 195
5.1 Gender action plan ........................................................................................................... 195
1 Scientific and technical quality relevant to the topics addressed by the call

1.1 Concepts and objectives

1.1.1 Introduction

Future environmental and socio-economic changes, mean that emerging vector-borne diseases will become an increasing challenge for human and veterinary public health in Europe, and, indeed, in the World as a whole. In a recent retrospective analysis of emerging infectious diseases (EID), Jones et al (2008) have shown that while EID events were most often detected in Europe or North America, the major risks were in southern countries, where many demographic, environmental, social and economic factors favour the emergence of vector-borne diseases (VBD), and where there are limited health facilities to prevent, monitor or control their spread. Controlling VBD must therefore be considered as a global public good: European research into VBD should be seen as a means of protecting and improving public health and the welfare of its citizens, as well as being part of a coordinated international effort.

To address the call for proposals “Biology and control of vector-borne infections in Europe” launched by the European Commission (Box 1), we will investigate the biological, ecological and epidemiological components of VBD introduction, emergence and spread, and, using the knowledge acquired, propose new tools for controlling them.

Human behaviour and risk perception are an important, if sometimes neglected, component of VBD introduction, emergence and spread. The impact of VBD on human and veterinary public health in Europe is beginning to emerge into the public awareness, as illustrated by recent events such as the Chikungunya outbreak in Italy, or the spread of Crimean-Congo haemorrhagic fever in Europe. The unprecedented spread of the bluetongue epizootics in western and northern Europe, with its huge consequences on animal health and the livestock industry, have raised similar concerns in farmers, veterinary services, other stakeholders, and as well as the general public. We will also cover this aspect of human and veterinary public health in our proposal.
All aspects of the project will benefit from, and amplify the strong scientific results, capacity building, and research networks established by the FP6 EDEN project on emerging, vector-borne diseases in a changing European environment.

Finally, the set of innovative research methods, tools and results delivered during the project will be a substantial contribution toward a generic approach to monitoring and early warning of Vector Borne Diseases, and will reinforce the general regional framework needed for an effective integrated pest and disease management system.

1.1.2 EDEN and EDENext

The EDENext project (Biology and control of vector-borne diseases in Europe) builds on the concepts, methods, tools and results of the FP6 EDEN project (Emerging diseases in a changing European environment). We adopt here the same general approach of understanding and explaining the biological, ecological and epidemiological processes in order to develop a set of state-of-the-art methods and tools to improve prevention, surveillance and control of vector populations, and vector-borne diseases (VBD). The EDEN project has been focusing on the effects of environmental changes on the emergence of VBD. Here, we want to explain and model the processes leading to the introduction, establishment, and spread of vectors and/or vector-borne diseases, and assess the possible control strategies to break the epidemiological cycles of vector-borne diseases.

The project structure follows that of EDEN that was so conspicuously successful, with a set of vertical disease related activities linked by horizontal themes providing integrated technical input to all vertical groups, thereby minimising duplication and ensuring a coordinated approach throughout the project.

1.1.3 Vector point of view

The “vectors” addressed in this document include not only arthropods but also rodents and insectivores which harbour a wide range of pathogens (viruses, bacteria, and parasites), some of them being infective to humans without the intervention of arthropod vectors (e.g., Hantaviruses, Bunyaviridae).

We have therefore selected for study rodents and insectivores as well as the main arthropod vector groups of human and animal diseases in Europe: hard ticks (Acari, Ixodidae), mosquitoes (Diptera, Culicidae), sand flies (Diptera, Psychodidae), and biting midges (Diptera, Ceratopogonidae). Each constitutes “vertical” group structuring EDENext research activities. With such a vertical structure, the EDENext consortium will be able to provide expertise and useful information regarding prevention of human or animal infection, control measures for vector populations, and implementation of vector surveillance networks, for any new emerging, VBD transmitted by vector / rodent / insectivore species belonging to these groups.

1.1.4 Model diseases

To focus the project objectives and produce specific results regarding VBD in Europe, we have selected a range of relevant diseases. The selection criteria used are (i) diseases with insufficient epidemiological knowledge or control measures to produce efficient intervention programmes, and (ii) priority diseases for European public-health agencies. For the latter, we have used the results of the V-Borne expert consultation which has been launched in 2008 by the European Centre for Disease Prevention and Control (ECDC, Stockholm): “Assessment of the magnitude and spread of vector-borne diseases in Europe”, ECDC public tender OJ/2207/04/13 – PROC/2007/003.
• Tick-borne diseases (TBD): tick-borne encephalitis and Lyme disease have been excluded because a lot of research has been done in EDEN, and scientific efforts are still devoted to them in other projects. We have thus chosen to focus on:
  ○ Crimean-Congo haemorrhagic fever with an on-going epidemic in Turkey, and poorly documented spread in south-eastern Europe (Vorou 2009).

• Mosquito-borne diseases (MBD):
  ○ West Nile (WN): though it was addressed in EDEN, a lot of research is still needed for a better understanding of WN epidemiology and the risk of large-scale spread in Europe. The recent outbreaks in Italy (Rezza, 2009), and the emergence of WN virus lineage 2 in Hungary and Austria has raised public-health concerns (Erdélyi et al 2007, Weissenböck et al., 2009).
  ○ Chikungunya: the recent outbreak in Italy has revealed the epidemic potential of *Aedes albopictus* (and other invasive mosquito species like *Ae. japonicus*) as a vector for Chikungunya virus, and other arboviruses like dengue (Chretien & Linthicum 2007, Sambri 2008).

• Sandfly-borne diseases (PBD): leishmaniasis and *Phlebovirus* infections. EDEN results have shown that sand fly distribution has changed in European countries (e.g., Dereure et al. 2009; Martin-Sanchez et al 2009). Jointly, an increase of human and canine leishmaniasis infections, as well as a spread of human infections by Toscana *Phlebovirus* has been reported (Charrel et al, 2005). Moreover, following intensification of migration and travelling, environmental changes, and other aspects of globalization, there is an increased risk for the introduction and spread of infections by *Leishmania* species like *L. tropica* or *L. donovani* in Europe (Antoniou et al 2009) and in the newly emerging *Leishmania* hybrids (Ravel et al, 2006; Volf et al, 2007).

• Culicoides-borne diseases (CBD). A striking feature of veterinary epidemiology during the last decade was the accelerated occurrence of waves of CBD epizootics in the Mediterranean Basin and Europe, with huge economic consequences. Bluetongue (domestic and wild ruminants) has been the most important so far, but other CBD are lurking on Europe’s borders: epizootic hemorrhagic disease (ruminants), African horse sickness and horse encephalosis (equids)… For years, the northward spread of these diseases, from sub-Saharan Africa and the Middle East to Europe, has been associated with the extension of the distribution of their main Afro-asiatic vector, *Culicoides imicola* (Purse et al 2005). The emergence of several bluetongue virus (BTV) serotypes in Northern Europe as from 2006 has confirmed that endemic *Culicoides* species are able to transmit BTV efficiently, and that overwintering mechanisms are able to maintain the virus in animal hosts and/or infected vectors (Carpenter et al 2009).

• Rodent- and insectivore-borne diseases (rainbo): *Hantavirus* (Bunyaviridae) infections have a significant public health impact in Europe and globally. Apart from the high case fatality rate caused by some *Hantavirus*, they cause considerable disease burden. Hantavirus infections are emerging infections: they are found in new areas, and the incidence has grown in several established endemic regions, (Heyman & Vaheri 2008). Very recently, new groups of potential zoonotic agents borne by rodents and other small mammals have been found in Europe (EDEN results, unpublished so far).
1.1.5 Rodents beyond rodent-borne diseases

Beyond their role in rainbo diseases, rodents and insectivores are also the hosts of many arthropod species. In EDENext, we want to assess the joint diversity and abundance of small (rodents and insectivores) and larger (e.g., cervids or domestic ruminants) reservoir hosts, arthropod vectors, and pathogen agents, for a better understanding of their joint dynamics. We also propose to assess the influence of major environmental factors such as land cover / land use, or masting in deciduous-forest regions (during mast years, vegetation produces a significant abundance of fruit). Assembling the different pieces of knowledge for the ecosystems of interest will provide a better basis for planning more efficient disease monitoring and early warning systems.

1.1.6 Introduction, emergence and spread of vectors and pathogens

Introduction, emergence and spread of vectors and pathogens are the sequence of events leading to epidemics of vector-borne diseases. Their understanding is crucial to develop science-based and data driven suite of preventative, control, or monitoring measures (intervention and control). However, the underlying mechanisms of each stage are completely different, and so will be investigated by using different model diseases to investigate the different stages.

There are many possible routes of introduction of vectors or vector-borne pathogens, and introduction risk is highly vector-dependent: pathways along which vectors and pathogens arrive may be very different, and may be strongly influenced by chance events that are difficult to quantify. We will develop methods to assess introduction risk that are generically applicable for distinct classes of vectors and pathogens / parasites.

To understand and model the emergence and spread of vector-borne and rainbo diseases, the description and explanation of vector and host competence and capacity will be the connecting thread of most research activities implemented in EDENext. The identification of biological mechanisms and ecological processes involved in competence and capacity are of particular importance to ensure a broad application of the results and a predictive power for the quantitative models that will be developed. For this purpose, the infection's natural cycle will be thoroughly studied for each host-vector-pathogen system, including basic biology of vectors and diseases reservoirs. The spread of vectors, hosts (rodents and insectivores), and pathogens will be specifically studied, either using proxies like wind analysis and dispersion models (biting midges), or with field studies (population genetics of ticks and tick-borne pathogens, pathogens and ectoparasites borne by migrating birds, etc.). A coordinated research network will be developed to replicate field studies with harmonised protocols in strategic places (disease-emergence or vector-invasion frontline, contrasted environmental or control conditions...). Laboratory experiments to study the life traits of vectors and pathogens, and vector / host competence will also be coordinated at the EDENext project scale.

A common goal for all the disease systems under study will be to develop predictive, quantitative models of vector-population dynamics, or disease transmission and spread. For this purpose, we will benefit from the datasets, experience, and capacity gained after the EDEN project. An important step forward will be to model vector and disease spread in a context of changing environment in space and time. Mathematical tools are now available and have already been applied for some VBD we want to address (Hartemink et al 2009: EDEN result). Moreover, methods and tools have been developed in EDEN to characterizing climatic and environmental changes, including landscapes, at various resolution scales (e.g., Linard et al 2007, Scharlemann et al 2008). Beyond epidemiological studies to assess the role of these environmental features in disease incidence, progress has been made to integrate the
environmental, landscape and (process-based) mathematical approaches to explain disease spread. This integration will be developed further within EDENext.

1.1.7 Vector control intervention

Many different methods are available to control vector populations and break epidemiological cycles. However, the massive use of insecticides is less and less acceptable from an environmental and societal viewpoint. The effectiveness of other possible control methods depends on the biology and ecology of the target vectors, as well as the nature of the pathogen agents as they affect, for example, the availability of vaccine or efficient prophylactic / curative treatments. The wide distributions of wild or domestic reservoir hosts further complicate the identification and implementation of effective control methods. Most vector- or VBD-control programmes therefore follow an integrated control strategy, in which several concepts and methods are used together.

In EDENext, research will be implemented to develop new vector-control research tools (e.g., laboratory colonization of vector species) which will allow missing information on the efficacy of specific control methods to be assessed using laboratory or field experiments. Simulation models will be used to assess control strategies (pest management or disease control, including vaccination, or host medical treatment) according to various scenarios (emerging disease, climate or environmental change, etc.) and control strategies which will be defined and selected with animal / human health stakeholders. Depending on the specific cases, field or laboratory experiments will be carried out to assess the efficacy of one or more components of the integrated control strategy. Then, we will use the predictive models, to assess the efficacy, or other indicators such as the cost/benefit ratio, of these control strategies.

1.1.8 Public health

A thorough understanding of biological, ecological and epidemiological processes and the availability of predictive quantitative models provide important tools to implement efficient preventive, surveillance and control programmes. However, we also need relevant and accurate data on risk perception in the public health agencies and in the exposed human population categories, as well as a clear understanding of the importance of these human population segments. Moreover, the human or veterinary public-health messages to be delivered must be adequately formatted in their content and style, to reach the targeted populations most at risk. These activities will be implemented in the Public-health work package, in close collaboration with human / animal health stakeholders, as well as national and international public-health agencies. We have chosen to focus these activities on two of the model diseases proposed for study as they are particularly important and are most likely to provide sufficient data to feed Public Health activities: Crimean-Congo haemorrhagic fever in south-eastern Europe, and haemorrhagic fever with renal syndrome in Fennoscandia, and Belgium, north of France, Luxembourg, and Germany.

1.1.9 References


1.2 Progress beyond the state-of-the-art

1.2.1 Tick Group (TBD)

1.2.1.1 TBD Emergence and spread

In the context of global warming and globalisation, vector-borne diseases, including TBD, are expected to emerge as increasingly important, heightening the risk of pathogen transmission to animals and humans worldwide. In terms of impact on livestock and public health in Europe, the tick-borne diseases caused by Anaplasma sp, Rickettsia sp., Bartonella sp., Babesia sp and Crimean-Congo hemorrhagic fever virus (CCHFV) are of the highest concern (Randolph 2009, Turell 2007). The Fourth Assessment Report of the Intergovernmental Panel on Climate Change (Christensen et al. 2007) predicts temperature increases of 1.5–2.5°C for northern temperate Europe, which may impact tick activity periods (potentially altering tick abundance and distribution), as well as the survival and abundance of tick hosts and pathogen-reservoir hosts. Such changes may affect infection transmission, which is the result of contact between reservoirs, vectors, and humans. Climate changes are also expected to increase the success of newly introduced tick species in Europe, such Dermacentor reticulatus, the vector of canine babesiosis (caused by B. c. canis), which is currently expanding into new areas (Srétér et al. 2005; Porchet et al. 2007; Nijhof et al. 2007). There is also great concern about the possible introduction of Rhipicephalus sanguineus, the primary vector of Mediterranean-spotted fever (caused by R. conorii).

Among the species of ticks associated with CCHF virus, most are either two- or three-host ticks. In southern Europe H. marginatum is the main vector that is usually activated by the increasing temperature in spring. Other CCHFV strains (Europe 1 and 2) have been isolated from other human biting ticks such as Rhipicephalus bursa, H. aegyptium and Dermacentor marginatus in European parts of Turkey, but nothing is known about their vector competence.

To address the public health issues resulting from this increased tick challenge and the risk of contracting TBD, an integrated monitoring system for predicting the emergence and spread of new TBD will be developed. In this context, understanding vector competence and capacity are central for generating such information systems.

Within the EDENext project, the TBD group will investigate the emergence and spread of new TBD by determining vector competence and capacity to transmit pathogens and developing advanced risk models for these diseases. Specifically, the aims of the TBD group are to:

- Determine the occurrence and geographical distribution of TBD of highest concern in eastern and western European areas in ticks and potential hosts;
- Characterize host and vector competence and vector capacity;
- Identify host/pathogen/vector factors determining pathogen transmission;
- Assess the risk of emerging pathogens of medical importance.

1.2.1.2 TBD Intervention and control

The tick I. ricinus uses a wide range of mammal, bird and reptilian species, including humans, to complete its blood meals. This species inhabits natural and semi-natural areas including peri-urban and urban parks and roadsides. The control of tick infestation by the regular application of acaricides on large numbers of wild hosts is not feasible, ethical or healthy, and vector control in the environment, although some progress in this approach has been achieved, is still not applicable to natural settings and large areas. Regarding CCHF, disease prevention in
humans is based on avoiding or minimizing the exposure to the virus. This can be achieved by antiviral vaccination, personal protection from the ticks and/or vector control.

Therefore, the most reasonable approach to the prevention of tick-borne disease is to promote the large-scale diffusion of information to human populations about risk, based on the monitoring of biological indicators which appear to act as proxies for TBD disease risk. The identification of these proxies is only possible by statistical approaches and mathematical modelling.

Modelling of tick-borne diseases is not a simple matter. For example, the temporal dynamics of *I. ricinus* is affected by a combination of abiotic and biotic factors, such as local climatic conditions and availability of hosts for blood meals. Rodent population dynamics is an additional key factor, although a series of ecological parameters, such as beech masting and habitat changes, can be used to reasonably predict the change in rodent abundance over time (Rizzoli et al., 2009; Tersago et al. 2008).

Although many disease transmission models have been developed for a series of tick-borne diseases, those for *I. ricinus* are fewer and might be developed further (see Background section for WP Modelling). In addition, many European models for disease risk are based on large geographical and/or climatic areas. Therefore, in close collaboration with the EDENext Rainbo and Modelling groups, FEM and INRA partners will concentrate on developing new and/or improved micro- to medium scale models using the vast amounts of data gathered in WP1. The usefulness of these models will be compared to that of the existing large scale models where available.

1.2.1.3 TBD References


1.2.2 Rodent Group (RBD)

1.2.2.1 RBD Emergence and spread

Technical note: This research proposal addresses the epidemiology and control of pathogens borne by rodents and insectivores. The finding of hantaviruses in insectivores has a bit outdated the established definition “robovirus” (rodent-borne viruses). We adopt here the new suggestion Rodent And Insectivore BOrne Viruses could be called rainbo viruses. Still, conventionally, our vector group is named RBD.

Hantavirus infections have a highly significant public health impact in Europe and globally (Vapalahti et al. 2003): apart from the high case fatality rate caused by some hantaviruses, they cause considerable disease burden. Hantavirus infections are emerging infections - found in new areas - and in several established endemic regions the incidence has grown. Thus the number of annual HFRS cases has increased during recent years in Europe (Heyman & Vaheri 2008), including countries in which the disease has been well known and virus-specific tests have been widely used. Environmental and political factors increase the contact rates between rodents and humans: these include changes in agriculture and forestry, the predicted high increase in use of bioenergy, changes in leisure time, and possible political crisis situations (Henttonen & Vaheri 2008). Even in Europe, in several countries there is a discrepancy between general human seroprevalence and number of diagnosed cases, clearly indicating that this disease group is underdiagnosed. Heyman & Vaheri (2008) documented over 35,000 human hantaviral cases in Europe. Very recently it has been found that in Europe there are new groups of potential zoonotic agents carried by rodents and other small mammals (e.g. hantaviruses in insectivores; LCMV is a multistrain complex, unpubl. EDEN results, and responds to rodent fluctuations, Tagliapietra et al. 2009). Among the old ones, Seoul hantavirus in rats, not too well-known in Europe, can be an increasing problem. For the grand scheme of robo disease dynamics and risks for humans in Europe we need to understand the roles of geographically varying rodent population dynamics (Hansson & Henttonen 1988, Hanski et al., 1991, Kallio et al. 2009) and differences in landscape structure. The knowledge gaps that we are addressing in EDENext, include 1) the role regional small species diversity affecting the pathogen transmission in the carrier species, 2) the impacts of environmental physical conditions on pathogen survival outside the host, relevant also for transmission among rodents and to humans (for preliminary work, Kallio et al. 2006), 3) the importance of immunogenetics in host species for rainbo emergence (for first work, Deter et al. 2008), and particularly, how do the immunogenetics dynamically respond to the host and pathogen fluctuations, 4) the role of secondary/spill-over species in pathogen maintenance, that is related to the pathogen – host competence between species, but also within species, 5) the very critical parameter for hantavirus risk modeling, the temporal patterns of virus shedding by rodent hosts (prel. work, Hardestam et al. 2009). 6) New Ro modeling will be used to understand the various spreading patterns of rainbos, utilizing recently collected field data, together with MOD group, and this is supported by the landscape epidemiological models utilizing detailed spatial genetic data and related new software.

1.2.2.2 RBD Intervention and control

Small mammals, rodents and insectivores, are hosts and reservoirs for many robo and tbd pathogens, in addition small mammals serve as hosts for many vectors carrying tbd pathogens. Therefore, population fluctuations of small mammals can strongly affect the human risk of contracting these diseases. The impact can occur without time lag, as in hanta or other rodent borne viruses, transmitted directly to human, or with time lags through vector population developments. In most of Europe, masting (heavy seed crops of deciduous trees) contribute to the rodent peaks, i.e. forest rodent species, that are carriers of many of the
zoonotic agents, respond in a concerted way to environmental factors (masting, habitat change) (Tersago et al. 2009). This should lead to a concerted response also by their vectors and pathogens, but possibly with varying time lags. Verifying in several regions the causal chain, i.e. higher than normal summer temperatures inducing flower buds and seed formation, masting, rodent outbreak and the consequent disease increase, could be utilized for a general early warning purposes. We, together with TBD group and PH work package, aim at this at selected study sites in Europe. The previous large masting event in Europe occurred in 2005, and therefore it is highly probable that the next event will occur in near future, i.e. during EDENext period.

1.2.2.3 RBD References


1.2.3 Mosquito Group (MBD)

1.2.3.1 MBD Emergence and spread

Zoonotic diseases are fascinating because they are complex, and West Nile virus (WNV) may be one of the most complex of all. It is essentially a migratory virus, one that may be more
versatile than others because it must be infective to local fauna wherever it travels. Lack of host specificity is a major theme of this proposal, for although WNV is regarded as a mosquito-borne avian virus, it is known to be highly infective by the oral and mucosal route (Kuno 2001), and can infect mammals, reptiles and amphibians. Moreover, it can survive as a chronic infection and be shed in the excreta and urine of birds and mammals long after viraemia has subsided, yet such details have been largely ignored in studies of its transmission in nature. This is the principal theme of this proposal, for if such routes of infection are significant in nature, and if chronic infections are common, we face a host of alternative cycles of transmission that do not involve arthropods at all. The second theme is the survival of virus in winter, when mosquitoes are inactive. WNV has been isolated from overwintering mosquitoes (EDEN) and we know that these feed on sugar, not blood, in preparation for diapause, so infection must be vertical, via the egg stage. This may be significant as an overwintering strategy, and indeed could also be at other times of the year, yet this too has not been studied in the field. In a sense, these themes are one, because they imply that overwintering vectors and chronically infected vertebrate hosts should both be viewed as reservoirs: they may both function as repositories for virus over extended periods of time when mosquitoes are not active.

Many factors will determine the future expansion of Aedes albopictus and Aedes japonicus in Europe; climatic conditions are a key parameter that we can study in advance. We will focus on: (i) the effects of temperature on the basic bionomics—development rate, productivity of breeding sites, survival and diapause—of these species. For field studies, Albania will be used as a proxy for latitudinal climates because it has been heavily infested with Ae. albopictus for more than 30 years and the species is present at all altitudes, even surviving under snow cover for several months per year. (ii) The rate of viral replication. Previous studies of viral replication have been conducted at constant temperature, but temperatures are not constant in nature; diurnal range can be comparable to seasonal range of means in some regions, yet we have no information on the effect of rapid variations on the rate of replication. We will deploy an array of digital data-loggers, distributed to volunteers in various European climatic zones, to monitor micro-climate in “typical” Ae. albopictus resting sites. This data will provide daily temperature and humidity profiles that will be simulated in an enviromental cabinet in a P3 insectary. Quantitative RT-PCR will be used to monitor daily titre of CHIK and DEN virus. We expect interesting results: a recent study (Westbrook et al. 2009) revealed that Ae. albopictus reared at lower temperatures had higher rates of infection. The study will be an important contribution to the debate on climate change and human health.

1.2.3.2 MBD Intervention and control

Strategies for mosquito control are determined by the ecology and behaviour of the target insect. For a zoonosis, little can be done, for outbreaks are rarely focal and and generally in rural or semi-rural habitat. In urban areas, preventive sanitation is the logical approach, but during outbreaks, ULV “fogging” with costly insecticidal aerosols is the emergency response. By contrast, dengue and chikungunya are mainly urban diseases. Source reduction—the elimination of infested containers—is the logical approach, but, since the era of DDT, successful control has rarely been achieved and never sustained; here again, fogging is the emergency response. Surprisingly, virtually no evaluations of the direct impact of fogging on target species have ever been performed—authorities relied on caged mosquitoes—but when methods to monitor wild population were developed (see references) variable impact was observed for Culex pipiens, and negligible impact on Aedes aegypti. Aedes albopictus may be a more vulnerable target because it is exophilic; we will evaluate impact of applications in several urban areas, with simultaneous monitoring of the Cx pipiens population. Source reduction is even more difficult for Ae. albopictus because its breeding sites are not restricted
to the peridomestic environment. We propose to study an entirely new and original concept: the exploitation of the “skip oviposition” behaviour of the vector to distribute a potent juvenile hormone analogue to the actual breeding sites, thus disrupting the development of the instars that are present. We will also explore the application of a rapid test, based on cuticular hydrocarbons, for determining the age of female mosquitoes. If effective this will be of importance in the evaluation of the impact of control methods, as well as studies on vectorial capacity.

1.2.3.3 MBD References


1.2.4 Phlebotome Group (PhBD)

1.2.4.1 PhBD Emergence and spread

Several data generated by the ongoing FP6 EDEN-LEI sub-project have provided historical and current distribution of sand flies and leishmaniases in regions of southern Europe and bordering countries of northern Africa and near East (Gramiccia & Gradoni, 2007). Results suggested that sand fly distribution has probably evolved due to environmental changes, global warming and human-made modifications (Dereure et al. 2009; Martin-Sanchez et al. 2009). Accordingly, an increase of human and canine leishmaniases infections, as well as a spread of human infections by TOS Phlebovirus (Charrel et al. 2005) is reported from several territories of the subregion. Leishmania infantum associated to Phlebotomus (Larroussius) vector species still represents the main risk for human infections in Europe. Due to increased migration and travelling, ongoing climate changes as well as various aspects of globalization, there is an elevated risk for the introduction and spread of infections by Leishmania species.
which are only sporadically endemic, or are non-endemic. An example is given by *Leishmania tropica* (an agent of human cutaneous leishmaniasis), which has very limited distribution although its natural vector *Phlebotomus sergenti* is endemic in several Mediterranean countries. Other examples are found in the emergence of the anthropopotic *L. donovani* in Europe (Antoniou et al 2009) and in the newly emerging *Leishmania* hybrids (Ravel et al, 2006; Volf et al, 2007).

One of the objectives of this research proposal is to generate or update vector and *Phlebotomus*-borne diseases (PhBD) risk maps of Europe and adjacent regions, and create public websites providing key information about sand flies, leishmaniases and Phlebovirus disease. Further objectives are to study spatial distribution of sand fly populations and their vector competence, as well as to exploit genetic factors associated with spreading, colonization and/or re-colonization of geographic areas by various sand fly species. Risk of PhBD epidemics will be addressed, with particular regards to southern Europe (Portugal, Spain, France, Italy and Greece) as well as bordering countries (Turkey, Georgia and Morocco) as possible sources of sand fly and disease spreading.

Pathogen diagnostic will be conducted in both vectors and vertebrate hosts. *Leishmania* infection rates in sand flies and canine reservoir will be assessed by serological, parasitological and molecular techniques to investigate on the trend of the disease distribution and spreading. Phleboviruses will be isolated and characterized from sand fly populations of the region.

1.2.4.2 PhBD Intervention and control

In Europe, residual insecticide spraying has limited use for ecological reasons, and culling of *Leishmania*-infected dogs is not considered an acceptable measure for social and ethical reasons. Therefore, main control measures aimed at reducing host-sand fly contacts are insecticide treated nets for human use (ITNs), and dermal application of insecticides on dogs for sand fly bite prevention, respectively (Alexander & Maroli 2003). A secondary control tool is the treatment of sick dogs with clinically effective drugs, which were shown to reduce temporarily the infectivity burden to phlebotomine vectors (Alvar et al, 1994).

The aim is to develop, optimize and evaluate effective tools for integrated control methods. Human protection from sand fly bites and reduction of disease incidence in anthropopotic foci of leishmaniasis will be studied using ITNs. Protection of the canine reservoir host from sand fly bites shall be evaluated using novel insecticides and anti-feeding products. The efficacy evaluation of control measures in field studies will be monitored by investigating sand fly population densities, kinetics of antibody against sand fly saliva (Hostomska et al., 2008) and assessment of incidence trends in protected areas.

Combinations of currently marketed anti-*Leishmania* drugs and immunotherapeutics under development, will be used in clinical trials and the efficacy in reducing sand fly infectivity of treated-dog’s shall be evaluated through xenodiagnostic procedures using colonized sand fly vectors.

1.2.4.3 PhBD References


1.2.5 Culicoides Group (CBD)

1.2.5.1 CBD Emergence and spread

The potential introduction of CBDs into new areas by wind-borne spread of infected midges (Ducheyne et al. 2007, Gloster et al. 2007) and livestock movements (Hoar et al. 2005) has recently been accommodated within risk analyses. This project will integrate information on these mechanisms with new data on other, poorly described key potential routes of entry such as trade in contaminated biological materials (including use of vaccines), transport of infected *Culicoides* with livestock or other cargos and import of exotic hosts. This project will also contribute to existing molecular phylogenetic databases of CBD strains upon which our current picture of the geographical origins of European strains is based (Mertens et al. 2007).

The risk of establishment of orbiviruses across different conditions (climate, landscape, hosts, vectors) in Europe is dependent on *Culicoides* vector competence and abundance, demography and habitat use. To date, the role of different vector species in Europe has been assessed largely using isolations from wild-caught adults in a few outbreak areas (e.g. Caracappa et al. 2003 ; Deliberato et al. 2005; Savini et al. 2005 ). On the basis of previous laboratory competence experiments (Carpenter et al. 2006 ; Paweska et al. 2002), susceptibility to orbiviruses is expected to vary within and between key vector species in Europe and to depend upon climatic conditions. This project will develop standardised protocols for assaying vector competence and levels of infection (using new RT-PCR based assays, e.g. Shaw et al. 2007) in wild caught adults of *C. imicola* and species within the *C. obsoletus* and *C. pulicaris* groups across different zones in Europe in relation to climate and geography. In addition, to understand the biological processes driving any differences in terms of vector competence, the molecular basis between *Culicoides* species and populations will be investigated. Modulation of the host immune system by vector saliva will be assessed using immunological approaches.
The distribution patterns and life-history parameters of *Culicoides* are highly dependent on climatic factors (Wittmann et al. 2000). Recent studies from Europe have revealed that host and landscape factors are also important drivers of midge distributions (Calvete et al. 2008, Conte et al. 2007, Guis et al. 2007). This project will directly examine the influence of temperature and humidity on demographic rates of adults of key European *Culicoides* species in the laboratory but also use existing surveillance datasets to evaluate the climate, host, and landscape drivers of geographical variation in their seasonal abundance, demography and phenology. The accuracy of these investigations will be improved by the development of novel techniques to grade the age of adult *Culicoides* (Cook et al. 2006) and drop-trap experiments to quantify the discrepancies between trap catches and the numbers of midges found biting hosts (Carpenter et al. 2008). The resulting vector model framework will lead to improved, predictions of the ‘vector-free period’, required to permit livestock movements in affected areas over winter, that are currently based only on the temperature requirements for viral replication (Wilson et al. 2007). The framework will also generate inputs for $R_0$ transmission models * (which quantify the risk that an epidemic will spread or die out) for CBSDs that have recently begun to incorporate spatial and seasonal heterogeneity in midge abundance and species composition (Hartemink et al. 2009) and sensitivity of transmission to temperature (Gubbins et al. 2007). $R_0$ is defined as the number of secondary cases which arise from the introduction of an infected individual in a naive population. Such frameworks could be employed to evaluate the importance of wild ruminants (Garcia et al. 2009) and trans-placental transmission in maintaining CBD transmission in Northern Europe under current and future climatic conditions.

### 1.2.5.2 CBD Intervention and control

Until recently control of BTV in Europe has relied upon restrictions of livestock movements, use of live attenuated vaccines and attempts to reduce midge-host contact rates through the use of insecticides, stabling and removal of larval breeding sites. Live vaccines have successfully been used to reduce BTV transmission in some countries (Savini et al. 2008). However, subsequent viraemia and/or clinical cases of bluetongue caused by these vaccine BTV strains have been reported (Veronesi et al. 2005), and transmission of these strains by midges has been observed in the field (Ferrari et al. 2005). Moreover, the use of such live vaccines increases the risk of virus re-assortment with wild-type strains (Batten et al. 2008). Fortunately, efficacious, safe inactivated BT vaccines have already been produced and are now widely used (Savini et al. 2008).

In this work package, we will develop state-of-the-art within- and between-herd transmission models (Heestebeek and Roberts 2007) with which to evaluate optimal strategies of timing and coverage of vaccine use against CBSDs in different regions under different conditions (climate, movement restrictions) and to explore for example the consequences of delays in vaccine production for newly emerging strains, or of the presence of large populations of infected wild ruminants that cannot be vaccinated.

Vector control strategies, targeted at key midge vector species are required for improved management of CBSDs in Europe. During the recent epidemic, several countries have used environmental spraying of pyrethroids to reduce the numbers of midges biting hosts. Little information is available regarding the efficiency of this method (Satta et al. 2004). This project will conduct experimental and field trials of the efficiency of chemical control methods including insecticides and repellents (especially those that are plant derived) and their application technology (pour-on, praying, bath) and mechanical methods such as netting at reducing contact rates between hosts and key European *Culicoides* species. Field estimates of population reduction will be integrated into vector population and transmission model
frameworks to evaluate impacts of different scenarios of vector control on *Culicoides* population sizes and disease transmission.

### 1.2.5.3 CBD References


Paweska, J. T., G. J. Venter, et al. (2002). Vector competence of South African *Culicoides* species for bluetongue virus serotype 1 (BTV-1) with special reference to the effect of


1.2.6 Modelling Group (MBD)

The modelling of vector-borne diseases (VBD) has received relatively little attention in the literature compared to directly transmitted infections. There are a number of factors that explain this from a methodological point of view. First of all, several layers of complexity are added by the fact that any VBD involves the modelling of at least three species: host, infectious agent and vector. Secondly, there is a dominant influence of the local environmental conditions (both spatially and temporally, and including aspects of landscape and land use) in determining vector and host life history, and consequently local vector abundance and VBD-transmission dynamics.

For directly transmitted infections, in contrast, this environmental influence on the host and transmission dynamics can, for many relevant questions, be ignored, at least as a first approximation (Diekmann & Heesterbeek, 2000). Such an approach has also been adopted for most mathematical models of VBD in the past. Only very recently have approaches been developed, for example to characterise the basic reproduction ratio $R_0$ in periodic environments (Bacaër & Guernaoui, 2006), that take into account multi-faceted environmental influences. Furthermore, too little is understood about the mechanisms involved at the individual life-history level to allow constructing process-based mathematical models that take more environmental dimensions into account.

Statistical models using remotely sensed data have been shown to be able to characterize a much fuller environmental influence on vector abundance (Rogers, 2000) by identifying which environmental variables are predictive of vector presence and absence, and then using trapping results to translate these insights into abundance estimates. Simultaneously with this, land use science now uses a wide range of data and techniques to reach an advanced level of understanding of land cover and land use change processes. Data include high resolution remote sensing maps, and techniques are a mix of statistical modelling and spatio-dynamic computer approaches, such as cellular automata and agent-based models. This field is now making important contributions concerning the influence of land cover, land use and environmental and human-induced changes, on the occurrence of VBD (Linard et al., 2009, Vanwambeke et al, 2007).

These environmental and landscape approaches, however, are not explanatory at a basic level of biological processes, and have, moreover so far modelled vector statics, given local
conditions, and not vector dynamics. For the questions involved in assessing emergence and spread in realistic European conditions one cannot hope to use either of the three approaches on their own. They need to complement each other. That this merger is technically possible has only recently been shown arising from the partnerships established within the EDEN project. There, abundance estimates from remotely-sensed environmental data and trapping results have been incorporated in an \( R_0 \)-model for transmission of bluetongue virus (BTV) by its *Culicoides* midge vectors to provide estimates of a key ingredient in \( R_0 \) for which no mechanistic biological description is yet available (Hartemink et al., 2009). A merger of all three approaches was achieved in close collaboration with the *Leishmania* team within EDEN, on the sandfly/*Leishmania*/dog system in a region in southern France (Hartemink, 2009).

1.2.6.1 MOD References


Rogers, D.J., 2000, Satellites, space, time and the African trypanosomiases. *Advances in Parasitology* 47, 129-171


Hartemink et al., 2009, Mapping the basic reproduction number (\( R_0 \)) for vector-borne diseases: a case study on Bluetongue Virus, *Epidemics*, 1, 153-161


1.2.7 Data Management Group (DMT)

1.2.7.1 DMT Infrastructure

The DMT EDENext proposal is founded on using the experience of 5 years of providing data management and web archive functions for the EDEN project (www.edendatasite.com). The EDEN data site currently represents the state of the art in delivering data and related services to a broad network of partners involved in a specific set of research tasks. It has a remarkably high profile with a data archive nearly 1000 datasets in more than 20 categories, amounting to several hundred GB; more than 400 registered users over half of which are from outside the EDEN project; a unique user hit rate in excess of 2000/month, with a more than 60,000 unique users from 160 countries, over three and a half years in full service.

One of the reasons for the site’s success is its multilevel user access regime that allows data download to be rigorously controlled, so that research data can be reliably posted for colleagues to share, without the risk of unauthorised access. At the same time there is a large amount of information that is available to all registered users, many of whom are not part of the project, so that the site attracts significant attention from outside the project- thus raising its profile as a whole. In addition the breadth of content also attracts attention – encompassing standardised spatial data, training and help files and utilities, a comprehensive links page and an associated site for PHD student built at their request that attracts 2000 visitors/day). The site also provides a publication search tool that provides georeferenced description of research
data holdings and results produced by EDENext members that allows potential collaborators to identify clearly what the EDENext community has achieved, and map the results, without releasing the actual data. This provides dissemination or research activities whilst retaining intellectual ownership.

Given the valuable function its site has performed for EDEN, it is proposed to provide a similar service for EDENext, but with significantly wider remit. There are a number of possibilities for providing an enhanced service. The website was provided primarily for its members, and attracted those largely specialist users who found the site using search engines. Few specific efforts were made to collaborate with other EU funded projects and networks to incorporate information they produced, or to allow them access to public domain data acquired for the project. This is a major opportunity to improve the service provided.

1.2.7.2 DMT Host Distribution Mapping

It is axiomatic that the availability of disease and vector hosts affects the distribution of both vector and disease, and that a number of host species might be involved in disease transmission, for example, as primary hosts, (wildlife) reservoirs, or hosts of the vectors. A knowledge of host numbers is also required as the denominator needed to quantify disease occurrence in terms of incidence or prevalence. EDENext partners will therefore need access to host distribution data in order to properly evaluate disease risk and to assess both actual and potential vector distributions. There is thus a strong case for acquiring standardised and consistent information about host and denominators in formats that are appropriate for both the Integration and Vector groups.

The activities needed to deliver these outputs are specifically designed to be fairly routine, and have been selected in order to make sure that, providing sufficient data are available, distribution maps can be produced for the other project Groups reliably and rapidly, and that the outputs do not rely on generating and validating new and untested methodologies. To achieve this DMT will use confirmed general modelling approaches (e.g. Hay et al. 2000, Elith et al. 2006), techniques specifically developed for livestock mapping (Wint and Rogers, 2000, Wint and Robinson, 2007, Gilbert et al. 2005, Neumann et al. 2009) and new methods developed as part of EDENext. The research content within this part of DMT will be focussed meanly on the provision, validation and quality control of new data with a wide relevance to the project and beyond and the development of spatial models using robust techniques, rather than the generation of new technology, which will be more the preserve of MOD.

1.2.7.3 DMT Wind Spread Models

Over the past few years EDEN DMT has developed a unique expertise in modelling the local and medium range wind-spread of midge-borne diseases and more specifically of bluetongue. The dispersal of Culicoides by wind is an important route of introduction (Gloster et al., 2007; Sorenson et al., 2007; Burgin et al., 2009) and spread of BTV (Ducheyne et al., 2007; Hendrickx et al., 2008; Ducheyne et al., submitted).

A new third generation predictive model (Ducheyne et al., submitted) has already been successfully applied to predict the spread during the 2006 outbreak of BTV8 in Belgium, the Netherlands and Germany and the 2008-2009 BTV1 epidemic in France. In addition it has been used to simulate the impact of preventive measures such as vaccination. The model takes into account parameters concerning the spatio-temporal distribution of the cases; incidence estimated from the epidemiological curve and the flight behaviour of the vector.

While the model correctly predicts the observed spatial and temporal distribution of cases, results also indicate that other factors might influence the disease transmission such as: topography and whether the vector is capable of survival to bite new hosts after wind
dispersal. Within EDENext DMT it is the aim to quantify the relationships between the wind spread of BTV vectors and these as yet semi-quantified factors.

1.2.7.4 DMT References


Ducheyne, E., De Deken, R., Bécu, S., Codina, B., Nomikou, K., Mangana-Vougiaki, O., Georgiev, G., Purse, B.V. and Hendrickx, G., 2007, Quantifying the dispersal of Culicoides species in Greece and Bulgaria by wind. *Geospatial Health* 1, 177-189


1.2.8 Public Health Group (PH)

Public health (PH) is the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public
and private, communities and individuals. It is concerned with threats to the overall health of a community based on population health analysis. The population in question can be as small as a handful of people or as large as all the inhabitants of several continents (for instance, in the case of a pandemic). Public health is typically divided into epidemiology, biostatistics and health services. Environmental, social, behavioral, and occupational health are also important subfields. There are 2 distinct characteristics of public health:

- It deals with preventive rather than curative aspects of health
- It deals with population-level, rather than individual-level health issues

The focus of public health intervention is to prevent rather than treat a disease through surveillance of cases and the promotion of healthy behaviors. In addition to these activities, in many cases treating a disease may be vital to preventing it in others, such as during an outbreak of an infectious disease.

The role of Public Health agencies is to (1) understand potential PH threats, and (2) set in motion prevention activities. EDENext is not a Public Health agency but can assist responsible agencies, stakeholders and decision makers in fulfilling their tasks/duties when, and also before, an epidemic or an epizootic begins. Hence the core idea of WP5 is to elucidate PH aspects of the research results that are obtained in the thematic WPs of EDENext, to find methods and modes to distribute this relevant information through adequate channels and means to governmental and non-governmental bodies/organisations (incl. EU) involved in PH policy and management and to assist by counselling all these players in setting up counter measures as much as can be accomplished.
1.3 Scientific and technological methodology and associated work plan

1.3.1 Overall strategy

EDENext is a project which provides a platform for integrative and multidisciplinary research between 5 Vector Groups and 3 Horizontal Integration Groups under the guidance of a General Coordinator and a Steering Committee. In this part the methodologies and workplan of each of these Groups, and how they interact within the EDEN community is described.

1.3.1.1 Tick Group

The TBD group – consisting of 11 partners from 7 countries – has identified a number of research questions related to the spread of various tick species and accordingly, to the emergence and prevalence of various tick–borne pathogens in various parts of Europe. Following a specifically targeted literature review on these subjects, a number of scientific gaps have been identified which will be studied through field and laboratory work involving standard and innovative tools. In particular new information will be acquired on tick biology, as well as on vector competence and capacity (through development of markers) of ticks for the various pathogens they can transmit. In addition, new information will be acquired on the geographical distribution, prevalence, taxonomy and genetic variability of emerging viral, bacterial and protozoan agents being transmitted by these ticks and the risk for their further spread in Europe. All pathogen detection will be performed according to harmonized methods for diagnosis and characterization. In order to identify natural reservoirs and vectors of pathogens, appropriate laboratory experiments will be performed using ticks, tick-cell cultures, and laboratory mouse models. Based on the data obtained from field and laboratory work, appropriate statistical and mathematical risk-modelling will be carried out at the local, regional and EU-level in order to provide the stakeholders with basic information for the development of control and intervention strategies against these various pathogens.

The TBD proposal is divided into three workpackages based on pathogen type and approach: the first WP comprises studies of the emergence and spread of four bacterial and protozoan tick-borne pathogens, and is clearly focussed on tick biology and vector competence for the transmission of these pathogens for which some information is already available. The second WP deals with emergence and spread of a very recent serious public-health concern, CCHF. Therefore, research in this WP is primarily directed at sero-epidemiological surveys to generate basic data on transmission risk of CCHF virus. The third WP aims at the intervention and control of (potentially) all the above-cited TBD, by producing assessment tools and predictive mathematical models, using ecological, genetic and climatologic data accumulated in WPs 1 and 2, as well as during the EDEN project. The innovation in WP3 lies in the fact that these models will be developed at the small and medium scales, and are expected to be integrated into, and considerably enhance, the predictive value of existing large scale models.

Organization and harmonization of field work and sampling strategies

In order to generate comparable data across all partner institutions, a consensus meeting will be organised prior to the beginning of the project work. At this meeting, all protocols for tick and host sampling and the parasitological, virological, serological and molecular techniques for species identification and detection of pathogens and antibodies (Anaplasma phagocytophilum, Rickettsia spp, Bartonella spp., Babesia microti, Babesia sp EU1 and CCHFV) to be used will be presented and harmonized accordingly. The chosen diagnostic protocols for the above-mentioned pathogens will be distributed among the participants from recent literature, guidelines, SOPs and unpublished data.
These diagnostic protocols will include: a) collection and shipment of tick specimens to the responsible laboratories; b) compliance on parasitological, virological, serological and molecular procedures; c) definition of cut-offs for the serological and molecular tests on the respective pathogens and infections.

In order to verify and compare the elaborated data, an ISO 9001:2008 certified and (planned by 2010) ISO 17025 accredited reference laboratory (LMU) will be defined and designated with a mandate to perform the reference laboratory analyses and to organize ring tests for the molecular and serological test methods to be used.

At the same time, a collection of engorged ticks from host animals (mostly large and small ruminants, rodents, insectivores) will take place in the same areas as the study sites for abundance and species spectrum and for molecular detection of pathogens in the ticks using the same methods as in the questing ticks.

From some host animals, blood samples will also be collected for serological analysis and from the rodents also tissue samples (spleen) for molecular detection of pathogens.

Where it is possible, plans have been made to reduce animal experimentation and any such experimentation will be carried out according to the respective national animal protection laws. The number of required animals can not be stated, since the number of isolates is not known. However, efforts will be made to use the minimum number necessary to obtain statistically sound data. All these experiments will be performed according to the 3Rs (replace, reduce, refine).

Organization of lab work and harmonisation of tests

For determination of the tick species (both questing and engorged), they will be collected in 95% ethanol. Subsequent morphometry analyses will be achieved to stage and species level using standard taxonomic keys from the respective countries.

From the ticks, DNA will be extracted by the same method in every laboratory (from only half of the tick in the case of full engorgement) and these samples will then be screened with sensitive and specific PCR methods (Masstaq PCR, real-time PCR and/or conventional PCR with sequencing) to assess the prevalence of *A. phagocytophilum*, *Rickettsia* spp., *Bartonella* spp., *Babesia* EU 1 and *B. microti*. A representative number of samples will be screened at the reference laboratory.

For CCHFV, RNA will be extracted from the relevant tick species under required biosafety containment and analysed by RT-PCR methods. In addition, CCHFV antigens will be searched and viral isolation will be attempted in BSL4.

Particular efforts will focus on determining reservoir hosts and limits of endemicity of the respective pathogens. Blood samples will be screened with a) blood smear examination for the detection of bacterial or protozoal agents; b) molecular methods as mentioned above for the detection of specific DNA or RNA of tick-borne pathogens; c) serological examination for the detection of antibodies against tick-borne pathogens.

Serological tests (ELISA, IHA and IFAT) and tissue analysis (molecular methods) will be conducted by several participants. The tick collection data and molecular and serological laboratory data will be analysed geographically to allow a spatial mapping of tick species and abundance and presence of pathogens for all countries involved.

The pathogens, especially *A. phagocytophilum*, *Bartonella* spp., *Rickettsia* spp. and CCHFV, will be isolated in vitro and characterized using a variety of molecular methods (PCR, PCR-RFLP, sequence analysis).

Identification of markers for characterizing vector competence will be done for *Babesia* spp. and *A. phagocytophilum* through feeding ticks under different experimental conditions, followed by RNA extraction, cDNA synthesis and subtractive hybridization, then sequencing and
identification of differentially expressed genes, analysis of correlation of differentially expressed genes with pathogen transmission and RNAi knock down of differentially expressed genes to assess role in pathogen transmission. This work also includes determining the pathogen dose on the viability of the tick and the assessment of differentially expressed genes to be used as a marker for the determination of the vector competence.

Isolation of *A. phagocytophilum*, *Bartonella* spp. and *Rickettsia* spp. from engorged ticks from potential reservoir hosts for subsequent in-vitro cultures including experimental tick infection and subsequent experimental transmission studies by selected tick species using the laboratory mouse model.

**Training and collaborative exchanges**

At the beginning of the project work, a standardization and harmonisation workshop will be organized for all scientists of the partner institutions involved in the project at the Reference laboratory partner (LMU). Thereafter, workshops for young scientists (preferentially MSc and PhD students, post-docs) will be organized once a year on relevant topics (such as tick-cell cultivation, bioinformatics tools, genotyping approaches, among others).

The performance of laboratory involved in diagnosis of CCHFV will be evaluated by a blind ring trial organized by ENIVD and OIE / WHO reference laboratories.

### 1.3.1.2 Rodent Group

Based on the existing literature data (Vapalahti et al. 2003,) and data collected in earlier projects (mainly EDEN; see EDEN publication list), there is already a fairly good knowledge of where geographically and how dynamically common rodent-bone hantaviruses (particularly Puumala virus) occur in Western Europe and Fennoscandia (Heyman & Vaheri 2008, Tersago et al. 2008, Olsson & Henttonen 2010). For Eastern Europe, there are still a number of undocumented areas; this is true also in most of the rest of Europe for the other hantaviruses and additional viruses in the project. Therefore, it is necessary to identify a number of target areas, at European scale, where collections will be focused.

The best-known and most common European hantavirus (Puumala) will be used to further collect basic parameters for modelling. Missing pieces include the role of biodiversity, the survival of virus outside the host in varying environmental conditions, the role of immunogenetics in virus occurrence, and the relation between genetic structure and landscape epidemiology.

In order to study the spreading of the virus, a mathematical modelling approach will be combined with specifically designed experiments. The experimental work will be concentrated in places that can offer appropriate biosafety conditions (METLA-HI, SMI, UA).

In selected study areas representing different biomes and host dynamics, a regular monitoring will be set up to follow temporal changes and possible concerted responses by rainbow and tick-borne pathogens. This pilot study will test the feasibility of an early warning system.

**Organization of field work**

Both exploratory and monitoring fieldwork will be standardized according to joint protocols, designed by the VG-leaders and discussed and agreed upon during the project kick-off meeting. In areas where there is no available team available, the VG leader will participate in the initial phases of the field work, so as to make sure that standard protocols are implemented. Standardization includes trapping methods (but, subject to agreement, adjusted where needed to accommodate specific characteristics of host species characteristics). Blood and tissue samples will be taken according to a fixed protocol and materials as well as data
stored in a standardised way. The latter also counts for samples taken during experimental work. For hantavirological methods, see Vaheri et al. (2008).

Organization of lab work

Serology and PCR-tests have been using basic materials (slides, primers, protocols) developed at two partner institutes (METLA-HI, SMI) and will further be standardised (FLI), and distributed from there to the other partners. Alternatively samples will be sent to above mentioned labs. Partners may decide to use commercial rapid tests so that observed infections can be used to quickly guide further steps during the implementation of a protocol, but additional parallel samples will be kept then for later confirmation with the standardised approaches. Methodologies have been published in EDEN (Vaheri et al. 2008).

Organization of training and collaborations activities

RBD-partners will meet at the annual project meetings and specific training workshops will be organised in connection with those meetings. PhD-students will spend periods of 1-3 months with at least one of the other partner institutes in RBD. Since most project partners in RBD have considerable field work experience and have collaborated before, there is no need for an explicit capacity building workshop. In the areas where so far no small mammal research was undertaken, capacity building will be on an ad hoc basis since for many places the actual people involved in this kind of work are fairly mobile in their career, meaning that capacity building workshops that come too early do not always target the people that later will do the actual work

1.3.1.3 Mosquito Group

Our study spans the breadth of Europe, from the southern tip of Spain (Guadilquivir Delta) to the Black Sea (Danube Delta). In four countries—Czech Republic, Hungary and Romania—our focus will be mainly on extensive reed-beds

Field studies, WNV

We have chosen dense reed-beds because there is ample evidence (from EDEN) that all elements of the transmission cycle are present:

- Large populations of migrant passerines (especially Acrocephalus spp Warblers) that arrive in spring from sub-Saharan Africa and have high WNV seroprevalence
- Two species of ornithophilic mosquitoes that have high competence for WNV and are super-abundant
- Large populations of a resident species, the Coot (Fulica atra), that also has a high WNV seroprevalence
- Reed-beds are a ubiquitous ecosystem in lacustrine wetlands in temperate regions (probably the principal site for transmission)
- Many of the reed-bed passerines in Europe overwinter in the same habitat south of the Sahara

Winter survival of vectors and virus

The annual appearance of Lineage II WNV since its emergence in Hungary in 2003, and similar events in Italy, call for studies on the winter survival of virus in Europe.

We have detected overwintering mosquitoes (EDEN); Infection of the diapausing cohort is probably by the “vertical” route because these feed on sugar, not blood, before entering their refuges. Vertical transmission has rarely been investigated in the field, and thus merits attention in the context of maintenance of virus in winter and at other times when populations are low or inactive.
We will use back-pack aspirators to monitor the period when the mosquito population is going into diapause to compare the parous rate of the dwindling adult population with that of the overwintering cohort; if the latter are nulliparous, and nullipars are no longer entering the traps, we will have confirmation that the overwintering cohort acquires virus via the egg stage.

Several species of ornithophilic mosquitoes are abundant in reed-beds, but their winter refuges have never been identified. We will take advantage of winter harvest of reeds in Hungary and Austria (exported for thatched roofing) to examine the interior of reed stems and the vegetation at their base to resolve this question. If fair numbers of adults are found, we will sample at regular intervals for indication of survival rate. Mosquitoes captured will be screened for virus.

Buildings are convenient sites for studies of overwintering; in some cities they may harbour thousands of mosquitoes. Teams in Czech Republic, Hungary and Romania will assess survival rates at such sites by marking them with fluorescent powders in early winter, and monitoring their numbers in successive months. Samples will also be screened for WNV.

Lastly, we will address vertical transmission in the rest of the year by collecting swarms of males and screening for virus (PCR positive pools will be submitted for isolation and sequencing). We may also continue laboratory studies funded by EDEN.

Host specificity of mosquitoes

Ornithophilic mosquitoes have been targeted for study (EDEN) with bird-baited traps, but species attracted to other vertebrate hosts may be important in transmission (see below); we will use traps baited with birds, mammals and amphibians to identify these and screen for virus. A modified version of a commercially available device, the BG-Sentinel, will be constructed from treated plywood for the purpose. These will be set out in an array along transects cut through areas of marshland, and on adjacent dry land. Collections will be made on a regular basis, at least twice a month for each bait.

Transmission cycles that do not involve arthropods

In the Americas, after it was first detected in 1999, WNV spread with astonishing speed; by 2003 it was widespread in every State west of the Rocky Mountains. In the Old World, mortality in birds is generally low—an exception may be the Lineage II virus recently identified in central Europe—but in the United States, WNV was fatal to more than 250 species of birds. Species of Corvidae (Crow family) were by far the commonest casualties. Several factors may have contributed to this: (i) WNV is highly infective by oral route; (ii) Crows are scavengers, feeding on carrion, including dead crows; (iii) they are social birds and roost in large colonies; (iv) they disperse widely (up to 100km) each day; (v) their feeding areas are not territorial, and overlap with crows from other roosts; (vi) virus is shed in excreta for days/weeks after viraemia ceases. Thus, dead or dying infected crows that have fed on WNV-infected carrion (as well as moribund birds and mammals) can pass the virus to crows from other, distant roosts by oral infection, establishing foci for local infection by mosquito-bird transmission. A model (EDEN) of this rapid dissemination of WNV indicated a significant role for crows, particularly when mosquito populations are low.

Other observations demonstrate transmission without mosquitoes in birds, mammals, reptiles and amphibians: (i) infection of crows and raptors during winter, when mosquitoes are in diapause; (ii) high and synchronous mortality in flocks of geese, attributed to cannibalism and faecal-oral infection; (iii) oral infection in mammals; (iii) persistence of virus in bird and mammal tissues after it is cleared from the blood stream (e.g. >eight months in hamster urine; (iv) infection of nocturnal owls that feed on rodents; (v) co-infection in penned alligators,
presumably by faecal/oral infection; (vi) infection in snakes, virus shedding in faeces; (vii) infection in frogs; (viii) infection in *Hyalomma* ticks.

Thus although WNV clearly has modes of infection in common with influenza viruses (faecal shedding, infection via mucosa) and Hantaviruses (chronic infections and prolonged shedding of virus). Little attention has been paid to these modes in nature, yet they may well play a major role in the transmission cycle.

In the context of this hypothesis, we can envison many possible infection routes: mosquito to bird, bird to bird (oral infection when feeding chicks, faecal-oral infection, ingestion of prey or carrion, ingestion of infected mosquitoes); bird to amphibian (faecal-oral); amphibian to bird (ingestion, viz. storks and herons); amphibian to mosquito and so on. Again, reed-beds offer a plausible scenario: passerines aggregate among the upper reed-stems, their droppings (25-50 per day) contaminate the water surface where Coots dabble on floating plants, and frogs and turtles are abundant; herons and storks feed on frogs and themselves shed virus and so on. It is even conceivable that fish and aquatic insects can be infected from droppings and faecal shedding by frogs and turtles.

For these reasons, we will capture birds in various habitat, test for seropositivity, and screen for virus in oral and cloacal swabs. We do this with (i) intensive yearlong captures of coots in reedbeds, and corvids in surrounding areas; (ii) mist nets set along transects cut through reedbeds; (iii) birds captured by ringing teams. We will also capture passerines that use a barren, mosquito-free island in the Baleric islands as a short stop-over point. These are of particular interest in that, after several weeks of migration, viraemia from infection acquired in sub-Saharan regions is likely to have been eliminated.

We will use live traps along reed-bed transects to capture small mammals; after capture a small pad of cotton will be place in the trap for a short time to sample urine. Frogs will be captured by handnet around a lure. Serum will be taken from both, oral swabs cloacal swabs from frogs.

**Experimental infections**

Frogs are abundant in wetland areas, and are important in the diet of Storks, Herons and other birds. Wild frogs are protected species in many countries; we will substitute Xenopus toads. These will be infected by sub-dermal injection and held in individual containers. Toads sacrificed at regular intervals will be screened for virus in blood, oral cavity, cloaca, intestines and other organs. Experiments will be made to test for faecal-oral infection between infected/non-infected pairs, and infection by contact with bird faeces.

**Laboratory processing**

Sera. Screening will be by IgG ELISA followed by confirmation with plaque reduction (PRNT-90) to confirm. Virus isolation will be on Vero or RK-13 cells.

**Invasive species: *Aedes albopictus* and *Ae. japonicus***

*Aedes albopictus* is an Asian species that suddenly appeared in the centre of the continental United States in 1982. Its mode of importation was traced to a world-wide commerce in used tires. It has now spread throughout the Americas, and to Europe, Africa and the Middle East. Its first appearance in Europe was in the early 1970s in Albania, and later in Italy, probably imported in shipments of second-hand tyres. Infestations in green-houses in Holland were attributed to cargoes of “lucky bamboos” imported from southern China, but did not persist outdoors, perhaps because they lacked winter diapause. *Ae. albopictus* is now established in at least 12 European countries, and there is every reason to believe it will continue its northward expansion, much as in the New World, where it is established as far north as Chicago. *Ae. japonicus*, an Asian species with similar habits and ecology, is now established in Switzerland.
and is also spreading northwards. Its role as a vector is unknown, although it is susceptible to WNV in the laboratory.

The introduction of West Nile virus to the Americas, the worldwide dissemination of Aedes albopictus, the introduction of Ae. japonicus and the pandemic of chikungunya virus in Italy are examples of the accelerating globalization of vectors and vector-borne diseases. Concern for this, and for the likely role of environmental change is an important element of this proposal.

Aedes albopictus is generally regarded as a “secondary vector” of dengue (DEN) and chikungunya (CHIK), mainly because it is not host-specific, yet it was the only vector in major outbreaks in La Réunion and Mauritius in 2006-7. In part this may have been because the strain of CHIK was particularly infective for the mosquito—the Italian outbreak was due to the same strain—but DEN epidemics transmitted by *Ae. albopictus* have occurred in the past, and millions of people arrive in Europe every year from dengue-endemic areas. Moreover, there is no obvious reason why *aae* could not be re-established in Europe.

Climate, particularly rainfall, is a significant parameter in mosquito populations, and temperature is significant in mosquito-borne transmission of vector-borne pathogens. In northern Asia, *Ae. albopictus* eggs laid towards the end of the mosquito season are dormant until the arrival of spring. This winter diapause is triggered by daylength, and daylength is determined by latitude. The same is undoubtedly true for *Ae. japonicus*, though this species has hardly been studied. The future expansion of both species will be determined, in part, by diapause and, of course, tolerance to low temperatures. In addition, temperature will determine the duration of the aquatic instars, which in turn may affect the size of populations and the number of generations per year. Many other factors—habitat, competition with other species, predation etc.—will determine the future expansion of both species, and the size of their populations, but climatic conditions are a key parameter that we can study in advance of this expansion.

The rate of viral replication is also affected by temperature, but despite frequent mention in the debate on climate change, surprisingly little attention has been paid to this, even in the laboratory; most studies have restricted focus to the duration of the extrinsic incubation period. Today, quantitative RT-PCR offers a powerful tool to investigate the effects of temperature on virus titre over time. For example, nothing is known of the effect of continual diurnal variations on replication, yet these may be crucial in transmission rates in nature, particularly at higher latitudes and altitudes. Results may be quite surprising. A recent study revealed that *Ae. albopictus* reared at lower temperatures had higher rates of infection (determined after a fixed period of extrinsic incubation) than those reared at high temperatures. This again may be critical in potential for future transmission in Europe.

A plethora of factors determine the advance of invasive species. In forecasting, the best we can do is to simulate the physical environment and extrapolate as best we can from this to nature.

Our main focus will be on *Ae. albopictus* in Rome—clearly, after the CHIK outbreak in 2007 and given its plentiful *Ae. albopictus* population, an example of a city at great risk. and in Albania.

We have chosen Albania as a proxy for northern areas of Europe because the country has been infested for more than 30 years, and the mosquito is abundant at high altitudes with extended winters. Our ultimate objective is to project which climates in Europe may be permissive for *Ae. albopictus* as the species expands northwards, and which among these are likely to support epidemic transmission.

We first need answers to fundamental questions: what are the main sources of the *Ae. albopictus* plague in the city? What is productivity of such sites? What is the longevity of the adults, etc.
We will then focus on the future: are there climate constraints for its expansion under present conditions, and how might this change in the future?

Volunteers in different parts of Europe will be given small digital data-loggers that record temperature and humidity at regular intervals. These will be placed in “standardised” patches of leafy vegetation in shaded sites that are “typical” habitat preferred as resting sites by *Ae. albopictus*; criteria for these will be determined by discussion with the volunteers who will man these stations. Sites will be chosen to represent climatic zones in several sites in Italy, at selected altitudes in Albania, and at other sites in other countries in Europe as far north as central Sweden. Data will be recorded every 30 minutes throughout the year, and downloaded (by volunteers) at least every month. The data will summarised to define the range of temperature/humidity profiles existant in the relevant regions.

We will simulate these in two environmental cabinets, one in an insectary and the other in a P3 arbovirus laboratory. In the insectary we can investigate rate of development of aquatic instars. In the P3 we will monitor the rate of CHIK and DEN viral replication by quantitative RT-PCR. The point of particular interest will be the effect of temperature *fluctuations* on the rate of viral replication as well as the temperatures themselves. We will also run trials on mosquitoes captured in the field, and will replicate at least some of our experiments with *Ae. japonicus*.

*Aedes albopictus* and *Ae. japonicus* are fairly easy to colonize. Laboratory colonies will be established from mosquito eggs collected by ovitraps. Eggs will be disinfected before hatching to reduce risk of pathogens. Mosquitoes used in experiments will be from early generations of these colonies. The origin of colonies will be determined by climate, latitude and altitude criteria.

An initial set of experiments will be made with *Aedes albopictus* reared at 24°C and held at 18°C, 24°C and 30°C. Mosquitoes will be infected orally and subsequent viral titre will be determined by quantitative PCR on samples taken every day, or at longer intervals when dictated by temperature, until titre reaches a plateau. Intervals between according to the temperature regime, until it reaches a plateau. Important features of the replication curve will be the interval between the infected meal and first detection of virus (probably at least five days) and the slope and duration of the increase thereafter.

In the subsequent, and longest series of experiments, conditions in the environmental cabinet will be set to simulate field profiles, including daylength regime, and infected mosquitoes monitored as with the baseline experiment. In each case, the objective will be to obtain a continuos curve from the day of infection until the titre of virus reaches a stable plateau.

In the next series, conditions in the environmental cabinet will be set at low (ca. 18°C), medium (ca. 24°C) and high (ca 30°C) ; insects will be reared under these conditions and infected adults monitored under selected temperature/humidity profiles.

In the final (programmed) series, adults will be held in light regimes equivalent to autumn daylength at progressive latitudes in Europe. Mosquitoes used will be derived from eggs collected in Rome, and at several altitudes in Albania. Eggs will be tested for diapause, and subjected to temperatures below 0°C. They will then be returned to long daylength to determine whether they will hatch. Samples will be treated with mild bleach to determine whether they are embryonated.

1.3.1.4 Phlebotomine Group

The PhBD Group, which includes 9 participants from 8 countries, has identified several research questions related to biology of sand flies and associated pathogens *Leishmania* and Phleboviruses. Based upon literature review and unpublished reports, a number of scientific gaps have been identified, which shall be exploited through field and laboratory work
involving standard and innovative tools. New information will be obtained on sand fly taxonomy, geographical distribution, vector competence and insecticide susceptibility. In parallel, taxonomy and genotyping of protozoan and viral agents will be elucidated, along with standardization of methodologies for their diagnosis and characterization. Control methods of PhB diseases will be addressed to both insect vectors and reservoirs. Starting from findings obtained at territory and then at country level, analysis of results will be performed at both regional and European level.

Organization and standardization of the field work, sampling strategies

Sampling areas will reflect topographic, altitudinal, vegetation and socio-economic properties of the study region. Site characteristics shall be georeferenced for appropriate spatio-temporal analysis. Sand flies will be collected periodically during the active season for at least two consecutive years. Three collection methods will be used: (i) sticky papers, (ii) aspirators, and (iii) CDC light (or CO2)-traps. They will be used for both, exophilic and endophilic, sand flies. Nocturnal activity patterns on selected localities will be performed using CDC light traps; data loggers recording temperature and humidity will be used for analyzing of resting microhabitats of blood-fed females. For *Leishmania* research, specimens will be dissected or stored in 96% pure alcohol for subsequent determination, morphometry analyses, blood meal identification and parasite identification. Procedures of specimen handling for Phlebovirus research are detailed below.

Because hyperendemic cutaneous leishmaniasis is reported in Turkey, the efficacy of insecticide-treated bednets for prevention and control of the disease will be evaluated in dozen of villages of recently described cutaneous leishmaniasis focus in Cukurova region. So far only the synthetic pyrethroid insecticides and the near-pyrethroid etofenprox are suitable for bednet treatment. They are also excito-repellent, quick acting, and effective in small quantities that can be made to adhere to fabrics. Deltamethrin or permethrin-based formulations will be used in this project. The experiment shall be replicated at least once a year in intervention and control areas (without any bednet). Intervention areas shall be further divided into “impregnated bednet” and “non-impregnated bednet” sub-areas. The core experiments shall be performed during the sand fly season (between May and October), overall trials including questionnaires must be conducted for the whole year. Initial questionnaires on epidemiological, physical, social properties of the implementation area will be followed by a second series of questionnaires after the distribution of insecticide-treated bednets.

Canine leishmaniasis surveillance will be carried out through field surveys in known endemic foci. In addition, selected geographical territories located at the borders of these endemic foci will be investigated to control the *L. infantum* spreading or the presence of unreported *Leishmania* spp. Dog populations will be sampled with the informed consent of their owners for subsequent serological analysis by IFAT or ELISA, bone marrow aspirate for microscopy and molecular assay, and popliteal lymph node aspirate for *in vitro* culture. A novel diagnostic tool for monitoring *Leishmania* dog-contact will be applied in selected areas by a non-invasive sampling method of conjunctival swab (CS) coupled with a sensitive a specific PCR-based analysis.

Organization of labwork, standardization of tests

Diagnostic protocols on human PhBD and canine leishmaniasis will be complied among participants from recent literature, guidelines and unpublished data. Diagnostic protocols will include: a) collecting and shipment of biological specimens to national reference diagnostic laboratories; b) compliance on parasitological, serological, and molecular procedures; c) definition of “cut off” for serological and molecular procedures for human PhBD and canine leishmaniasis. Dog populations will be sampled with the informed consent of their owners for subsequent parasitological and serological analysis by IFAT or ELISA, using standard
EDENext

protocols. Particular efforts will focus on determining the limits of endemity of leishmaniasis, e.g. the presence/absence of autochthonous dog infections involving different *L. infantum* strains/populations and nonendemic *Leishmania* species. Then parasite shall be necessarily isolated *in vitro*. The isolated parasites will be typed using a range of isoenzyme and molecular tools (PCR, PCR-RFLP, microsatellites, etc).

 Conjunctival swab (CS) samples will be obtained from the dogs. The tubes with CS will be delivered at room temperature to diagnostic reference laboratory. Total genomic DNA will be extracted from the swabs and subjected to nested-PCR. Results will be compared with standard serological and parasitological methods.

 The project will bring for the first time the task of producing Phlebovirus maps distribution at European level. For the centralization system of isolation and identification of Phlebovirus a devoted sand fly collection will be requested from all collaborating partners. Field collections will be in selected geographical transects know for distribution and abundance of sand fly species. As more and more virus species are being identified (for which RT-PCR detection is not available), the main aim will be to obtain virus isolates. Specimens collected by CDC traps (the whole insect is required for viral isolation) will be assembled in pools of 10-20 flies (distinguished for locality, date, sex) and stored at –80°C deep freezer within 24h from collection. The sand fly species identification will be ‘indirect’. For each participant, one batch will be collected twice a month, 6 months/year. Several sand fly batches can be collated during time and sent at once to MIPI Department of ISS. Received collected sand fly pools will be homogenized, centrifuged and the supernatants used for virus isolation, performed by inoculation of suckling mice and/or Vero cells. Isolates identification will be made by different serological and molecular methods. Molecular characterization of newly isolated viruses and phylogenetic studies and evolution studies from sequence data will be carried out.

 For molecular identification of sand flies and studies on of sand fly population genetics, the thorax of specimens from selected species (e.g. *Larroussius* spp.) will be used for molecular analyses, using direct sequencing of both mitochondrial and nuclear genes, microsatellites. Comparisons of the population structures will be supplemented by geometric morphometric of wings and terminalia. For blood meal identification, cyt B sequencing and cyt b PCR-RLB (Reverse Line Blotting) methods will be used.

 Vector competence of various sand fly species for *Leishmania* will be studied in laboratory conditions. Female sand flies obtained from laboratory colonies (4-6 days old) will be infected by feeding through a chick-skin membrane on a heat inactivated rabbit blood containing $10^6$ *Leishmania* /ml from a 5 day old culture. Blood-engorged females will be separated and maintained at constant temperature. At various intervals post infective bloodmeal, half of females will be sacrificed for microscopic examination of parasite location and grading the intensity of infection according to the criteria reported previously, second half will be used for quantitative PCR to obtain more precise information on parasite numbers.

 In studies on insecticide resistance/susceptibility, sand flies will be exposed in a confined space to surface treated with a standard concentration of insecticide for a given standard time and recording the ensuing knock down and mortality at the end of exposure, at the end of each discriminated time interval and at the end of a 24-hour holding period. The various methods of susceptibility testing on adults are as follows: exposure to several concentrations for the same length of time and the construction of a regression line from which the LD50 is determined, exposure to a single concentration for different times and the determination of the LT50, determination of the minimum LC100 and the establishment of a discriminating dosage near to the minimum LC100 in respect of most sand fly species. The tests will be replicated at least 3 times for each species and each concentration of used insecticide. At least 1 control kit
(including 3 replicates) will be prepared for test of each insecticide. Total tube number will be, at least, 12 (9 trial tubes + 3 controls) for each insecticide according to 3 concentrations.

For standardization among the laboratories, the insecticide(s) will be selected according to recommendations of updated WHO reports published yearly for actual mosquito and sand fly control programs in Europe. In addition, the laboratories can add other insecticides used in their own countries’ pest control programs and agricultural activities. In this case, the laboratory that uses other insecticide(s) will inform other laboratories and obtain the insecticide(s) for them to provide the sustainability of standardization.

For measuring dog exposure to the sand fly *P. perniciosus*, ELISAs will be developed. The tests will be based on detecting antibodies (Abs) against sand fly saliva in blood or in saliva of subjects bitten by the vector. ELISAs using whole native salivary gland lysates (SGL) to detect antibodies against sand fly saliva in human, mouse and dog sera have been developed by partner CUNI. However, production of sufficient native antigens for upscaled production of such ELISA is not feasible. Therefore, the current native antigens in the ELISAs will be replaced by recombinant antigens. The performance of an Ab detection test is primarily defined by the identity and quality of the applied Ag. For assessing the antigenicity of *P. perniciosus* salivary components for dogs, we will use sera collected from Beagle dogs experimentally exposed to this sand fly species. The major antigenic components of *P. perniciosus* saliva will be identified using Western blotting. Salivary gland cDNA libraries have been constructed for *P. perniciosus* and sequences of the most abundant salivary transcripts are available at GenBank. Recombinant salivary proteins will be produced through expression in the eukaryotic (mainly *Pichia pastoris*) and prokaryotic expression systems (*E. coli*). Purified HIS-tagged proteins will be controlled by Western blotting and their diagnostic performance will be assessed in ELISA. With the best antigen(s), ELISAs for detection of anti-saliva Abs will be constructed and evaluated. Part of the evaluation will focus on the ability to monitor the Ab response after challenge over time. For this investigation, sera will be collected from dogs living in endemic areas that underwent biting by *P. perniciosus*.

Standard and novel drug regimens for canine leishmaniasis treatment shall be evaluated in clinical trials as regards the ability of reducing the reservoir infectiousness to sand flies. Representative dogs from each treated and untreated (control) group shall be submitted to xenodiagnosis by colonized *P. perniciosus*. The animals will be sedated under veterinary care, put into a cage containing 50 female sand flies and exposed to bites for 2 hrs. Blood-engorged insects will be collected and dissected 4-6 days after the blood meal. The number of promastigote-infected flies, as well as the grading of infection will be obtained and findings compared between treated groups.

1.3.1.5 *Culicoides Group*

**Field site network**

To enhance our ability to predict the behaviour of the CBDs under future novel conditions, and the applicability of control measures across agricultural zones in Europe, a field site network will be established across the partners within which to investigate vector competence, life-history parameters and habitat use of key European midge vectors and efficacy of different vector control methods. Sites will be selected on the basis of proximity to P3 laboratory facilities, but will cover a range of eco-climatic zones and include areas inside and outside of the distribution of *C. imicola*. A partner from from sub-Saharan Africa (Senegal), which has recently reinforced its human and technology capacity as a partner of the EDEN project, has also been included in the proposal. Senegal is an area of active, endemic transmission of many serotypes of BT and AHS viruses, with important local economic consequences (AHS). The main vector is *C. imicola*, which is abundant and has a year-long activity. Senegal may
also be seen as a sentinel for the risk of introduction of new serotypes of these viruses in northern Africa and Europe.

**Standardisation of field protocols**

Given the relatively short period (around a decade) of study of CBDs in Europe and the rapidly changing epidemiology of the transmitted pathogens, standardisation of existing field and laboratory protocols is a key theme for the CBD project. Building on the harmonisation of surveillance protocols achieved during the FP6 MedReoNet project (and the forthcoming DYNVECT project) coordinated by the CBD leader, standardised protocols will be developed prior to each field season at annual general meeting and interim telephone conferences. Training in field and laboratory techniques will be achieved when necessary by reciprocal visits between partners.

**Standardisation of laboratory protocols**

In the laboratory, standardisation of techniques for feeding *Culicoides*, storage of infected midges and virus detection and isolation is required (see WP1.3.3.3) and again will be achieved by annual meetings, prior to the field season and reciprocal visits. Efforts will be made to apply the same primer sets for RT-PCR-based assays carried out in different partner laboratories within this project.

**Interaction of CBD project modellers with Horizontal Modelling Team**

The CBD group includes partners with complementary modelling expertises and datasets on spatial heterogeneity in *Culicoides* populations, and disease/serological incidence of CBDs at a range of spatial scales. Through collaborative visits and regular contacts, the CBD modellers will establish strong links with the Horizontal Modelling Team as outlined in Table 1 below.

**Table 1 – Collaborative modelling activities of CBD with MOD**

<table>
<thead>
<tr>
<th>WP</th>
<th>Model Type (CBD Lead partner)</th>
<th>ZOOX LRRS</th>
<th>UCL HRRS</th>
<th>FVM R0</th>
<th>ULB Spread</th>
<th>Key Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergence and Spread</td>
<td>Phenological models of key vector groups (CEH)</td>
<td>X</td>
<td>X</td>
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<td>Predictions of the ‘vector-free’ period for early warning</td>
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<td></td>
<td>Models of impacts of environmental factors on the demographic rates of key vector groups (CEH)</td>
<td>X</td>
<td>X</td>
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<td></td>
<td>Spatial and seasonal predictions of vector numbers at a regional scale</td>
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<td></td>
<td>Models of the landscape correlates of midge abundance and BTV transmission (CIRAD)</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>An indication of the potential impacts of farm husbandry on vector control</td>
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<td></td>
<td>R0 models for BTV and AHSV integrating the lab and field data on life-history parameters and predictions of vector numbers (CEH/DTU/CIRAD)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>Understanding of the drivers of BTV establishment across Europe</td>
</tr>
</tbody>
</table>
Vector population models to evaluate impacts of vector control on vector abundance (CEH)                  X  X  X  An understanding of the optimal timing and extent of vector control
R0 models of optimal vaccination strategies for disease control and potential impacts of wildlife reservoirs on transmission (CEH/CIRAD/DTU)            X  An understanding of the optimal timing and extent of vaccination

1.3.1.6 Modelling Group
Mathematical and statistical modelling are important tools to assess, analyse and predict the emergence and spread of VBD, and the potential impact of new and existing control and intervention methods. Biology brings knowledge of the life history and ecology of the vector and of individual-level interaction with the infectious agent; the modelling approach brings methods to integrate this knowledge in an assessment of ecological and epidemiological fitness, and to quantify and understand population-level spread and dynamics in a heterogeneous landscape. Integrating knowledge of the basic biology/ecology of the vector with the integrative quantitative methods will ideally allow predicting the emergence and spread of (new) vector-borne diseases in Europe. Once such understanding has been reached, it will be possible to use models to assess adequately and systematically the efficacy of control and intervention at the population level, as a preliminary assessment prior to wide-scale application in the field. It is therefore essential that, despite the complexities involved, modelling methods are integrated better, to take full advantage of their complementarity, to give increased insight into factors influencing emergence and spread of vectors and VBD into Europe.

The phenomenon of emergence and spread of an infection at a given location is typically divided into three different phases, each calling for its own biological research, its own data, and its own quantitative methodology: Introduction, Establishment, and Spread. For VBD these phases typically hold for both the suitable vector species and the infectious agent they transmit, and may, in particular cases, also hold for (one or more of) the host species. The infectious agent is of course linked to the vector, but some local environmental, epidemiological and ecological conditions may allow the vector to become established, spread and grow to higher abundance, but may not allow the infectious agent to be transmitted above threshold (similar to the well-recognised phenomenon of ‘anophelism without malaria’).

Table 2 provides a matrix of the relative importance of these three phases for the vectors and VBD represented in EDENext. These phases will be studied by developing generic quantitative methods and modelling approaches in WP3, tuned to the specifics of each vector-VBD-system in turn, and guided by direct interaction with the vector teams. Basic biology and biological process-based modelling approaches will be merged with statistical and computer modelling.

<table>
<thead>
<tr>
<th>Vector</th>
<th>Introd.</th>
<th>Vector</th>
<th>Establishment</th>
<th>Vector</th>
<th>Spread</th>
<th>VBD</th>
<th>Introd.</th>
<th>VBD</th>
<th>Establishment</th>
<th>VBD</th>
<th>Spread</th>
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</table>

Table 2 – Relative importance of Introduction, Establishment and Spread for VBD
The relevance for collaboration and the development of methods, for the various epidemiological/ecological phases, from the point of view of the different vector teams. * of secondary interest; ** of interest; *** of main interest

The three phases together with the importance of control and intervention naturally lead to four sub-work packages within WP3:
- WP 3.1 – Quantifying introduction risk for vectors and VBD in Europe
- WP 3.2 – Spatio-temporal $R_0$-risk maps for the establishment of VBD (and some specified vectors) in Europe
- WP 3.3 – Models for the spread of vectors and VBD in a heterogeneous European landscape
- WP 3.4 – Population effectiveness of control and intervention for vectors and VBD in Europe

The expertise needed for these four work packages consists of: process-based biological and ecological modelling (partner FVM, partner ULB); statistical biological modelling (partner UOXF); high and low-resolution remote sensing (partner UCL, partner UOXF); $R_0$-modelling (partner FVM); computer modelling of spread (partner ULB, partner Euro-Aegis), cellular automata and agent-based modelling (Partner ULB, Partner UCL).

A rough division of work for the partners in WP 3 is given in Table 3 below. In practice, almost all tasks require the interaction between all four partners and integration of their approaches.

<table>
<thead>
<tr>
<th>Partner</th>
<th>WP 3.1</th>
<th>WP 3.2</th>
<th>WP 3.3</th>
<th>WP 3.4</th>
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<tbody>
<tr>
<td>FVM</td>
<td>MOD Group leader</td>
<td>Leader WP 3.1</td>
<td>Active collaborator</td>
<td>Active collaborator</td>
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<td>UCL</td>
<td>Active collaborator</td>
<td>Leader WP 3.2</td>
<td>MOD Group Deputy</td>
<td>Active collaborator</td>
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<tr>
<td>ULB</td>
<td>Active collaborator</td>
<td>Active collaborator</td>
<td>Leader WP 3.3</td>
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<td>Active collaborator</td>
<td>Leader WP 3.4</td>
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<tr>
<td>Euro-Aegis</td>
<td>Active collaborator (host distributions)</td>
<td>Participant (data)</td>
<td>Active collaborator (wind spread)</td>
<td>Participant (data)</td>
</tr>
</tbody>
</table>

All work packages will involve close collaboration with all vector teams, and with the experts in the data management work package WP4. Work package 3.4 on control and intervention will involve close interaction with the public health experts in WP5.

*Training and collaborative exchange*
A method of working that has proved particularly successful within the FP 6 integrative project EDEN, and which we therefore want to continue here, is to work along two lines: 1) joint research mode; 2) consultancy/service mode.

In the ‘joint research’ mode, we aim to develop the methods needed for the three phases mentioned above, where the aim is to produce generic methods and models, but to let the development be guided by the interaction with specific vector teams, on specific vector-VBD-systems. This will benefit both the modelling team and the vector team.

In the ‘consultancy/service mode’ we aim to provide guidance and assistance to the vector teams and help to address specific questions they have where the expertise of the modelling teams can be of help. Examples are: performing requested analyses of remotely sensed data and training in this area; statistical and \( R_0 \) modelling; producing rough \( R_0 \)-maps and vector suitability and distribution maps; support and training on process-based, statistical and computer modelling. In all cases, joint publications are the ideal way to achieve progress, but depending on the ‘mode’ of operation, the modelling partner or the vector partner will take the lead in this. We imagine there will be at least one training workshop on modelling (as there was during EDEN) which will involve formal training in each of the ‘consultancy mode’ approaches.

We will furthermore organise one collaborative modelling meeting each year, where all modelling experts that represent the different vector, data and public health teams will meet to exchange ideas and progress. Apart from the initial meeting, we aim to organise these meetings at each annual scientific conference of the project.

Capacity building

One additional aspect of training deserves to be mentioned explicitly. As outlined in the introduction, and as shown in the WP3-description, a diverse range of quantitative skills is required to meaningfully address relevant problems in vector-borne disease emergence, spread, intervention and control. At the start of the project no single person accommodates the full range of skills. In the course of the four-year project, however, we will train young scientists (PhD and postdoc level) in all areas of the work package. We do so by frequent long-term cross-visits between our groups and by having serial appointments with different partners for postdocs within MOD. Because, through the nature of our work and our approach to collaboration, these young scientists will also have close interactive contact with many of the vector, data and public health teams, EDENext will, in this way, deliver a group of future European researchers thoroughly embedded in both quantitative methods and biological/public health knowledge and contacts, as future experts in tackling the problems of vector-borne infections. The exchange between the labs of the MOD partners will be natural events as most of the tasks to be performed require close collaboration of all partners and integration of approaches.
Publication strategy

We envisage three types of scientific publication. In collaborative joint research mode we address biological questions posed by, and therefore of relevance to, the various vector, data and public health teams, but most probably develop new methods and approaches especially for that purpose. We would produce joint publications, but members of the MOD team will take the lead in producing these. In the service consultancy mode, we would support work initiated by, and orchestrated by, the various other teams. We would collaborate on, and provide input for, scientific publications where the lead is taken by members of the various non-modelling teams. Finally, the new methods and approaches we develop must also be published in more technical journals to allow in depth peer review by modelling experts to establish the value of the advances made.

The PhD students in MOD will produce a PhD thesis, consisting of various first-author scientific publications. The postdocs in MOD are the contribution of EDENext to future modelling expertise in VBD in Europe. In order for them to be established as such they will need to produce scientific publications in a recognised important authorship position.

1.3.1.7 Data Management Group

The overall strategy of the EDENext Data Management Team (DMT) is to provide a service and research outputs which contribute not only to achieve the objectives of EDENext in particular but which also are of interest to the wider spatial epidemiology community active in the field of vector-borne and other infectious diseases.

To achieve this the EDENext DMT members have a unique experience in the development of spatial databases and information systems including the area-wide modelling of host distribution/ biodiversity and the modelling of wind-spread of midge-borne diseases.

Therefore the objectives of EDENext DMT are:

1. As a DMT service component to provide all EDEN partners with a centralized DMT facility to assist with spatial epidemiological studies in general and in particular:
   a. To develop and strengthen the data management infrastructure established under EDEN.
   b. To acquire, transform, harmonise and update PAN-European spatial data sets of particular interest to the spatial epidemiology of vector-borne diseases.
   c. To develop spatial information systems to disseminate EDENext outputs and which establish the link with other spatial information systems such as ECDC E3 and VBORNET.
   d. To provide GIS and spatial data management training to EDENext partners.

2. As a DMT research component to contribute to achieve the objectives of EDENext in general and in particular:
   a. To develop area-wide (Pan-EU) host distribution/biodiversity maps and models using existing state-of-the-art tools and models developed by the MOD (low-resolution component) group.
   b. To develop fourth generation wind spread models for midge-borne diseases based on the experience of DMT and in close collaboration with the MOD (spread-component) and CBD groups.

1.3.1.8 Public Health Group

The comparative analysis of public risk perceptions in different countries and the particular risk communication strategies needed will be one core element of the PH framework of EDENext.
EDENext WP 5 will be explicitly built upon understanding of PH issues related to TBD, RBD, MBD, PhBD, CBD. We will cover all three societal levels as well as deal with risk factors (that is part of a risk assessment strategy) and risk management approaches. In order to come up with a robust common understanding of PH and a shared idea of an adequate PH framework in the context of vector-borne diseases and environmental change, all relevant PH actors and decision-makers, as well as stakeholders and even individuals, will be included in the study (“inclusive governance”).

The EDENext coordination, Steering Committee (SC), Advisory Group (AG) and consortium partners will be consulted throughout this process.

Adequate risk management, and in its wake, risk communication, which is comprehensible to members of the public, and, in turn, creates trust in risk management, needs to reconstruct and efficiently implement ideas of what is perceived as risk within a given society. An important pillar of WP 5 is therefore attributed to develop an adequate PH risk perception and communication strategy on emerging VBDs. To get the messages of PH across the public and its stakeholders and, for example, to increase the compliance of the concerned public (e.g. farmers) with recommendations and actions taken in case of actual outbreaks of these diseases, we consider it not enough to rely just upon classical public relation measures. Instead, risk communication of the EDENext approach will be based on solid social scientific knowledge on the risk perception of selected European countries that were identified by the team as the most relevant.

Two diseases of PH importance in Europe will be studied exemplarily in this WP: nephropathia epidemic (NE), a rodent-borne disease caused by the Puumala Hantavirus mainly occurring in Northern Europe (Fennoscandia, Belgium, France, Luxembourg, Germany), and Crimean-Congo haemorrhagic fever, an emerging, tick-borne disease in Turkey and south-eastern Europe caused by a Bunyaviridae. The latter is both an occupational disease (agricultural workers, slaughterhouse employees, butchers, veterinarians…), as well as a nosocomial disease. Details on these diseases can be found in the RAINBO and TBD vector groups. Close collaboration with the PH integrative group (workpackage) will be sought with the partners engaged in these vector groups.

The importance of sound science knowledge and science-based risk assessment is essential for risk communication for the public as well as for a professional audience. Risk communication is seen as the mediator between the actual risk (as defined by risk assessment) and the perceived risk (as identified within risk perception study). We consider, hence, the information and communication with professionals working in the field of public health (medical doctors) and animal health (veterinarians) as well as risk assessors working in the field of emerging diseases from public sector research domain and academia as a second important pillar of risk communication in this area and have attributed individual sub-WP to the professionals and risk assessors respectively. In addition, the EDENext AG will also be involved in for advice on specific questions of communication aspects in regard to PH.

To sum up: a PH approach on EDENext should deal with the identification of risk factors (clinical as well as social, environmental or agent-related, e.g. virulence) and the identification of measures that are beneficial for human and animal health, including preventive measurements. A PH approach has to examine the risk perception of the public, including stakeholders. Finally, a PH approach should analyse the institutional arrangements of and the supply network for PH. According to the PH definition of WHO, public health concerns all three levels of society: micro-, meso- and macro-level. For EDENext these levels mean on the:

- **macro-level**: public (health and veterinary) authorities, ministries in charge, government;
• *meso-level:* industry, stakeholders (such as National Farmers Union) non-governmental medical and veterinary associations and societies;
• *micro-level:* individuals such as consumers or concerned farmers.
## 1.3.2 Project timing

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### 1.3.3 Detailed workpackage description

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<td>M48</td>
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<tr>
<td>D1.4.09</td>
<td>Peer-reviewed publication on the effect of temperature on Leishmania development in sand flies.</td>
<td>WP1.4</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<td>D1.4.10</td>
<td>Optimization of the conjunctival swab method for Leishmania diagnosis.</td>
<td>WP1.4</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
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<tr>
<td>D1.4.11</td>
<td>Publicly available database of CanL prevalence by territory through conjunctival swab method and a peer-reviewed publication.</td>
<td>WP1.4</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>D1.5.01</td>
<td>Understanding Culicoides associated parameters in risk assessment of orbivirus establishment and transmission: preliminary report.</td>
<td>WP1.5</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
</tr>
<tr>
<td>D1.5.02</td>
<td>Understanding Culicoides associated parameters in risk assessment of orbivirus establishment and transmission: mid-term report.</td>
<td>WP1.5</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<td>D1.5.03</td>
<td>Understanding Culicoides associated parameters in risk assessment of orbivirus establishment and transmission: final report.</td>
<td>WP1.5</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>D1.2.1</td>
<td>Set-up of 3D climatic sensors; validation of approach</td>
<td>WP2.1</td>
<td>R</td>
<td>PP</td>
<td>12</td>
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<tr>
<td>D1.2.2</td>
<td>Microclimatic data collected (Year 2)</td>
<td>WP2.1</td>
<td>R</td>
<td>PP</td>
<td>24</td>
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<tr>
<td>D1.2.3</td>
<td>Development and validation of small to medium scale dynamic transmission and site models using 3D climatic data and other ecological data collected in WP1 (Year 3)</td>
<td>WP2.1</td>
<td>R</td>
<td>PP</td>
<td>36</td>
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<tr>
<td>D1.2.4</td>
<td>At least one scientific articles submitted for each the above 3 deliverables</td>
<td>WP2.1</td>
<td>R</td>
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<tr>
<td>D2.2.1</td>
<td>Evaluation of the first year, internal document in 1st annual report.</td>
<td>WP2.2</td>
<td>R</td>
<td>PU</td>
<td>12</td>
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<tr>
<td>D2.2.2</td>
<td>Peer-reviewed publications and progress evaluation in each annual report</td>
<td>WP2.2</td>
<td>R</td>
<td>PU</td>
<td>24-48</td>
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<td>D2.2.3</td>
<td>Final evaluation of the approach and feasibility. Final project report</td>
<td>WP2.2</td>
<td>R</td>
<td>PU</td>
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<td></td>
<td>Ae. albopictus &quot;emerging-traps&quot; prototypes designed and assembled</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>12</td>
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<tr>
<td>Deliverable number</td>
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<td>Work package number</td>
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<td></td>
<td>Efficacy of fogging and/or UV fogging on Ae. albopictus and Culex pipiens adult densities populations assessed.</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>24</td>
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<td></td>
<td>Ae. albopictus &quot;emerging-traps&quot; performance assessed</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>24</td>
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<td></td>
<td>Ae. albopictus mean Distance Travelled in urban areas assessed</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>36</td>
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<tr>
<td></td>
<td>Age-grading method for Ae. albopictus standardised</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>36</td>
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<td></td>
<td>Age-grading method for Ae. japonicus proved as possible</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
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<td></td>
<td>Most important targets for Ae. albopictus larval control in urban areas identified</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
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<td></td>
<td>Large-scale efficacy of MGR-T on Ae. albopictus densities assessed</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Large-scale efficacy of fogging and/or UV fogging on mean age of Ae. albopictus populations assessed</td>
<td>WP2.3</td>
<td>R</td>
<td>PU</td>
<td>48</td>
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<td>D2.4.01</td>
<td>Report on the establishment of laboratory standard methodologies to monitor emergence of insecticide resistance of wild caught sand flies.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
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<td>D2.4.02</td>
<td>Peer-reviewed publication on the efficacy data of ITNs against cutaneous leishmaniasis transmission.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<td>D2.4.03</td>
<td>Publicly available database and review publication on insecticide and repellent activity against sand flies, including possible resistance, a peer-reviewed publication on novel products assayed.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M48</td>
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<tr>
<td>D2.4.04</td>
<td>Peer-reviewed publication on salivary antigens of <em>P. perniciosus</em> and dynamics of anti-saliva antibodies in experimentally bitten dogs.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M24</td>
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<tr>
<td>D2.4.05</td>
<td>Peer-reviewed publication on salivary recombinant antigen(s) from <em>P. perniciosus</em> for serology testing.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M48</td>
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<tr>
<td>D2.4.06</td>
<td>Publicly available database of canine prevalence by territory of antibodies to salivary recombinant antigen(s) from <em>P. perniciosus</em></td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M48</td>
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<tr>
<td>D2.4.07</td>
<td>Publicly available database of xenodiagnosis results in groups of dogs treated with different drug regiments, a set of peer-reviewed publications presenting the obtained results.</td>
<td>WP2.4</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<tr>
<td>D2.5.01</td>
<td>Reporting potential strategies for vector control and final scenarios for modelling vector control.</td>
<td>WP2.5</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D2.5.02</td>
<td>Reporting results from first field evaluation of vector control and final scenarios for modelling R0.</td>
<td>WP2.5</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<td>D2.5.03</td>
<td>Reporting final field evaluation of vector control. First models results of vector control and of vaccination.</td>
<td>WP2.5</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<tr>
<td>D2.5.04</td>
<td>Spatio-temporal specific overall recommendations for prevention and control and confidence of</td>
<td>WP2.5</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>Deliverable number</td>
<td>Deliverable name</td>
<td>Work package number</td>
<td>Nature</td>
<td>Dissemination level</td>
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<td>D2.5.05</td>
<td>Assessment of the effect of the use of insecticides and repellents on non-targeted arthropods and other species of special relevance. Final recommendations on insecticide and repellents use for vector control.</td>
<td>WP2.5</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D3.01</td>
<td>Review of spread-modelling literature</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
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<tr>
<td>D3.02</td>
<td>Report on first EDENext modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
</tr>
<tr>
<td>D3.03</td>
<td>Report on R0-integration at country-scale level</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
</tr>
<tr>
<td>D3.04</td>
<td>Report on first Public health-modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
</tr>
<tr>
<td>D3.05</td>
<td>Review of introduction pathways and assessment methods</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M18</td>
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<tr>
<td>D3.06</td>
<td>Review of landscape permeability</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M18</td>
</tr>
<tr>
<td>D3.07</td>
<td>Report on public-health alert maps</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M24</td>
</tr>
<tr>
<td>D3.08</td>
<td>Report on second EDENext modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M24</td>
</tr>
<tr>
<td>D3.09</td>
<td>Report on second Public health-modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M30</td>
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<tr>
<td>D3.10</td>
<td>Report on spread model simulations</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<tr>
<td>D3.11</td>
<td>Report on landscape indicators and spread</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<tr>
<td>D3.12</td>
<td>Report on integrated R0-mapping in changing environments</td>
<td>WP3</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<tr>
<td>D3.13</td>
<td>Report on final Public health-modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PU</td>
<td>M40</td>
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<td>D3.14</td>
<td>Report on final EDENext modelling workshop</td>
<td>WP3</td>
<td>R</td>
<td>PU</td>
<td>M40</td>
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<tr>
<td>D3.15</td>
<td>Two extended summaries of PhD theses</td>
<td>WP3</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>D4.1.01</td>
<td>First technical report on DMT infrastructure and content.</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D4.1.02</td>
<td>DVD with Spatial geo-Explorer and SPD to be distributed at AGM.</td>
<td>WP4.1</td>
<td>R</td>
<td>PP</td>
<td>M12</td>
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<tr>
<td>D4.1.03</td>
<td>First technical report on training activities and developed training materials.</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D4.1.04</td>
<td>Second technical report on DMT infrastructure and content.</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<tr>
<td>D4.1.05</td>
<td>Updated DVD with Spatial geo-Explorer and SPD to be distributed at AGM.</td>
<td>WP4.1</td>
<td>R</td>
<td>PP</td>
<td>M24</td>
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<tr>
<td>D4.1.06</td>
<td>Second technical report on training activities and developed training materials.</td>
<td>WP4.1</td>
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<td>D4.1.07</td>
<td>Third technical report on DMT infrastructure and content.</td>
<td>WP4.1</td>
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<td>PU</td>
<td>M36</td>
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<tr>
<td>D4.1.08</td>
<td>Updated DVD with Spatial geo-Explorer and SPD to be distributed at AGM.</td>
<td>WP4.1</td>
<td>R</td>
<td>PP</td>
<td>M36</td>
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<tr>
<td>D4.1.09</td>
<td>Third technical report on training activities and developed training materials.</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<td>D4.1.10</td>
<td>Last technical report on DMT infrastructure and</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>Deliverable number</td>
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<td>Work package number</td>
<td>Nature</td>
<td>Dissemination level</td>
<td>Delivery date</td>
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<td>D4.1.11</td>
<td>Final DVD with Spatial geo-Explorer and SPD to be distributed at AGM.</td>
<td>WP4.1</td>
<td>R</td>
<td>PP</td>
<td>M48</td>
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<tr>
<td>D4.1.12</td>
<td>Last technical report on training activities and developed training materials.</td>
<td>WP4.1</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D4.2.01</td>
<td>Technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D4.2.02</td>
<td>Technical report on the results of the &quot;slope factor&quot; study.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D4.2.03</td>
<td>Updated technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<tr>
<td>D4.2.04</td>
<td>Technical report on distribution and biodiversity models of selected first priority hosts.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<tr>
<td>D4.2.05</td>
<td>Technical report on the results of the &quot;landscape factor&quot; study.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<tr>
<td>D4.2.06</td>
<td>Updated technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<tr>
<td>D4.2.07</td>
<td>Technical report on distribution and biodiversity models of selected second priority hosts.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<td>D4.2.08</td>
<td>Technical report on the improved wind-spread model.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<tr>
<td>D4.2.09</td>
<td>Relevant host distribution/ biodiversity papers.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D4.2.10</td>
<td>Slope factor paper.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D4.2.11</td>
<td>Landscape factor paper.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D4.2.12</td>
<td>Improved BTV-spread model paper.</td>
<td>WP4.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<td>D5.1.1</td>
<td>PH white paper on VBD</td>
<td>WP5.1</td>
<td>R</td>
<td>PU</td>
<td>M18</td>
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<tr>
<td>D5.2.1</td>
<td>Relevant literature on risk perception and risk communication examined. Report on EDENext website</td>
<td>WP5.2</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D5.2.2</td>
<td>Guidelines for conducting the interviews with the stakeholders are developed</td>
<td>WP5.2</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>D5.2.3</td>
<td>Comparative report of the risk perception of stakeholders in five countries, based on the analysis of the in-depth interviews, completed</td>
<td>WP5.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>D5.2.4</td>
<td>Comparative report of the public risk perception in five European countries, based on the focus group analysis, completed.</td>
<td>WP5.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
</tr>
<tr>
<td>D5.2.5</td>
<td>Scientific publication of the results in international journal (scientific as well as social scientific and PH specific)</td>
<td>WP5.2</td>
<td>R</td>
<td>PU</td>
<td>M48</td>
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<tr>
<td>D5.3.1</td>
<td>Report on already existing risk assessments for CCHF and Hantavirus infections ‘meta-analysis’</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M12</td>
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<tr>
<td>Deliverable number</td>
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<td>D5.3.2</td>
<td>Harmonized CCHF and Hanta virus diagnostic protocols the diagnostic laboratories (incl. involved ENIVD laboratories). Report to Steering committee and publication on EDENext website</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M24</td>
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<tr>
<td>D5.3.3</td>
<td>Collection of the data for the present state of the art for the diagnosis of Hanta and CCHF infections completed</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M30</td>
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<tr>
<td>D5.3.4</td>
<td>Report on questionnaire study on the diagnostic capacities and quality for Hanta and CCHF in all European countries including Turkey completed and publication on EDENext website.</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M36</td>
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<tr>
<td>D5.3.5</td>
<td>Report on questionnaire study on the existing knowledge of local physicians for the CCHF and Hantavirus infections in two endemic areas completed and publication on EDENext website.</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M42</td>
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<tr>
<td>D5.3.6</td>
<td>Leaflets and brochures implementing risk perception and risk communication knowledge (WP 5.2) for the public as well as for professionals have been worked out.</td>
<td>WP5.3</td>
<td>R</td>
<td>PU</td>
<td>M42</td>
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<tr>
<td>D6.01</td>
<td>Management Structure and Plan</td>
<td>WP6</td>
<td>R</td>
<td>PU</td>
<td>M1</td>
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<tr>
<td>D6.02</td>
<td>EDEN website, leaflet and poster</td>
<td>WP6</td>
<td>R</td>
<td>PU</td>
<td>M2-24-48</td>
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<td>D6.03</td>
<td>Kick-off meeting</td>
<td>WP6</td>
<td>R</td>
<td>PU</td>
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1.3.3.3 Workpackage interdependencies

The relationship between workpackages in EDENext as depicted in Figure 1 below is very straightforward and reflects the general strategy adopted by EDENext: providing a Pan-European Platform to coordinate and integrate research activities on the biology of VBDs as described in the objectives. Whilst EDENext may be a complex project, its structure has been kept as simple as possible.

To achieve this the project is subdivided in FIVE VECTOR GROUPS, respectively on Tick Vectors (TBD), Rodent Vectors (RBD), Mosquito Vectors (MBD), Phlebotomine Vectors (PhBD) and Culicoides Vectors (CBD), as well as THREE INTEGRATION GROUPS, respectively on Modelling (MOD), Data Management (DMT) and Public Health (PH). Each group is coordinated by a Group Leader and its Deputy and integration is achieved both within and between groups under the umbrella of the General Project Coordination.

![Figure 1 – EDENext Work Package Structure](image)

Based on the call text each Vector Group has two Work Packages: WP1 is devoted to Research on “Emergence and Spread” and WP2 on “Intervention and Control”. Thus each of both WPs has been subdivided in five parts (TBD, RBD, MBD, PhBD, CBD). Research topics have been selected both based on currently perceived priorities in the EU context and on a detailed knowledge of the state of the art. Given the specificities and differences between each Vector Group, each Groups Strategy and Workplan has been adapted accordingly.

It is important to note that for TBD, WP2.1 has been further subdivided in two parts given significant work breakdown differences: WP2.1.1 deals with TB protozoan and bacteria, WP2.1.2 deals with CCHF.

Each of the three Integration Groups operates from one Work Package (WP3-5). To ease management and external review, some of these have been further sub-divided:
• WP3-MOD is not further subdivided and harbors all modelling activities including both original and supportive research activities.

• WP4-DMT has been subdivided in two WPs:
  o WP4.1 is devoted to the implementation of a Data Management Infrastructure and Service for all project partners and spatial epidemiologists outside EDENext.
  o WP4.2 is devoted to DMT research activities within their area of expertise and the objectives of EDENext. It includes host distribution modeling and wind spread modeling in close collaboration and complementary to the research activities of MOD and in support of research conducted by Vector Groups.

• WP5-PH has been divided in three parts:
  o Defining PH in the framework of VBDs,
  o PH Risk perception in framework VBDs,
  o PH Risk control in framework VBD.
1.3.3.4 Workpackage description

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Objectives

1. To study the spatial distribution, prevalence and phylogenetics of Babesia EU 1, B. microti, Rickettsia spp., Bartonella spp. and A. phagocytophilum in eastern and western Europe in questing and engorged ticks and reservoir vertebrate hosts (in particular, small mammals, and domestic and wild ruminants);
2. To characterize Ixodes ricinus vector competence (marker identification) and capacity for these pathogens;
3. To further estimate vector competence of these pathogens and their different strains by isolating them from reservoir hosts and culturing them in vitro, and using these isolates to perform experimental infections of rodents;
4. To study the tick-cell responses to these pathogens and their role in determining the outcome of the infection
5. To analyse pathogen transmission potential in relation to medium / long-range tick dispersal by vertebrate hosts using population genetics of ticks and mathematical modelling;
6. To develop dynamic transmission and micro/medium scale site models.

Description of work and role of participants

Background

Anaplasma phagocytophilum, Rickettsia spp., Bartonella spp., Babesia microti and Babesia EU 1 are zoonotic pathogens transmitted in Europe mainly by the widespread tick Ixodes ricinus. However, little information is available about the occurrence, genetic variability and the possible future spread of these pathogens in the EU, and the range of possible reservoir hosts has yet to be established. In addition, the relative role of hosts in affecting I. ricinus vector competence and capacity for these pathogens also need to be established. This information is indispensable for modelling potential future pathogen and disease spread.

In WP1 we intend to examine in detail the ecology of the above pathogens on various scales by removing I. ricinus ticks from potential small-mammal hosts and by collecting questing ticks from the same areas, in order to analyse these vectors using standardized techniques for the presence and prevalence of pathogens that they carry. Ticks and serological samples will also be collected from other potential reservoir hosts such as wild and domesticated ruminant species, and humans (hospital patients). Established protocols will be used to study the genetic variability of the four pathogens to identify new strains. In the laboratory, we will test host transmission capacity for various pathogen strains using in vitro cultivation and experimental transmission in laboratory mice.

As well as pathogen ecology, aspects of vector ecology also need to be addressed, as underlined in previous studies. For example, little is known about passive medium- and long-range dispersal of I. ricinus by its wide range of competent and reservoir host species, locally and between altitudes and different geographical regions. Because of their small body size and large population sizes, traditional capture-mark-recapture methods are not appropriate; instead, a population genetics approach appears to be the most suitable method to estimate tick dispersal. Therefore, in this WP, a significant number of ticks from numerous host and questing populations across Europe will be collected and genetically analysed for tick genetic variability. The host species used for the previous blood meal will also be identified for questing ticks and this information will be used to aid the interpretation of tick genetic structure. The comparison of vector and pathogen genetic variability will help to understand the role of both host and tick dispersal in disease spread.

Finally, all the above information gained in WP1 will be used in WP2 to develop mathematical models in collaboration with the EDENext Modelling Subproject, to quantify the basic reproduction number for each of the pathogens under study and to predict the possibility of spread into new area/habitat in relation to changes in climatic conditions, habitat use and

1 For practical reasons WP1.1 on emergence and spread of TBD has been subdivided in two WPs, WP1.1.1 deals with bacterial and protozoal TB pathogens, WP1.1.2 specifically with CCHF.
host assemblage (see below).

**Approach**

The work conducted in this work package will include four major parts which are detailed in the work breakdown part below: (1) Tick collection and host sampling; (2) Pathogen identification, phylogenetics and pathogenicity; (3) Vector competence studies, and (4) Tick ecology and dispersal studies.

**Work breakdown**

1 – Tick collection and host sampling

1.1 – Protocol harmonization of: sampling site selection within partner countries; tick sampling from questing and host animals; host sampling; serological and molecular pathogen detection methods

In order to generate verifiable and comparable data across all partner institutions and between groups, especially the ROBO and Modelling groups, a consensus meeting will be organized prior to the initiation of field and laboratory work. At this meeting, all protocols for sampling procedures and parasitological, serological and molecular techniques to be used will be presented, discussed and standardized accordingly. In order to check and compare the laboratory data, an ISO 9001:2008 certified and (planned by 2010) ISO 17025 accredited reference laboratory (LMU) will be defined and designated with a mandate to perform the reference laboratory analyses and to organize ring tests for the various test methods to be used. This procedure will allow a better characterization of the various tick-host-pathogen associations, and an efficient use of funds.

1.2 – Sampling of questing ticks and engorged ticks from selected host populations

A geographically and statistically relevant tick collection (questing ticks) will be performed for 2 consecutive tick reproductive seasons in order to determine their presence and abundance. Collection of engorged ticks on the principal host species (mainly small mammals, wild ungulates, humans) will be carried out in the same areas as above (SAS, IVB, FEM, INRA, Szie, LMU, RCB).

1.3 – Sampling of blood and tissue (rodents); blood sampling (domestic and wild ungulates)

A geographically and statistically relevant host blood and tissue collection will be performed for 2 consecutive tick reproductive seasons (IVB, SAS, FEM).

2 – Pathogen identification, phylogenetics and pathogenicity

2.1 – Molecular identification of pathogens from ticks

The presence and prevalence of *A. phagocytophilum*, *Rickettsia spp.*, *Bartonella spp.*, *Babesia EU 1* and *B. microti* will be estimated from ticks using molecular methods and mapped (SAS, IVB, FEM, INRA, Szie, LMU, RCB).

2.2 – Serological identification of pathogens from hosts

The presence and abundance of pathogens from hosts will be estimated from host blood and tissue samples using serological/tissue analyses (host serum: ELISA, IHA, IFAT, etc./tissue: PCR) and mapped (SAS, IVB, FEM, Szie).

2.3 – Analysis genetic variability of pathogens and identification of new strains and geographic distribution

Genetic sequences of appropriate markers for each pathogen genus (already available) will be produced for a subset of pathogens detected in Task 1.1.1.2.1 from the entire geographical area and tick populations covered by the WP. New strains will be identified. Phylogenetic analysis will be carried out using the most up-to-date methods available (INRA, FEM).

2.4 – Studies to investigate potential genotype-associated pathogenicity of *A. phagocytophilum* and of *Babesia spp.*

Several genotypes of these pathogens have already been reported; however, the association of these genotypes with some degree of pathogenicity or even infectivity for potential hosts is unknown. Therefore, a subset of pathogens genotyped in Task 1.1.1.2.3 will be isolated and pathogenicity studies with isolates will be performed using tick-cell cultures and experimental infections (SAS, LMU).

3 – Vector competence

3.1 – Transmission potential of pathogens to ticks from reservoir hosts (*A. phagocytophilum* and *Rickettsia spp.*)

*A. phagocytophilum* and *Rickettsia spp.* will be isolated from engorged ticks collected from potential reservoir hosts for in vitro cultures and experimental tick infection. Subsequently, experimental transmission studies using selected tick species will be carried out in a laboratory mouse model (SAS, LMU, RCB, IVB).

3.2 – Identification of markers characterizing vector competence

This work will be done for Babesia spp. and *A. phagocytophilum* through feeding ticks under different experimental conditions, followed by RNA extraction, cDNA synthesis and subtractive hybridization, then sequencing and identification of differentially expressed genes, analysis of correlation of differentially expressed genes with pathogen
transmission and RNAi knock down of differentially expressed genes to assess role in pathogen transmission. This work also includes determining the pathogen dose on the viability of the tick and the assessment of differentially expressed genes to be used as a marker for the determination of vector capacity (RCB).

3.3 – Tick-cell and cell cultures for various pathogens and their use for studying vector competence (A. phagocytophilum, Bartonella spp., Babesia EU 1 and B. microti)

A. phagocytophilum, Bartonella spp., Babesia EU 1 and B. microti will be isolated and maintained, then cultivated in cell and/or tick-cell cultures and used for experimental transmission studies with different ixodid tick species (using a laboratory mouse model) in order to assess their vector competence by quantitative RT-PCR (SAS, IVB, LMU). This task will also include tick feeding and pathogen transmission under different experimental conditions.

3.4 – Characterization of the molecular mechanisms of tick competence

For Bartonella, the genes / molecules involved in pathogen transmission and molecules of tick saliva influencing host receptivity (immunomodulation) will be identified. A comparative animal / human approach will be adopted to further characterize/understand the zoonotic potential of some pathogens (e.g. adhesion and infective potential of red blood cells of various species including humans to predict host receptivity) and the diversity of effects of saliva on target cells (particularly dendritic cells) of various host species including humans. The nucleotide diversity of these molecules linked to transmission could also be directly used in tick population genetics (Task 1.1.1.4.5) using genes under selection pressure to complement to neutral microsatellite marker studies. The identification of active molecules could also lead to the development of treatments or preventive methods (transmission blocking vaccines) (INRA).

4 – Tick ecology and dispersal

4.1 – Analysis of genetic variability of ticks from main host and questing populations at small and large scales using a population genetics approach

A large number of tick and host population samples will be collected at various altitudes on small (based at FEM) and large (based at INRA) scales and genetically analysed with appropriate markers. All questing ticks will be analysed to identify the host of their previous blood meal using a recent reverse line blotting method (INRA, FEM). We will also attempt to identify the previous blood meal of unengorged attached ticks collected from humans. For statistical analysis, we will use the most up-to-date methods available to us at the time (FEM, INRA).

Tasks

TASKS YEAR 1

- T 1.1.1.1: Organization of First Meeting: Protocol harmonization of: sampling site selection within partner countries; tick sampling from questing and host animals; serological and molecular pathogen detection methods (LMU with all partners)
- T 1.1.1.2: Describe in detail all collection sites (coordinates, habitat type, microclimatic condition, host community etc.) (all partners)
- T 1.1.1.3: Begin sampling of questing and engorged ticks from selected host populations, sampling of blood and tissue (rodents); blood sampling (wild and domestic ungulates) (all partners)
- T 1.1.1.4: Develop and standardize a common DNA extraction protocol for the ticks sampled to process numerous samples simultaneously and maximize the amount and quality of DNA extracted since the same sample will be processed by different partners (genotyping of ticks for population genetics studies, identification of the host used for the previous bloodmeal and molecular characterization of the genetic variability of the pathogens found within ticks) (INRA, FEM)
- T 1.1.1.5: Begin molecular and serological detection of pathogens from ticks and hosts (FEM, LMU, SAS, SZIE, KAU, IP, IDVET)
- T 1.1.1.6: Begin molecular characterisation of the genetic variability of the pathogens found within ticks; identification of new strains; molecular identification of species used for last blood meal in questing ticks (INRA, FEM)
- T 1.1.1.7: Begin adjustment and validation of the in vitro model allowing the study of early dendritic cells mobilization and activation during tick bite (INRA)
- T 1.1.1.8: Begin identification of markers characterising vector competence (RCB)
- T 1.1.1.9: Begin in vitro isolation and propagation of pathogens (LMU)

TASKS SUBSEQUENT YEARS

- T 1.1.1.10: Continue sampling of questing and engorged ticks from selected host populations, sampling of blood and tissue (rodents); blood sampling (wild and domestic ungulates) (all partners)
- T 1.1.1.11: Continue molecular and serological detection of pathogens from ticks and hosts (FEM, LMU, SAS, SZIE, KAU, IP, IDVET)
- T 1.1.1.12: Continue molecular characterisation of the genetic variability of the pathogens found within ticks; identification of new strains; phylogenetic analysis of the isolated pathogen strains; continue molecular identification
Contingency plan

This is a fairly complex WP including a list of tasks that are expected to render a large dataset on the ecology of four tick-borne pathogens. It will be essential that sampling protocols are harmonized, and this will be done at an initial meeting, and will include collaboration with the ROBO group. Many of these partners have worked together in previous projects and are used to this kind of collaboration. Project databases for sampling sites and samples collected will be kept strictly up to date to allow protocols to be re-evaluated when necessary. Other tasks are well-within the expertise of the partner laboratories, and we feel that the usual sorts of methodological problems (such optimizing molecular or serological techniques, or setting up experiments using rodent models) will be easily overcome. All tasks are shared between partners, or will done in collaboration with other groups within the proposal, and such sharing of expertise will further ensure the successful outcome of the TBD subproject.

Milestones

- ML 1.1.1: First meeting to define field and laboratory protocols. Means of verification: a document agreed and signed in by all partners.
- ML 1.1.2: Definition of collection sites. Means of verification: collection site database (Q1)
- ML 1.1.3: All molecular, serological and experimental protocols standardized and optimized in participating laboratories: adoption of contingency methods if necessary. Means of verification: reports to coordinator (Q12)
- ML 1.1.5: End of second year of tick and host sampling: evaluation of sampling sites and decision to extend sampling into third year to fill gaps. Means of verification: sample database.
- ML 1.1.6: Genotyping of I. ricinus populations completed; population genetics analysis; comparison with blood meal analysis; comparison of micro- and macro-geographic studies. Means of verification: results in tick database; genetic analysis completed.
- ML 1.1.7: Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers.

Deliverables

D 1.1.1.1 Tick and host databases (M12)
D 1.1.1.2 Pathogen strain sequence database (M24)
D 1.1.1.3 Publication of first results (M36)
D 1.1.1.4 Publication of the final results (M48)
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**Objectives**

7. Bionomics of the main hard-tick species (Ixodidae) possibly involved in CCHFV transmission
8. qRT-PCR survey in tick populations within known CCHFV-infected area (human cases or infection in wild / domestic animal populations), to list candidate CCHFV vector species.
9. Large-scale cross-sectional sero-epidemiological survey in humans, as well as domestic and wild ruminant sera for CCHFV antibodies, as indicator for the presence of a local virus circulation. The human survey will target segments of populations exposed to a high risk of CCHF, such as livestock farmers and herd keepers, slaughterhouse employees, butchers, veterinarians etc. Collection of human sera will be performed in respect of local ethic committees. A specific consent form explaining the purpose, procedures, benefits, risks, discomforts, and precautions will be provided to candidates for reading and signature prior agreement to participate in research activity. All information gathered from the study will remain confidential by hiding participants’ identities from sampling to possible publication. Participants will not be paid to participate in this research project.
10. Modelling CCHFV transmission risk by ticks, using statistical and mathematical approaches.

**Description of work and role of participants**

**Background**

A clear picture for the risk of introduction and endemic spread of CCHFV in South-Eastern Europe, including the Balkans is currently not available. The discovery of CCHF cases in the respective countries is almost exclusively based on passive surveillance. Therefore, it is of importance to carry out a large-scale epidemiological study in the countries at CCHF risk on the South Eastern Europe, with an assessment of infection spread in humans, domestic ruminants and selected wild hosts. Further studies are also needed to understand the factors involved in the ecology of vector species.

**Approach**

The occurrence and geographical distribution (mapping) of Hyalomma marginatum and other CCHF vector competent ticks in eastern and south-eastern Europe will be recorded and targeted tick surveillance activities will be conducted. A seroprevalence study for CCHFV antibodies in humans and animals in eastern and south-eastern Europe will be conducted. A CCHFV diagnostic test will be developed and validated, including: the production of CCHFV diagnostic test kits, Sample collection, Antibody testing, Analysis of results. Finally a spatial transmission model will be developed.

**Work breakdown**

1. Occurrence and geographical distribution (mapping) of Hyalomma marginatum and other CCHF competent ticks in eastern and south-eastern Europe

During the first months of the project efforts will be made on the decision of standard methodologies and study site selection. Tick surveys will be conducted with biweekly or monthly intervals for period of 2 years on sites selected within each involved partners country. Tick collection will be made from domestic animals (cattle preferably) and if applicable (by hunting) also from wild animals and ground dwelling birds. Questing ticks also will be collected by applying appropriate methodologies (e.g. flagging/dragging, live bait, CO2). Apart of the regular study sites, wide area occasional samplings will be made in order to obtain maximum necessary data for habitat modelling.

Collected ticks will be transferred to laboratories (alive), identified and stored according to last published keys and stored in liquid nitrogen for further testing. Attempts to obtain eggs / larvae from engorged live ticks will be made and resulting material will be stored for further use.

All results will be compiled in a database which will be used for preparing tick habitat suitability maps and further

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<sup>2</sup> For practical reasons WP1.1 on emergence and spread of TBD has been subdivided in two WPs, WP1.1.1 deals with bacterial and protozoal TB pathogens, WP1.1.2 specifically with CCHF.
modelling.

2 – Targeted tick surveillance

Based on the results obtained in subtask 3 a targeted surveillance for relevant CCHF vector tick species will be carried out in two local areas where a high CCHFV-seroprevalence is found in humans and/or animals. The species distribution and abundance of questing ticks as well as from engorged ticks from animals will be determined. Ticks together with selected material from subtask 1 will be screened by antigen ELISA (VectorBest) and positive samples will be tested by PCR for the presence of CCHFV strains and, if applicable, virus isolation will be attempted. Particular attention will be paid to individual screen of questing ticks. Selected positive samples from different geographical areas of south-eastern Europe will be sequenced.

3 – Seroprevalence study for CCHF antibodies in humans and animals in eastern and south-eastern Europe

3.1 – CCHF test development/validation study (IP, FLI, IDVET)

There are several ELISA tests for CCHF IgG antibodies currently available. Two commercial tests by BDSL (www.bdsl2000.com) as well as by a Russian company called VectorBest (IgG, IgM, antigen ELISA) which are extensively used in Russia are available, as well as two custom made ELISAs by the OIE reference laboratory for CCHF (Bouloy, Pasteur Institute) and by the partnering company ID-Vet-Pourquier. Moreover, a competitive ELISA is under development (IDVET), and an immuno-fluorescence assay (IFA) is commercially available from Euroimmun (Lübeck, Germany). In a pre-validation phase involving a comparison to the commercial tests, the custom-made tests will undergo re-optimisation phase of the reagents.

3.2 – Production of CCHF test kits (IDVET)

IDVET will achieve a ready-to-use format kit under GLP conditions from antigen / antibodies obtained from the partners. This will include: Optimisation of assays; Immunochromesty: purification of antigens and antibodies, production of conjugates etc.; Stabilisation of reagents, optimisation of robustness, Industrialisation of production, quality control, registration etc.; Definition of Quality Control, Production of reproducible batch ELISA kits, Providing kit (80.000 tests) to partners for field assay validation, survey etc”.

3.3 – Sample collection

More than 35,000 serum samples from humans and domestic and wild animals will be collected in Albania, Bosnia, Bulgaria, Croatia, Cyprus, Greece, Hungary, Macedonia, Romania, Serbia, Slovakia and western parts of Turkey. In order to assure a representative distribution, sample sets will reflect districts / provinces (National units of Territories http://de.wikipedia.org/wiki/NUTS = NUTs 2 level) of these countries. In Turkey, only the seven most western provinces will be included because a) they may function as a bridge to the European continent and b) major studies have already been conducted in Central Turkey.

In humans, the CCHF risk (proxy = serological prevalence) will be assessed in highly-exposed population segments: agricultural / forest workers, slaughterhouse employees, butchers, veterinarians, etc. Apart from surveys in domestic animals, wild animals (ruminants and boars) and rodents may be screened, depending on the availability of samples.

The precise goals, design, implementation and analysis of these animal and human surveys will be thoroughly discussed with national and international human and veterinary public-health agencies, and with the support of the EDENext coordination.

3.4 – Antibody testing

Using the selected test(s) sera will be screened for CCHFV antibodies at FLI, Germany and/or at Budapest University or alternatively directly at the state or local medical or veterinary investigation centres (will be agreed upon before testing phase). The performance of all laboratories involved (including local investigation centres) will be verified by blinded ring trials organised by ENIVD and/or OIE / WHO reference laboratories that have to be passed before field samples are tested. All results will be reported to FLI / Budapest University.

3.5 – Analysis of results

Test results will be analysed by local test laboratories/authorities in collaboration with FLI / Budapest University.

4 – Spatial and transmission modelling

Modelling will be done by the Modelling WP in collaboration with FLI (Staubach). Data analysis and modelling for the distribution of ticks and CCHF infection should take into account the following aspects: The distribution of ticks and the estimation of habitat suitability models; The estimation of the spatial distribution of infection, with appropriate statistical methods; Modelling the population dynamics of Hyalomma and CCHF transmission will be developed by the Modelling WP.

Tasks

TASKS YEAR 1

T 1.1.2.1: Complete the mapping of the occurrence and geographical distribution of Hyalomma marginatum and other
CCHF vector competent ticks in eastern and southeastern Europe (FLI, SZIE, KAU, SAS)

- **T 1.1.2.2:** Initiate CCHF test development/validation study and production of CCHF test kits (IP, FLI, IDVET)

**TASKS SUBSEQUENT YEARS**

- **T 1.1.2.3:** Use data from WP1 and other records to develop a population dynamics model applied to Hyalomma spp. (INRA, FLI, SZIE, KAU)
- **T 1.1.2.4:** Validate Hyalomma spp. model (INRA, FLI, SZIE, KAU)
- **T 1.1.2.5:** Use the Hyalomma/CCHFV model to test the effect of control measures (INRA)

**Contingency plan**

Tick bionomics studies have already been carried out in Turkey by KAU partner and colleagues, hence there is ample expertise. Serological tests for CCHF are available in principle (although they have never before been validated as planned above). Regarding the epidemiological surveys in humans and animals, discussions with international agencies (such as ECDC, WHO, OIE and FAO) will be sought. FLI is the OIE collaborating centre for zoonoses in Europe and has numerous official and collegial contacts in particular to for Eastern European countries. Likewise is the Budapest university partner networked with his close and far neighbouring countries. On the other hand IP is an OIE Reference Laboratory for RVFV and CCHFV.

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<td><strong>ML1.2.3:</strong> Mapping of the occurrence and geographical distribution of Hyalomma marginatum and other CCHF vector competent ticks in eastern and southeastern Europe complete. Means of verification: map available (Q36)</td>
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<tr>
<td><strong>ML1.2.4:</strong> End of first year of development of CCHF test kits: re-evaluate approach if necessary. Means of verification: report to coordinator. (Q12)</td>
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<tr>
<td><strong>ML1.2.5:</strong> Development and validation of a population dynamics model applied to Hyalomma spp. Means of verification: model available (Q42)</td>
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<tr>
<td><strong>ML1.2.6:</strong> Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers (possibly from Q18 on depending on results).</td>
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</table>

**Deliverables**

- D 1.1.2.1 Tick and host databases (M12)
- D 1.1.2.2 Publication of first results (M36)
- D 1.1.2.3 Publication of the final results (M48)
Workpackage number | WP1.2 | Starting date or starting event | M0
---|---|---|---
Workpackage title | Emergence and Spread RBD | |
Activity type | RTD | |
Participant number | 29 30 31 32 33 39 | |
Person-months | 14 28 48 46 55 10 | |

Objectives
The main objectives in WP1 in RBD are 1) the better understanding of rainbo diversity in Europe and adjacent regions and 2) particularly to study those still poorly known factors / parameters we need for better modelling of rainbo disease spread and dynamics.

Description of work and role of participants

Background

1. Towards better understanding of “rainbo” viral diversity in Europe

The occurrence of rodent borne viruses, including the most important ones, hantaviruses (hantas), is poorly known in eastern Europe, e.g. Bulgaria and Romania, Ukraine and Belarus, and adjacent areas like Turkey and Caucasus. These regions harbor potential host species for new viruses. A major achievement of our proposal will be to have a detailed picture of rodent and insectivore biodiversity, linked to pathogen biodiversity. This research will be designed and done together with local scientists. The most important role of EDENext rainbo team would be to stimulate, coordinate and advise local scientists, and to reinforce their scientific and technical capacity.

Recently new hantas have been found in insectivores, like shrews and moles. We have very recent new findings on shrew hantaviruses in many species in Europe. Nothing is known so far about the human connection of these new hantaviruses. We have, as a first group, shrew hantaviruses growing in cell cultures which enables the development of human serotests. EDENext rainbo team will coordinate further collection on shrew species in Europe. Development of human serotests for insectivore hantaviruses will be done separately, but in close connection with EDENext.

Cowpox is found in many rodent species, and it is not know yet whether there is strain variation and consequent host selection by various strains, and if the pathogenicity of various strains to human differ. So far, there is no clear indication to this, even though seroprevalences can differ substantially among sympatric rodent species. During EDEN work, cowpox has been found in a number of rodent species all over Europe. Cowpox material to be collected will be serologically screened in WP 1 but the detailed genetic aspects will be done separately, but in close connection with EDENext.

Interactive work with other vector groups:

Rodents play a major role in most of VBD’s and therefore coordinated research actions will be implemented to assess this in the different vector groups (see also WP 2 a joint monitoring work). In addition:

As a joint part of TBD work, RBD group will participate in rodent collecting and screening when necessary, e.g. in
CCHF studies in Turkey and Balkan.
RBD will help MBD sampling of mammals and collecting weather data in N Europe.
RBD will help PhBD in rodent sampling when needed.

2. Modeling distributions

Several host species of rainbo viruses have a distribution only partly covering Europe. Preliminary modeling, with Avia-
Gis (EDENext partner in the Data management WP) of the environmental factors affecting the distribution of host species
has given a promising starting point for a more detailed approach to analyse potential future changes in the distributions
of rainbo host species with changing climate. These models must be further informed also by mechanistic insights in the
transmission dynamics.

3. Varying epidemiologies

In Europe the rodent population dynamics and consequently rodent-borne disease patterns differ between boreal and
temperate environments. Also tick-borne diseases can reflect these rodent fluctuations, but with different time lags than
directly transmitted rainbo diseases. In the North, the rodent host species exhibit 3-4 year population cycles, presumably
due to the delayed density-dependence caused by specialist predators, related to low diversity of mammalian guilds
(Hansson & Henntonen 1988) Hanski et al. 1991), while in temperate Europe, the forest rodent populations are more stable
(with seasonal variations). Occasional mast years (heavy seed crops of oak and beech) lead to abundance of seed-eating
forest rodents which act as reservoir species to rainbo viruses, but which are also competent hosts for several tick-borne
pathogens. The mast years, probably induced by a series of favourable climate conditions over a period of two years,
including higher than normal summer temperatures (Tersago et al. 2008), can be synchronous over large areas in Europe,
and consequently can give rise to human epidemics over large areas, like the record year for hantavirus disease in 2005 in
Belgium, Northern France, Luxembourg and Germany (Heyman & Vaheri 2008). Since rodents are important hosts for
(juvenile) ticks, this can lead to concerted increases both in rainbo and tick-borne diseases (albeit with different time
lags).

A simplified scheme of factors affecting rainbo diseases dynamics in Europe (based primarily on EDEN studies, (topics
needing clearly more research in EDENext in bold)

- Differences in rodent dynamics
- Differences in landscape structure
- Landscape change:

  - Dilution by sympatric species
    - The variation in species diversity geographically
    - Impact of physical environmental conditions on virus survival
    - Differences in the quality rainbo carrier rodents
    - The geographic differences in immunogenetics of rodent hosts

3.1 Diversity of small mammal species and dilution impact

The dilution impact may not occur only among vector-borne diseases (the diversity of competent and non-competent
hosts) but also among directly transmitted diseases like rainbos. The mediating factors could be either 1) the interspecific
competition/territoriality reducing the density of the primary host species (an apparent dilution effect), or 2) the presence
of several species affecting the contact rate and transmission among individuals of the carrier species, thus decreasing the
prevalence (an effective dilution effect). This will be tested by comparing rodent community structure and pathogen
prevalence among sites in Europe (taking into consideration the confounding factors like seasonality etc). Knowing the
regional species diversity could thus help in predicting the risk of rainbo diseases. Simultaneously, small-scale field
experiments will be set up to manipulate the diversity of small rodent species and then follow the spreading of Puumala
hantavirus in such community.

3.2. Impact of physical environmental conditions on virus survival

The survival of a rainbo virus outside the host is a critical parameter for transmission models, and affects strongly the
transmission threshold densities. So far, there is only one published study (Kallio et al. 2006), done in EDEN project,
documenting much longer viability of a hantas in the excreta outside the host than earlier anticipated. The survival of the
virus is also critical for controlling the human risk. We need more data in several respects here:

1) Are there geographic differences in survival within a virus species, as an adaptation to different geographic
environmental conditions? Outdoor enclosure experiments in different climatic conditions with local virus strains are
needed.

2) Accordingly, what is the impact of temperature and moisture? The cell culture experiments suggest that temperature
and moisture are important factors. Outdoor experiments in different season are needed.

3) Are rainbo viruses equal in their survival outside the host, or do they have different adaptations to environmental physical conditions, which could explain different geographic ranges of viruses in rodent host species are spread over a much wider area.

3.3. The geographical and dynamical variation in immunogenetics in relation to rainbo emergence

The extensive work in EDEN on the phylogeographies of the bank vole, based on mt-DNA (cytB), and Puumala hantavirus (PUUV), did not reveal any close concordance, probably due to the very complicated evolutionary history. Instead, there seems to be a relationship between some immunogenetic genes and hanta prevalence. The relevant question therefore is: do immunogenetics, in addition to above mentioned environmental factors, contribute to the differences in hanta geographic occurrence in Europe? Several topics will be addressed:

a) The relationship between geographic variation in relevant immunogenetic loci and hantavirus prevalence,

b) Dynamical immunogenetics 1: immunogenetic variation in relation to density cycles of the host and PUUV occurrence – comparison of the predation driven system in boreal zone and mast driven system in temperate zone.

c) Dynamical immunogenetics 2: host individual level immunogenetic properties and PUUV reassortment patterns in a local population.

d) Immunogenetics and contact zones of host and virus lineages: We have identified three different phylogeographic combinations in the bank vole and PUUV in N Europe; one virus lineage over the contact zone of the hosts lineages, contact zone of PUUV lineages within the same host lineage, and both host and virus lineages meet at the same contact zone. How do the host immunogenetics react at these different combinations, and in relation to PUUV reassortment patterns within a contact zone?

4. Host- robovirus competence

Basically hantaviruses are host species specific. However, spill-over is often found at different levels: seropositivity to a non-specific virus but no RNA positivity or if RNA positivity is found, the virus load is low, and finally almost nothing is known of shedding in the latter case. The debate of virus species problems is irrelevant if these quantitative and ecological aspects are not included into evaluations. We need to know:

1) The patterns of seropositivity, RT-PCR positivity, and the virus shedding, if any, in secondary/accidental host species. Cross-species infections are needed.

2) Geographical variation in Host – virus competence within a single host-virus system.

5. A missing piece in transmission models: shedding

Epidemic outbreaks of robo-disease in humans require a massive presence of virus material in the environment. Simultaneous presence of a large number of infectious rodent individuals is necessary to produce large enough quantities of virus for this to achieve. This is met only in boreal cyclic populations during the peak phase and during peak abundance following mast years in temperate zone.

To predict the human risk, and to model the transmission dynamics, it is absolutely essential to know the shedding patterns of a rainbo virus in a chronically infected host rodent. The first results in lab conditions using PUUV and bank voles suggest that the actual shedding period is rather short, about 2 months, even if the host is chronically infected much longer. However, in the wild in seasonal environments there are many confounding factors. Virus shedding period and possible reactivation may depend on seasonality and breeding - hormonal status of rodents. It is plausible that non-breeding voles infected in autumn shed differently from the breeding old ones. It is important to know the density of actively shedding voles to model the temporal infection risk to humans. The risk is highest during and soon after the high transmission rate, not necessarily at all during the highest seroprevalence if the infections are old.

Therefore, high sero- or even RT-PCR prevalence in rodent populations as such does not tell the whole truth about the human infection risk. We need to know the length and constancy of shedding period in different seasons, if there are seasonal differences depending on the population structure, if maturation and hormonal changes can reactivate the shedding in old animals in spring. For this work, we plan a combination of mathematical modeling, field observations and experimental work. Some of the mathematical modelling will be done together with prof. D. Pontier, Univ.Lyon.

6. Landscape epidemiological approach

Landscape epidemiology analyses how both landscape ecology and evolution of host-pathogen interactions shape disease distribution, dynamics and severity over complex geographic landscapes. We plan to use landscape epidemiological tools to analyse the PUUV spread patterns: 1) From the distribution of neutral genetic variation within populations (microsatellites) we can detect signals of demographic expansion or decline, and evaluate the impact of habitat fragmentation or of the introduction of a pathogen on the host population dynamics. 2) From individual neutral genetic data (microsatellites, software Geneland), we can find geographic / landscape barriers to gene flows between host or
We can thus describe landscape connectivity, and potential pathogen spread, in terms of genetic exchange between individuals. In rainbo research, we evaluate the impact of habitat fragmentation on *M. glareolus* gene flow and its consequences for PUUV transmission between habitats and the impact of *M. glareolus* mitochondrial differentiation (contact zone, see also 1.3.2) on PUUV gene flow. The results of genetics-based analyses will be compared with $R_0$ analyses (see 1.7).

7. Interaction with WP 3: models for the spread of vectors and VBD in a heterogeneous European landscape

Using an approach through metapopulations, spatial networks and percolation, that has been developed recently to explain outbreaks of plague in rodent population, will be extended in close collaboration with the Modelling WP, to obtain insight into the observed differences in persistence threshold of rodent-borne infectious agents in different species and different parts of Europe. Recent studies from temperate Belgium with heterogeneous landscapes and boreal Finland with homogenous taiga landscapes, gave opposite results on the existence of a transmission thresholds: yes in temperate Belgium (Tersago et al. 2009); no in boreal Finland (Kallio et al. 2009). These differences probably are related to the landscape structure and connectivity between populations. $R_0$ modelling will be used together with MOD for these landscape based data sets.

Because capture-recapture studies are not usually possible at larger landscape scale, the approach presented above (1.6.), using genetic methods, can give valuable tools to analyse the spread of hosts and their pathogens. Using these tools for rodents is very feasible.

**Approach**

In RBD, many or all partner teams collaborate in each specific topic, with the role of lead team changing depending on the topic. The important role of RBD coordinator is to promote interactions among the teams within the research plan. This way, the European-wide material collection is maximized and the flow of ideas enhanced, and not a single partner is alone responsible for specific topic.

**Work breakdown:**

**TASKS YEAR 1**

- Task 1.1. Collection of the rainbo materials, and establishing collaboration in E Europe
- Task 1.2. Modelling first generation distribution maps
- Task 1.3.1. Compiling the first dilution analyses in host diversity – pathogen prevalences
- Task 1.3.2. Collecting materials for immunogenetic work
- Task 1.4. Cross experiments and quant. PCR for spill over studies started
- Task 1.5. Serial collection of excreta from individually marked voles in field, and first quant. PCR analyses
- Task 1.6. Collection of material for landscape genetic analyses
- Task 1.7. Data base for $R_0$ analyses from Belgian and Finnish data

**TASKS SUBSEQUENT YEARS**

- Task 1.1.-1.7. Continuation of projects started.

**Contingency plan**

The strategy of RBD, that all or most teams contribute to and interact with each specific research topic, ensures the completion of topics.

**Milestones**

ML 1.2.1: Schedule of collections and sampling protocol decided and available,. 1st annual report.
ML 1.2.2: First generation distribution maps. 1st annual report.
ML 1.2.3: Database constructed of existing data on community diversity and PUUV prevalence. 1st annual report.
ML 1.2.4: Field experiments for virus survival designed and initiated. 2nd annual report.
ML 1.2.5: Immunogenetic field material collection accomplished. 2nd annual report.
ML 1.2.6: Immunogenetic molecular data available. 3rd annual report.
ML 1.2.7: Cross experiments and quant. PCR for spill over studies started. 2nd annual report.
ML 1.2.8: Landscape epidemiological genetic field material collected. 2nd annual report.
ML 1.2.9: Serial collection made of excreta from individually marked voles in field, and first quant. PCR analyses. 2nd annual report.
ML 1.2.10: Field material and data base ready for $R_0$ modelling. 2nd annual report.
ML 1.2.11: All field materials collected and analyses in process. 3rd annual report.
**Deliverables**

<p>| D 1.2.1. | Final work list and protocols at kick off meeting. Internal report, Mo 5 and 1st annual report (M12). |
| D 1.2.2. | at least one 2nd generation maps on the occurrence of rainbo viruses in Europe (M48). |
| D 1.2.3. | At lest one peer-reviewed paper on new hantaviruses (M24-48). |
| D 1.2.4. | A t least one peer-reviewed paper on LCMV complex (M36-48). |
| D 1.2.5. | At least one peer-reviewed paper on the dilution impacts by sympatric species in Europe (M26-48). |
| D 1.2.6. | At least one peer-reviewed paper on impacts of physical environmental conditions on virus survival (M36-48). |
| D 1.2.7. | At least on peer-reviewed paper on immunogenetics of hosts and rainboviruses (M24-48). |
| D 1.2.8. | At least one peer-reviewed paper on host-rainbo virus competence (M13-48). |
| D 1.2.9. | At least one peer-reviewed paper on the temporal shedding patterns of a rainbow host (M24-48). |
| D 1.2.10. | At least one peer-reviewed paper on landscape epidemiology nbased on genetics (M24-48). |
| D 1.2.11. | A peer-reviewed publication on Ro dynamics of PUUV (M36). |
| D 1.2.12. | A spatially explicit model of hantavirus transmission dynamics (M42). |</p>
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**Objectives**
Assess whether winter survival of WNV-infected adult mosquitoes is significant in the epizootic cycle; seek evidence of vertical transmission during the mosquito breeding season; assess whether oral and faecal-oral infection in birds, mammals, amphibians and other fauna is a significant component of the epizootic cycle; intercept migrant passeniers on their last stop before arriving on the European continent to establish seroprevalence and to screen for virus; monitor seasonal profile and host preference of reed-bed mosquitoes; assess degree of synchrony between the advancement of spring broods of mosquitoes and the arrival of migrant passerines; determine whether ectoparasites are infected in experimentally infected chickens; monitor viraemia and viral shedding in experimentally infected frogs and assess whether infections are chronic; sequence selected WNV isolates; study bionomics of *Aedes albopictus* and *Ae japonicus* in Italy, Albania and Switzerland; develop temperature/humidity profiles of “typical” resting sites of *Ae. albopictus*, simulate a selection of these in an environmental cabinet and monitor rate of viral replication of CHIK and DEN in *Ae. albopictus* and *Ae. japonicus*; determine light regime that triggers winter diapause and test insects hatching from diapausing eggs for vertical transmission.

**Description of work and role of participants**

**Approach**
1. Preparyatory phase
   1.1. Standardization of techniques and selection of study sites
   1.2. Equipment and legal matters
   1.3. Selection of field collection sites
2. Winter survival and vertical transmission
   2.1. Winter survival of adult *Culex pipiens*
   2.2. Overwintering refuges of *Culex spp* in reedbeds
   2.3. Vertical transmission in two cohorts of mosquitoes
3. Post viraemia shedding of virus
   3.1. Resident Coots and Corvids
   3.2. Resident and migratory passerines
   3.3. Migrant passerines at point of entry into Europe
   3.4. Birds captured by local ringing teams
   3.5. Surveillance beyond study sites
   3.6. Small mammals
   3.7. Amphibians
4. Mosquito activity
   4.1. Host preference of blood-seeking adults, seasonal profile
5. Interaction of hosts and vectors
   5.1. Synchrony of arrival of migrant birds with new generation of mosquitoes
6. Ectoparasites
   6.1. Nestlings and nesting material
   6.2. Experimental infection of chickens: evidence for infection of ectoparasites
7. Amphibians
   7.1. Experimental infection of frogs: evidence chronic infection and prolonged shedding
8. Serology and virology
   8.1. Serology and detection and sequencing of virus
9. *Aedes albopictus*: field
| 9.1. | Installation of microclimate monitoring stations |
| 9.2. | *Aedes albopictus* bionomics and surveillance |
| 10. | *Aedes albopictus* and *Ae. japonicus*: laboratory studies |
| 10.1. | Establishment of laboratory colonies |
| 10.2. | Baseline infection study |
| 10.3. | Viral replication under selected temperature/humidity profiles |
| 10.4. | Viral replication with mosquitoes reared at different temperatures |
| 10.5. | Vertical transmission |
| 10.6. | Diapause, freeze-tolerance and vertical transmission |
| 10.7. | *Aedes japonicus* |

**Work breakdown**

*Standardisation of techniques and selection of study sites.* At least one participant from each partner institution will attend a meeting at the start of the project to agree on procedures for field sampling, storage, transport and shipping of samples, laboratory protocols—serology, virus isolation, molecular sequencing, sharing of common tasks etc. A common format for sample labelling will be discussed, as well as rules of engagement on communication, data sharing and publications.

*Equipment and legal matters.* Build apparatus for mosquito capture: a modified version of the BG-Sentinel trap will be constructed by all entomology teams according to set specifications. IRB issues, local permits and licences, and other legal requirements.

*Selection of field collection sites.* Reed-beds are the principal habitat selected for the studies. An effort will be made to standardize the sites that are selected. Teams will make their selection according to convenience of local transport and accessibility, but some ecologic criteria and other factors, such as history of known transmission, will also be considered. As far as possible, entomologic and vertebrate sampling sites should be linked in the same area. A brief description of a number of possible sites, including photographs and other visual material (co-ordinates for Google maps etc.) will be shared and managed by the project co-ordinator.

*Winter survival of adult Culex pipiens.* Mosquitoes in winter refuges (cellars, caves, bunkers etc.) will be captured in November, marked with fluorescent powders and released. The sites will be revisited at least twice a month; surviving adults will be counted with the aid of a portable UV lamp. Temperature and humidity will be recorded by data-logger. An attempt will be made to monitor sites with different degrees of protection from outdoor climate.

*Overwintering refuges of Culex spp in reedbeds.* In Hungary and Romania, reeds are harvested in winter, when lakes are frozen. Bundles of reeds will be encased in plastic film, removed to a warm room, and inspected/dissected for mosquitoes. Searches will also be made by back-pack aspirator at the base of the stems while they are being cut.

*Vertical transmission in two cohorts of mosquitoes.* Two cohorts of mosquitoes will be screened: (i) overwintering mosquitoes captured in refuges; (ii) regular collections of males by back-pack aspirator from evening swarms (until the end of the “mosquito season”).

*Post viraemia shedding of virus: Resident Coots and Corvids.* Oral and faecal shedding of WNV in Coots and Corvids. A trio of samples—serum, plus oral and cloacal swabs—will be taken from Coots (*Fulica atra*) and Corvids captured twice monthly in reed-bed areas in Spain (La Doñana National Park) and Romania (Danube Delta National Park) using traps baited with grain. The oral and cloacal samples will be stored in liquid nitrogen for shipment to Vienna. All birds will be ringed before release.

*Post viraemia shedding of virus: Resident and migratory passerines.* Mist-nets will be set up along transects cut into reed-beds to capture resident and migratory birds. A sound lure (recorded call) will be used to maximise capture of *Acrocephalus* spp, and and *Swallows* (*Hirundo rustica*). Samples as for Coots and Corvids. All birds will be ringed.

*Post viraemia shedding of virus: Infection in migrant passerines at point of entry into Europe.* In two successive years, during the Spring migration, the Spanish team will mist-net passerines for four weeks on Isla del Aire, a barren, mosquito-free island that is a stopover for migrant birds on arrival from sub-Saharan Africa and the Maghreb. Samples as for Coots and Corvids.

*Post viraemia shedding of virus: birds captured by local ringing teams.* Liaison with bird ringing teams will provide additional samples.

*Surveillance beyond study sites.* Evidence of circulation of WNV may arise outside study sites; diversion of resources should minimise impact on routine collections.

*WNV infection and post viraemia shedding of virus: Small mammals.* Small mammal traps will be deployed along reed-bed transects and surrounding areas. On capture, a small pad of cotton (make-up remover) will be placed in the cage to sample urine. Faeces will also be sampled. Seropositive animals will be sacrificed for tissue sampling, if this is legal.

*WNV infection and post viraemia shedding of virus: Amphibians.* Frogs will be captured by hand-net using a red cloth as
a lure (large numbers of males can be captured in this way). After euthanizing, in addition to a serum sample, and oral and cloacal swabs, a selection or organs will be retained.

**Host preference of blood-seeking adults.** An array of BG-Sentinel traps will be set up in or near the reedbeds, and baited with pigeons, mice or frogs. Traps will be run every two weeks. Insects will be identified and screened for WNV and other virus. Traps will not be moved between captures. Collections will also provide seasonal profile of species and population fluctuations.

**Synchrony of arrival of migrant birds with new generation of mosquitoes.** Dates of transit of migrants on Isla del Aire will indicate dates of arrival in reed-bed study sites. The developmental stage of larvae collected for the overwintering study (see Winter Survival) will be monitored to determine development time of the first generation. Additional information will be available from the profiles of species collected in the baited traps.

**Nestlings and nesting material.** Where feasible, ticks and other parasites will be collected from nests of colonial birds, e.g. Storks, Cormorants sparrows.

**Experimental infection of chickens: evidence for infection of ectoparasites.** Farmyard chickens and/or city pigeons will be experimentally infected in a P3 animal facility; birds will be sacrificed at set intervals and ectoparasites collected for virus screening. Oral and cloacal swabs, plus tissue samples will be retained. Excreta will be collected and stored at regular intervals, screened for virus, and retained for experiments on virus stability and oral/dermal infectivity to frogs.

**Experimental infection of frogs: evidence chronic infection and prolonged shedding.** Wild frogs are protected species in France. We will use Xenopus toads for experiment. Frogs will be infected by sub-dermal injection and held in individual containers. Samples will be sacrificed at regular intervals and screened for virus in blood, oral cavity, cloaca, intestines and other organs. Experiments will be made to test for faecal-oral infection between infected/non-infected pairs, and infection by contact with bird faeces.

**Serology and detection and sequencing of virus.** TaqMan PCR will be used for all samples. Isolation on Vero cells will be attempted for PCR-positive samples. A selection of viruses will be sequenced.

**Installation of microclimate monitoring stations.** Small digital data-loggers that record temperature and humidity at regular intervals will be placed in “standardise” patches of leafy vegetation in shaded sites that are “typical” habitat preferred as resting sites by Ae. albopictus; criteria for these will be determined by discussion with the volunteers who will man these stations. Sites will be chosen to represent climatic zones in several sites in Italy, at selected altitudes in Albania, and at other sites in other countries in Europe as far north as central Sweden. Data will be recorded every 30 minutes throughout the year, and downloaded (by volunteers) at least every month. The data will summarised to define the range of temperature/humidity profiles existant in the relevant regions. These profiles will be simulated in an environmental cabinet in a P3 insectary.

**Aedes albopictus bionomics.** Sites in Rome, Albania and Switzerland will be selecte for routine studies described in WP2. At least four sites in Albania will be selected to represent altitudinal gradient. B-G sentinel traps and sticky traps will be used for seasonal surveillance

**Establishment of laboratory colonies.** Aedes albopictus and Ae. japonicus are fairly easy to colonize. Laboratory colonies will be established from mosquito eggs collected by ovitraps. Eggs will be disinfected before hatching to reduce risk of pathogens. Mosquitoes used in experiments will be from early generations of these colonies. The origin of colonies will be determined by climate, latitude and altitude criteria.

**Baseline infection study.** A set of experiments will be made with Aedes albopictus reared at 24°C and held at 18°C, 24°C and 30°C. Mosquitoes will be infected orally and subsequent viral titre will be determined by quantitative PCR on samples taken every day, or at longer intervals when dictated by temperature, until titre reaches a plateau. intervals will be determined by climate, latitude and altitude criteria. intervals will be determined by climate, latitude and altitude criteria. intervals will be determined by climate, latitude and altitude criteria.

**Viral replication under selected temperature/humidity profiles.** Conditions in the environmental cabinet will be set to simulate field profiles, including daylength regime, and infected mosquitoes monitored as with the baseline experiments.

**Viral replication with mosquitoes reared at different temperatures.** Conditions in the environmental cabinet will be set to simulate field profiles, including daylength regime, and infected mosquitoes monitored as with the baseline experiments.

**Vertical transmission.** Infected mosquitoes will be allowed to lay eggs, feed a second time, and oviposit again; two large, custom-built glove boxes are available for this. Subsequent experiments will include diapausing eggs.

**Diapause, freeze-tolerance and vertical transmission.** Adults will be held in light regimes equivalent to autumn daylength at progressive latitudes in Europe. Mosquitoes used will be derived from eggs collected in Rome, and at several altitudes in Albania. Eggs will be tested for diapause, and subjected to temperatures below 0°C. They will then be returned to long daylength to determine whether they will hatch. Samples will be treated with mild bleach to determine whether they are embryonated.
Aedes japonicus. A selection of the experiments will be repeated with Ae. albopictus.

Tasks Year 1
[Work is seasonal; this list assumes start date on 1st January]

TASKS YEAR 1

- **Task1.1.1**: Basic organization, functioning and management: (IP, VETMEDUNI, IVB, SZIE, NIRDMI, UNIROMA1, UZH, IPHA, CSIC. DDNI): Preparatory meeting to discuss organization of the entire project, establish all protocols and routines, and agree on terms of engagement.
- **Task1.1.2**: Preparatory: (IP, VETMEDUNI, IVB, SZIE, NIRDMI, UNIROMA1, UZH, IPHA, CSIC. DDNI). Purchase equipment, reagents etc. Construction of traps and other hardware. Certification, IRB approval, and other legal matters. Select reed-bed and other study sites, cut transects, search for overwintering refuges. Deploy microclimate monitoring stations.
- **Task1.1.3**: Seasonal field collections: (IVB, SZIE, NIRDMI, IPHA). Initiate field activities when all relevant preparations have been completed. This will be too late for early season studies, such as vertical transmission.

**TASKS SUBSEQUENT YEARS**

- **Task1.1.4**: Continuation of all routine field operations; decisions to cease certain activities will be made according to results
- **Task1.1.5**: Laboratory studies of temperature on viral replication in Aedes albopictus, and later on Ae japonicus (IP)
- **Task1.1.6**: Laboratory infections of chickens and frogs (AFFSA)
- **Task1.1.7**: Organize stakeholder’s meeting with local Health Authorities and other interested partners

**Contingency plan**

If transmission is detected in participant countries, and if institutions involved in epidemiologic and other investigations are not associated with EDENext, a liaison should be suggested. EDENext must give priority to work funded by the EC, but advice and limited assistance should be given if requested.

If new infestations of Ae. albopictus or Ae. japonicus are detected, and the infestation sites are at significant distance from currently identified sites, samples from such sites should be incorporated in the laboratory studies.

**Milestones**

ML1.3.1: Detection of WNV shedding in seropositive Coots, Crows and migratory passerines without detectable viraemia. Laboratory verification

ML1.3.2: Isolation of virus from male mosquitoes. Laboratory verification

ML1.3.3: Detection of WNV in mammals or frogs. Laboratory confirmation

ML1.3.4: Analysis of data from micro-climate stations.

**Deliverables**

D1.3.1: Peer-reviewed manuscript on survival rates of marked Culex mosquitoes in winter refuges, for two full winters (M30).

D1.3.2: Peer-reviewed manuscript on evidence for vertical transmission of West Nile virus (WNV) in Culex spp. in overwintering mosquitoes and in the breeding season (M44).

D1.3.3: Peer-reviewed manuscript on post-viraemia viral shedding in birds, mammals and amphibians captured in the field (M44).

D1.3.4: Peer-reviewed manuscript on infection experiments on Xenopus (M24).

D1.3.5: Peer-reviewed manuscript on seasonal profile of species captured to traps baited with pigeons, mice and frogs (M40)

D1.3.6: Fully summarized data-base on temperature/humidity profiles of "typical" resting sites of Ae. albopictus in different European climatic regions (M44)

D1.3.7: Peer-reviewed manuscript on viral replication under diurnal temperature regimes (M44)
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**Objectives**
The objectives of this WP are to:

1. Identify potential Phlebotomine vectors, to study their biology and epidemiological role in the transmission of PhB-viruses and leishmaniasis,
2. Explore the recent spread of sand fly species/populations into new geographical areas,
3. Investigate recent changes in the abundance of vectors and transmitted pathogens,
4. Generate vector and disease (leishmaniasis and Phlebovirus infections) risk maps of Europe and adjacent regions (including Mediterranean and EECA countries).

**Description of work and role of participants**

**Approach**
The developed approach will include the study of the diversity and origin of pathogens (*Leishmania* + PhB viruses), of sand fly biology and population diversity, of the susceptibility of sand flies to various *Leishmania* species, effect of temperature on *Leishmania* development in sand flies and of *Leishmania* reservoirs, as described in the work breakdown below.

**Work breakdown**

1. **Standardization and harmonization of diagnostic methods for human PhB diseases.** Through the organization of a consensus meeting, experiences and protocols will be shared between participants to formulate standardized guidelines for serological, parasitological and molecular diagnosis of PhB diseases/infections, and *Leishmania* identification. Reference laboratories of endemic countries included in this proposal will be appointed for protocol collection and distribution. As regards Phlebovirus, see 1.4.1.3 for the centralization of the virus identification.

2. **Spread of Leishmania infantum into the North and “new” strains and hybrids of L. donovani and L. tropica in the Mediterranean.** The surveillance of *L. infantum* spreading will continue by a network of medicals and veterinarians in the sentinel area of Northern Italy. Entomological field research will continue in these territories and in the Iberian peninsula and France to assess the spread of vectors. In accordance with the activity of 1.4.4.2, ISS, IHMT and UoC will investigate the risk of *L. tropica* introduction in Sicily and Crete by direct *Leishmania* molecular identification (PCR-RFLP) from bioplastic and/or fixed samples of human and canine leishmaniasis cases. Special attention will be paid to new strains of *L. donovani* complex currently spreading in Cyprus and South Turkey and Portugal.

3. **Spread of PhB-viruses in Europe.** ISS will implement and carry out the centralization of monitoring the spreading of Phleboviruses in Europe, through isolation and identification of agents from sand fly samples received by partners of the PhBD group. The main objective would be the isolation (in cells and newborn mice) and unequivocal identification of any Phlebovirus which may be present in the entomological samples. These standard methods need to be used as more and more virus species are being identified, for which RT-PCR detection tools are unavailable. Isolates and sequences will be made available to other WP members and dissemination and training will be organized for optimal technological transfer.

2.1. **Seasonal dynamics of sand fly populations.** Samplings will be conducted for the duration of the sand fly active season for at least two consecutive years. Previous sampling methodology as defined by EDEN-LEI sub-project will be followed, which includes a standardized (geo-referred) geographic grid distribution of collecting sites and the uniform use of 20cm x 20cm sticky paper traps set twice a month during the whole transmission season CDC light traps have been recommended as a suitable sampling method for measuring abundance of sand flies and determining seasonal activities. Aspirators will be used during daytime for studying resting habits, indoor density and distribution of endophilic species. All the collected specimens will be preserved in ethanol until the identifications of the species and parasites. Males and females will be identified by their morphological characteristics and by using molecular markers, if necessary.

2.2. **Resting microhabitats, nocturnal activity and host-feeding preference.** For studies on nocturnal activity patterns CDC light traps will be set up and controlled each hour. To determine whether the local variations in temperature and relative humidity might affect abundance or nocturnal activity of sand flies in the study area, data loggers will be placed to each
site trap to record temperature and humidity every half hour. They will be also used to determine the environmental conditions (temperature and humidity) of resting microhabitats. To study host-feeding preferences, characteristics of each sampling site and the presence of probable hosts will be recorded. Blood meal identification will be performed on blood fed females using molecular methods (e.g., by cytochrome b sequencing and PCR-RLB).

2.3. Distribution and spreading of Larroussius species, their population genetics. Genetic population structure and history of colonization and re-colonization of geographic areas by various sand fly species will be studied by molecular biology techniques (microsatellite analysis for P. papatasi and P. perniciosus, RAPD and other methods for other sand fly species). One aim of the study is to make a robust identification of Larroussius species by using both morphological characters and molecular data and then to clarify the geographical distribution of these species in Europe and adjacent regions (Mediterranean and EeCa countries).

3. Susceptibility of sand flies to various Leishmania species, effect of temperature on Leishmania development in sand flies. Vectors naturally occurring in Europe (like P. papatasi, P. sergenti, P. perniciosus, and P. tobbi) will be studied for susceptibility/refractoriness against various Leishmania species/strains. Colonies of these species are already available in partner CUNI, ISCIII, ISS and HUESRL. Experimental infections of colonized sand flies will be done using membrane feeding on blood mixed with suspensions of Leishmania. Special attention will be paid to strains newly detected in Europe, including hybrids or strains resistant to anti-Leishmania drugs. In every experiment, Leishmania strain with known developmental parameters will be used as a control. Microscopical and molecular techniques (qPCR, RT-PCR) will be used to study infection rates and parasite loads. Localization of parasites in sand fly gut will be studied microscopically. Susceptibility/refractoriness to Leishmania are closely related to glycosylation of sand fly midgut epithelium. Midgut glycoproteins will be characterized by electrophoretic methods and western blotting with commercially available lectins. Effect of temperature on Leishmania development in sand flies will be studied under experimental conditions. Females infected by membrane feeding will be kept at different temperatures ranging from 20 to 30°C and dissected at various intervals to study parasite loads and location of infections. These results will be used to assess the risk of Leishmania transmission in areas representing the northern limit of sand fly distribution.

4.1. Standardization and harmonization of current tools for monitoring canine leishmaniasis (CanL). As for human diagnosis, a number of techniques are currently available for diagnosis of CanL in dogs, which however exhibit different performances according to target (e.g., in detecting asymptomatic infection vs. overt disease). By organizing a consensus meeting, experiences and protocols will be shared between participants to formulate standardized guidelines for serological, parasitological and molecular diagnosis of PhB diseases/infections, and agent identification. Reference laboratories of endemic countries included in this proposal will be appointed for protocol collection and distribution. In Portugal, protocols will also be distributed to veterinarians through the ONLeish (The Portuguese Observatory for Leishmaniases) network (www.onleish.org).

4.2. Surveillance of dogs as sentinel hosts for Leishmania. Networks of veterinary practitioners and vet faculties are already set in several regions. Healthy and clinically suspected dogs will be regularly surveyed in sentinel clinics by means of CanL diagnostic procedures standardized as reported in 1.4.4.1. Non-endemic, endemic and borderline settings will be monitored.

4.3. Application of novel diagnostic tools for monitoring Leishmania-dog contact. A surrogate marker indicating dog exposure to bites of infected sand flies would consist of the early evidence of Leishmania deposition in the dog’s skin. Recently, a non-invasive sampling method (conjunctival swab, CS) coupled with a sensitive and specific PCR-based analysis, was proposed for CanL diagnosis. A study will be planned to evaluate the role of CS n-PCR analysis for the earliest detection of Leishmania DNA in dogs exposed to different transmission season(s).

TASKS YEAR 1

- Task 1.4.1 (CUNI, ISS, IRD, IHMT ISCIII, UoC, EGE): Collection and exchange of diagnostic protocols for PhB diseases, identification of reference diagnostic laboratories, and organization of a consensus meeting; collection of existing information about autochthonous and imported human leishmaniasis cases, using a standard database which includes available information on parasite identification; Implementation of a centralized system for the isolation and identification of phleboviruses.
- Task 1.4.2 (CUNI, ISS, IRD, NCDC, UoC, IHMT, ISCIII, HUESRL, EGE): Identification of new, or confirmation of previous target geographical areas; consensus on the main approach for collection site spatial distribution and trapping methodology; field collections during the appropriate period which includes a sand fly season.
- Task 1.4.3 (CUNI, ISS, IRD, HUESRL): Standardization of experimental infections with existing sand fly colonies; sharing techniques among partners; establishment of new colonies.
- Task 1.4.4 (CUNI, ISS, IRD, IHMT ISCIII, UoC, EGE): Collection and exchange of diagnostic protocols for CanL, identification of reference diagnostic laboratories, and organization of a consensus meeting; collection of information about autochthonous and imported CanL cases, using a standard database which includes available information on parasite identification; optimization of the conjunctival swab method for Leishmania diagnosis.

TASKS SUBSEQUENT YEARS
- Task 1.4.1: Standardization and harmonization of diagnostic methods for human PhBD diseases; Assessment of northward spreading of L. infantum in Europe; Investigation on the potential spreading of exogenous or low endemic Leishmania species and strains; Assessment of phlebovirus species and strains distribution, associated to human disease and to different European biotopes.

- Task 1.4.2: Studies on seasonal dynamics of sand fly populations, their resting microhabitats, nocturnal activity and host-feeding preferences; Assessment of Larroussius species/genotypes distribution and spreading.

- Task 1.4.3: Experimental studies on susceptibility of various Larroussius and Transphlebotomus species to different Leishmania species/strains recently emerged in Europe and neighbouring countries; laboratory studies on the effect of temperature on L. infantum development in target Larroussius sand fly species.

- Task 1.4.4: Standardization and harmonization of current tools for monitoring of CanL; surveillance of indigenous and imported Leishmania infections in dogs; field evaluation of novel diagnostic tools for monitoring Leishmania-dog contact.

**Contingency plan**

Since all partners are established and recognized research institutes with a long-standing experience in sand flies and PhBD, and most of them already collaborating in other projects, only minor risks are identified at the scientific and technical level. Samples will be collected and diagnostic tests evaluated by several partners simultaneously so that failure of one partner will have only minor influence on this activity.

**Milestones**

ML1.4.1.1 Reference diagnostic laboratories for human PhBD identified and consensus protocols established – Means of verification: Appropriateness of structures and efficiency evaluation of reference laboratories.

ML1.4.1.2 Database of human leishmaniasis cases and infecting agents established – Means of verification: Appropriateness of data input verified.

ML1.4.1.3 Centralized system for Phlebovirus isolation established – Means of verification: Efficiency of sample collection and analysis.

ML1.4.2. Study areas identified and entomological collections performed – Means of verification: Representative samples of sand fly populations collected.

ML1.4.3. Experimental vector/parasite interaction studies performed – Means of verification: Appropriateness of methodology employed.

ML1.4.4. Reference diagnostic laboratories for canine leishmaniasis identified and consensus protocols established. – Means of verification: Appropriateness of structures and efficiency evaluation of reference laboratories.

ML 1.4.4.1 Database of canine leishmaniasis cases and infecting agents established – Means of verification: Appropriateness of data input verified.

ML 1.4.4.2 Development of a non-invasive method for Leishmania infections in dog – Means of verification: Comparative performance with standard assays.
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<td>D1.4.1. Establishment of inter-partner reference diagnostic laboratories for human PhB diseases, canine leishmaniasis and centralized system for Phlebovirus isolation. (M12)</td>
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<td>D1.4.2. Databases of PhBD agent identification in hosts and sand flies available to EDENext consortium, peer-reviewed publication on distribution of phleboviruses. (M48)</td>
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<td>D1.4.3. Report on the establishment of study areas and standard methodologies for sand fly collections and biology investigations. (M12)</td>
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<td>D1.4.4. Publicly available maps of sand fly species/populations distribution, biology/ecology databases available to EDENext consortium. (M24)</td>
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<td>D1.4.5. Peer-reviewed publication on sand fly population genetics. (M48)</td>
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<tr>
<td>D1.4.6. A set of peer-reviewed publications on seasonal dynamics, resting microhabitats, nocturnal activity and host-feeding preferences. (M48)</td>
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<tr>
<td>D1.4.7. Report on the establishment of standard methodologies for laboratory vector competence investigations and Leishmania / vector interactions. (M12)</td>
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<td>D1.4.8. Peer-reviewed publication on sand fly species/populations susceptibility to PhBD and associated molecular factors and vector competence to Leishmania infection by sand fly. (M48)</td>
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<td>D1.4.9 Peer-reviewed publication on the effect of temperature on Leishmania development in sand flies. (M36)</td>
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<td>D1.4.10. Optimization of the conjunctival swab method for Leishmania diagnosis. (M12)</td>
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<td>D1.4.11. Publicly available database of CanL prevalence by territory through conjunctival swab method and a peer-reviewed publication. (M48)</td>
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**Participant number**: 1 11 12 13 14 15 16 17  
**Person-months**: 81 18.5 32 69 34.5 2.7 0 0

**Objectives**
The objectives of this WP are to:

1. Examine potential entry routes of Culicoides midges into the EU via globalised trade and transport networks.
2. Define standardized vector competence protocols that can be used to consistently and accurately test vector susceptibility to infection with Orbiviruses in the laboratory.
3. Carry out parallel studies in areas of Orbivirus transmission that can be used to infer vector status in the field.
4. Derive data regarding lifecycle parameters in the laboratory for input into midge population modelling and R0 frameworks.
5. Use existing surveillance datasets to examine and predict the impacts of environmental drivers on the phenology, abundance survival and mortality rates of key vector groups (at regional and landscape scales) and build seasonal midge population modelling frameworks.
6. Carry out field-based investigations to quantify the discrepancy between population sizes and composition of Culicoides sampled using the ‘gold-standard’ light trap used across the EU or on host species.

**Description of work and role of participants**

**Background**
This work package carries out an integrated assessment of several aspects of Culicoides vector capacity across different countries. It involves studies of potential introduction routes of Orbiviruses, examination of vector susceptibility to infection with Orbiviruses in the laboratory and field examination of behavioural patterns that may influence both their role as vectors and our ability to define control and monitoring techniques. This understanding will be integrated into the development of models of phenology and seasonal population changes, using existing surveillance datasets, for key European vectors and *C. imicola* in Senegal. The latter will contribute to R0 transmission model frameworks for predicting the likelihood that Orbiviruses will establish in different zones and times within Europe and also to develop frameworks within which the quantitative impacts of vector control strategies on midge demography can be evaluated in WP2.

To study the spread of BTV, dispersion models have recently been developed to describe the movement of infected *Culicoides* at a landscape level and employed in combination with records of livestock movements to provide timelines of incursion events. Nevertheless, other potential routes of incursion for Orbiviruses remain poorly defined such as the trade and use of contaminated biological materials (including vaccines), import of exotic animals with an unknown potential to develop a transmissible viremia or the movement of infected *Culicoides* with livestock or other cargos. Our study will concentrate primarily on the latter area with a view to defining the methods by which infected *Culicoides* could be transported into the EU and subsequently feed upon indigenous livestock.

Due to the relatively recent incrimination of indigenous European vector groups in BT epidemiology, the *C. obsoletus* and *C. pulicaris* groups, our understanding of the bioecology of *Culicoides* species in the EU and their potential to vector extant and novel strains of Orbiviruses remains extremely poor. While studies have demonstrated the presence of virus in field caught pools of midges in Italy, Greece, Spain and other southern European countries, the prevalence of infection in the vector population, or the extent of viral dissemination through individuals have not been determined. The emergence of RT-PCR based assays has the potential to revolutionise species-level assessments of vector susceptibility but requires a thorough understanding of the limitations of this technique. In addition, the increasing use of *Culicoides*-based cell lines will provide us with a far more epidemiologically relevant means of isolation for field strains than was available previously.

Laboratory investigations of vector competence require standardisation for comparative estimates of vector susceptibility to infection and onward transmission potential. Specifically, standard midge-feeding methods are required that work across *Culicoides* species and reliably approximate the natural host to vector transmission. Attempts will be made to transfer membrane techniques used in African BTV systems to northern Palearctic species, though pledge feeding techniques already in use for these species will be initially rolled out across the site network so that baseline field estimates of interspecific and intraspecific variation of levels of susceptibility to Orbivirus infection can be made. In addition, to understand the biological processes driving any differences we will observe between *Culicoides* species and populations, the molecular basis of vector competence and modulation of the host immune system by vector saliva will be...
investigated using immunological approaches.

Detailed knowledge of Culicoides life-history parameters and habitat use, and how these alter under different environmental conditions, are essential for prediction of the risk of establishment of Orbiviruses. The lack of such data for European Culicoides species has necessitated the use of surrogate parameters in models from Culicoides species that originated in other continents - subject to different pathogens strains, hosts and climate regimes. This workpackage aims to address this knowledge gap by combining estimates of life-history parameters in adults taken from field Culicoides populations across the network with modelling of existant surveillance datasets to investigate the role of environmental factors in driving phenology and demographic rates of Culicoides in the field. Useful in the latter, are accurate estimates of the age structure of adult Culicoides populations. This workpackage will trial new molecular tools for age-grading of adult Culicoides populations that can no longer be reliably done on the basis of abdominal pigmentation. Finally, light trap catches are commonly used as a surrogate for population sizes of Culicoides biting ruminants (i.e. to calculate vector-host ratios), but have been shown to underestimate both abundance and diversity of Culicoides. Hence drop-trap field experiments will be developed to standardise these traps, generating conversion factors, against Culicoides populations found at hosts across the network to facilitate the production of accurate population estimates for use across models of vector control and Orbivirus establishment and spread.

Approach

The approach taken will involve a combination of systematic field and laboratory experimentation that will encompass entomology, molecular biology and mathematical modelling. All partners involved will contribute to data collection although a certain degree of specialisation is inevitable given previous track records. Emphasis will be put upon transfer of knowledge and skills with training meetings and discussion conducted prior to implementation in the field.

TASKS YEAR 1

- Task 1.1: Carry out initial assessment of potential Culicoides pathways into the EU and make a preliminary selection of key ports of entry to the EU (12,14).
- Task 1.2: Quantitatively test trial methods available for membrane feeding of C. imicola (1,14)
- Task 1.3: Assess those storage methods currently available for virus infected Culicoides in colony C. sonorensis for both collection in light traps and long-term storage and initiate collections of adults across the network for isolation attempts (1,12).
- Task 1.4: Standardise virus isolation methods for use with high-throughput Tissuelyser system and C. sonorensis KC-cell derived lines (1,12,13,15).
- Task 1.5: Initiate contacts with collaborators who can assist with collection of ruminant or Equid derived field strains of Orbiviruses in endemic areas (taking account of season and training required where appropriate) (12,13).
- Task 1.6: Carry out preliminary studies to trial drop-trapping methodologies for use in standardised experiments with OVI and CDC light trap designs at multiple EU sites (1,12,13,14,17).
- Task 1.7 Use existing surveillance datasets to develop phenological models for key European Culicoides to better predict the ‘vector-free’ period in different zones and seasons. Work with Modelling Team to integrate existing static predictions of vector abundance into R0 models at landscape and regional scales (1,11,12,14,17).

TASKS YEAR 2

- Task 1.8: Carry out surveys of port areas identifying any key patterns in import control that may facilitate successful Culicoides incursion (12,14).
- Task 1.9: Apply information gained regarding C. imicola feeding preferences to devise optimal methods of feeding for northern Palaeartic species, targeting potential vectors of orbiviruses in this region (1,12,13,14).
- Task 1.10: Assess laboratory infection and dissemination rates of orbivirus strains in C. imicola including comparison with infection rates in South African populations carried out in parallel studies using genetically similar strains at identical titres (12,14,17).
- Task 1.11: Examine oogenesis, fecundity and adult survival in C. imicola and northern European vectors at constant temperature and humidity regimes and define an optimal method of storage for this development process (1,12,13,14).
- Task 1.12: Continue screening of field collected individual Culicoides from virus epidemic areas (1,13,15).
- Task 1.13: Carry out initial comparison of light traps against CO2 and drop trap catches across the network (1,12,14,17).
- Task 1.14. Use existing surveillance datasets and preliminary life-history data to develop biological population models for key European Culicoides in North Africa and Europe. Work with Modelling Team to integrate existing seasonal predictions of vector abundance into R0 models at landscape and regional scales (1,11,12).
- Task 1.15 Examine the landscape correlates of midge abundance and transmission in France (and other countries as appropriate) and work with the Modelling Team to develop models (cellular automata models) for Culicoides and
BTV spread (1,12,14).

**TASKS YEAR 3**

- **Task 1.16:** Initiate age grading analysis by emergence trapping, membrane feeding and then storage of field caught populations and naturally blood-fed *Culicoides* from animals (1,12,17).
- **Task 1.17:** Carry out first year examination of *C. obsoletus* group competence using membrane-based techniques (or pledget-based techniques if these fail) (1,12,14).
- **Task 1.18:** Continue to examine oogenesis, fecundity and adult survival in *C. imicola* and northern European vectors at constant temperature regimes (1,12,13,14).
- **Task 1.19:** Assess survival of adult *Culicoides* under known climate conditions in the laboratory including in the presence or absence of sugar and blood meals (1,12,13,14).
- **Task 1.20:** Continue screening of field collected individual Culicoides from virus epidemic areas (1,13,15).
- **Task 1.21:** Culicoides saliva and immunomodulation: impact on antigen presenting cells capacity to initiate an efficient immune response and evaluation of the presence of receptors involved in the BTV transmission (1).
- **Task 1.22:** Carry out second year of comparison of light traps against CO2 and drop trap catches (1,12,14).
- **Task 1.23:** Finalise phenological and population models for key European *Culicoides* in North Africa and Europe. Work with Modelling Team to integrate seasonal predictions of vector abundance into $R_0$ models at landscape and regional scales and Initiate work with Modelling Team to integrate seasonal predictions of vector abundance into $R_0$ models at landscape and regional scales (11,12).

**TASKS YEAR 4**

- **Task 1.24:** Complete age grading analysis and oogenesis relationship with temperature (1,12).
- **Task 1.25:** Identification of transcripts playing a role in the virus transmission (1,12).
- **Task 1.26:** Carry out second year examination of *C. obsoletus* group competence using membrane-based techniques (or pledget-based techniques if these fail) (1,12,13,14).
- **Task 1.27:** Carry out third year of comparison of light traps against CO2 and drop trap catches (1,12,14).
- **Task 1.28:** Finalize $R_0$ models at landscape and regional scales and produce seasonal transmission risk maps (1,11).
- **Task 1.29:** Complete reports for final project submission (1,11,12,13,15).

**Contingency plan**

Significant issues that could prevent the successful completion of this area of work include an inability to define suitable artificial feeding techniques for *Culicoides* of EU origin. For this reason, broad scale assessments of vector competence will be made using existing successful methods (e.g. pledget feeding for vector competence studies and natural feeding on hosts for use in oogenesis determination). In addition, for *C. imicola*, techniques have been successfully defined in South Africa providing a framework to address this issue with this species in the EU. Addressing this issue requires a calculated risk based on the benefit of not only completing the objectives of this study but also eventually allowing the production of short term colonies useful for addressing questions of genetic inheritance of traits.

**Milestones**

**MILESTONE YEAR 1**

- **ML1.5.1:** Preliminary investigation of incursion routes. Means of verification: Deliverable D1.5.1.
- **ML1.5.2:** Membrane feeding assessment of *C. imicola*. Means of verification: Deliverable D1.5.1.
- **ML1.5.3:** Field collection of *Culicoides* and standardisation of detection systems.
- **ML1.5.4:** Collaborative assessment of drop trapping techniques. Means of verification: Deliverable D1.5.1.
- **ML1.5.5:** Develop phenological models for European *Culicoides* integrate static vector predictions into $R_0$ frameworks Means of verification: Deliverable D1.5.1.

**MILESTONE YEAR 2**

- **ML1.5.6:** Carry out assessment of incursion routes. **Means of verification:** Deliverable D1.5.2.
- **ML1.5.7:** Membrane feeding assessment of *C. obsoletus* group. **Means of verification:** Deliverable D1.5.2.
- **ML1.5.8:** Initiate studies of oogenesis. **Means of verification:** Deliverable D1.5.2.
- **ML1.5.9:** Assess laboratory vector competence of *C. imicola*. **Means of verification:** Deliverable D1.5.2.
- **ML1.5.10:** Continue field collection of *Culicoides* for screening via optimised protocols. **Means of verification:** Deliverable D1.5.2.
- **ML1.5.11:** Carry out initial drop trap comparison study. **Means of verification:** Deliverable D1.5.2.
ML1.5.12: Develop biological population models for European *Culicoides* and integrate seasonal vector predictions into R0 frameworks: **Means of verification:** Deliverable D1.5.2.

**MILESTONE YEAR 3**
ML1.5.13: Initiate age grading studies. **Means of verification:** Deliverable D1.5.3.
ML1.5.14: Assess laboratory vector competence of *C. obsoletus* group. **Means of verification:** Deliverable D1.5.3
ML1.5.15: Identification of receptors which may play a role in the transmission and characterization of factor(s) present in *Culicoides* saliva that could interfere with the host dendritic cells biology- **Means of verification:** Deliverable D1.5.3.
ML1.5.16: Continue to assess oogenesis at constant temperatures. **Means of verification:** Deliverable D1.5.3.
ML1.5.17: Assess survival of *Culicoides* under laboratory conditions. **Means of verification:** Deliverable D1.5.3
ML1.5.18: Continue field collection of *Culicoides* for screening via optimised protocols. **Means of verification:** Deliverable D1.5.3.
ML1.5.19: Carry out second year of drop trap comparison study. **Means of verification:** Deliverable D1.5.3.
ML1.5.20: Finalise phenological and population models and outputs for BTV and Culicoides spread.

**MILESTONE YEAR 4**
ML1.5.21: Complete age grading and oogenesis studies. **Means of verification:** Deliverable D1.5.3.
ML1.5.22: Complete assessment of laboratory vector competence of *C. obsoletus* group. **Means of verification:** Deliverable D1.5.3.
ML1.5.23: Complete field collection of *Culicoides* for screening via optimised protocols. **Means of verification:** Deliverable D1.5.3.
ML1.5.24: Complete drop trap comparison study. **Means of verification:** Deliverable D1.5.3.
ML1.5.25: Complete R0 risk maps **Means of verification:** Deliverable D1.5.3.

**Deliverables**
D1.5.1: Understanding *Culicoides* associated parameters in risk assessment of orbivirus establishment and transmission: a preliminary report. **Month of delivery:** 12
D1.5.2: Understanding *Culicoides* associated parameters in risk assessment of orbivirus establishment and transmission: an interim report. **Month of delivery:** 24
D1.5.3 Understanding *Culicoides* associated parameters in risk assessment of orbivirus establishment and transmission: a final report including spatio-temporal maps of transmission risk (R0) in Europe. **Month of delivery:** 48
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<td>WP2.1</td>
<td>Intervention and control of TBD</td>
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**Activity type**
RTD

**Participant**
SAS | SZIE | IVB | LMU | RCB | KAU | IDVET | FEM | FLI | IP | INRA
---|---|---|---|---|---|---|---|---|---|---
4 | 16 | 4 | 14 | 0 | 3 | 0 | 2 | 56 | 0 | 12

**Objectives**
To produce early-warning tools and predictive quantitative models to better inform human populations about the potential risk of contracting Ixodes ricinus transmitted diseases in Europe (in collaboration with ROBO group and Modelling WP)

**Background**
The tick *I. ricinus* uses a wide range of mammal, bird and reptilian species, including humans, to complete its blood meals. This species inhabits natural and semi-natural areas including peri-urban and urban parks and roadsides. The control of tick infestation by the regular application of acaricides on large numbers of wild hosts is not feasible, ethical or healthy, and vector control in the environment, although some progress in this approach has been achieved, is still not applicable to natural settings and large areas. Therefore, the most reasonable approach to the prevention of tick-borne disease is to promote the large-scale diffusion of information to human populations about risk, based on the monitoring of biological indicators which appear to act as proxies for TBD disease risk. The identification of these proxies is only possible by statistical approaches and mathematical modelling.

Modelling of tick-borne diseases is not a simple matter. For example, the temporal dynamics of *I. ricinus* is affected by a combination of abiotic and biotic factors, such as local climatic conditions and availability of hosts for blood meals. Rodent population dynamics is an additional key factor, although a series of ecological parameters, such as beech masting and habitat changes, can be used to reasonably predict the change in rodent abundance over time.

Although many disease transmission models have been developed for a series of tick-borne diseases, those for *I. ricinus* are fewer and could be developed further (see Background for WP Modelling). In addition, many European models for disease risk are based on large geographical and/or climatic areas. Therefore, in close collaboration with the ROBO group and Modelling WP, FEM and INRA partners will concentrate on developing new and/or improved micro- to medium scale models using the vast amounts of data gathered in WP1. The usefulness of these models will be compared to that of the existing large scale models where available.

**Description of work and role of participants**

**Approach**
The work will include the development of both dynamic transmission models and of micro/medium scale site models.

**Work breakdown:**

1. **Development of dynamic transmission models**

   Tick-borne dynamic transmission models will be developed for a small spatial region where detailed host, vector and environmental data are available. Seasonal population models will be used to investigate how tick dynamics is influenced by some abiotic variables (e.g. temperature, humidity, altitude) and to explore how seasonal tick dynamics may affect the transmission of tick-borne diseases. In addition, the basic reproduction number (R0) for some tick-borne diseases at small spatial scale will be computed. The information resulting from mathematical models will be integrated into geo-referenced statistical models in collaboration with ROBO and Modelling groups (FEM).

2. **Micro/medium scale site modelling**

   Relevant environmental parameters of several intensively studied tick/rodent collection sites (where high resolution maps are available) will be monitoring in 3 dimensions using a series of environmental sensors (OGC Sensorweb standard will be used as the protocol for data exchange). A microclimatic model will be created, validated and integrated into a medium scale site model based on GIS and remote sensing data. These models will also be used to study various aspects of tick and host ecology, distribution and dispersal collected in other tasks and to test if these microscale models can contribute significantly to enhance existing macro-scale models for disease risk predictions. (FEM, ROBO and Modelling groups)
### Tasks

**TASKS YEAR 1**
- T 1.2.1: Set-up of remote sensors for 3D microclimatic data collection (FEM)

**TASKS SUBSEQUENT YEARS**
- T 1.2.2: Development and validation of a microscale dynamic transmission model and a micro/medium scale site model (FEM)

### Contingency plan

The innovation in this WP lies in the fact that these models will be developed at the small and medium scales, and are expected to be integrated into and considerably enhance the predictive value of existing large scale models. The microclimatic site modelling also requires the setting up of a series of sensors in 3D (which is also innovative). Although these approaches are ground-breaking, the necessary mathematics, theory and technology already exist and the expertise of the partners will allow their adaptation to the proposed tasks.

### Milestones

ML 2.1.1: First meeting to define field and laboratory protocols. Means of verification: a document agreed and signed in by all partners.


ML 2.1.3: Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers.

### Deliverables

D 2.1.1: Publication of first results (M36)
D 2.1.2: Microscale dynamic transmission and micro/medium scale site models (M48).
D 2.1.3: Publication of the final results (M48)
**Workpackage number**  WP2.2  
**Starting date or starting event**  M0

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**Objectives**

Many rainbo and tick-borne diseases follow, with varying time lags, small mammal fluctuations. We perform a continent-wide pilot study to test the feasibility of an early-warning system, by monitoring small mammal dynamics and consequent rainbo and tick-borne pathogen emergence. This would be a joint work by RBD and TBD teams.

**Description of work and role of participants**

**Background**

There is a considerable amount of information on single pathogen biology and dynamics, but many rodent and other small mammal species carrying rainbo and tick-borne pathogens show similar response patterns (a concerted response) to environmental factors, like masting, or habitat change. This can be utilized for general early warning purposes. As reported recently in EDEN project (Tersago et al. 2008), summer temperatures strongly affect masting. These results should be verified over Europe on continent-wide basis. We aim 1) at looking geographically larger areas in Europe to verify the temperature - masting relations, and how the temperature data could accordingly be used to predict the increase of rainbow / tick-borne diseases, and 2) establishing a pilot network for early warning system, where rodents, rainbo pathogens, important vectors parasitizing rodents, and common TBD pathogens, would be monitored. This pilot network will produce valuable experience on the feasibility of such approach. Specifically, we aim at studying the impact of masting on the rodent dynamics and this way on the emergence of rainbo and tick-borne diseases, and time lags between causal factors and disease emergence and how concerted the pathogens responses are. To be monitored (suggested topics): rodents, shrews, ticks, rainbo pathogens (hantas, arenas, cowpox), tick-borne pathogens (borrelias, anaplasmas, rickettsias, TBEV, tularemia, leptospira).

**Approach**

Study areas, representing landscape level approach, will be selected in N Italy, Slovakia, France, Germany, Sweden and Finland. Collections will be done annually 2-3 times in locally relevant seasons to maximize the amount of information to be collected. Material will be shared and each pathogen group will be analysed by one or two expert teams using standardized methods. There will be collaboration with non-EDENext expert groups.

**Work breakdown:**

**TASKS YEAR 1**

- Task 2.2.1. Establishing the collection system, protocols and final selection of pathogens to be monitored
- Task 2.2.2. Selection of the study sites
- Task 2.2.3. First collections and analyses

**TASKS SUBSEQUENT YEARS**

- Task 2.2.3. Collections every year, and host, vector and pathogen analyses

**Contingency plan**

We have a diversity of study areas, and failure in one will not endanger the whole approach. Flexibility is maintained so that the list of items to be monitored can be changed if found necessary.

**Milestones**

ML2.2.1. Monitoring network established and study sites selected. 1st annual report.
ML2.2.2. First year collection done. 1st annual report.
ML2.2.3. First year analyses done. 1st and 2nd annual report
ML 2.2.4. Evaluation of the first year. Internal report, 1st and 2nd annual reports
ML 2.2.5,6,and 7. Completion of tasks in the following years. Annual reports.

**Deliverables**
| D2.2.1. | Evaluation of the first year, internal document in 1\textsuperscript{st} annual report (M12). |
| D2.2.2. | At least one peer-reviewed publication on each of the main host/pathogen groups (M36-48). |
| D2.2. | Final evaluation of the approach and feasibility. Final project report (M48). |
| D2.2. | Peer reviewed publications, one from N., another from W-C Europe, with PH wp, on general results of monitoring in relation with PH epidemiology (M48). |
Workpackage number | WP2.3 | Starting date or starting event | M0
--- | --- | --- | ---
Workpackage title | Intervention and control MBD |  |
Activity type | RTD |  |
Participant number | 18 21 25 |  |
Person-months | 16 16 8 |  |

Objectives
We will here focus on the following objectives: i) to acquire a better knowledge on specific aspects of the *Ae. albopictus* bionomics (i.e. larval bionomics and adult dispersal capacity), which would be instrumental for improving control approaches (i.e. recognition of most important targets for larval control and optimization of adulticide treatments after a first human cases of CHIK or DEN, respectively); ii) to test the impact of ovipositing *Ae. albopictus* females transferring growth-regulator compounds among oviposition sites as a mean to decrease population densities in urban sites; iii) to assess the impact of adulticide ULV-fogging as an emergency approach in case of urban epidemics of WNV, DEN or CHIK; iv) to provide new approaches to assess the efficacy of different interventions (i.e. by developing an easy-to-use method for large-scale age-grading of *Ae. albopictus* population and optimize collection methods for monitoring presence/absence and densities before and after control interventions).

Description of work and role of participants

Background
Little attention has been paid to *Aedes albopictus* in the past because it was generally considered a “secondary” vector, of lesser importance than *Aedes aegypti*. Assumption has been that methods for control of *Ae. aegypti* should be applicable to *Ae. albopictus*, but the latter is much less restricted to the human peridomestic environment (it does not feed exclusively on humans) and so presents a much more difficult target. On the other hand, it may be more susceptible to outdoor Ultra Low Volume (ULV) aerosol treatments because it is an exophilic species. Whatever the case, despite high expenditure on control of *Ae. aegypti* by several methods in dengue-endemic countries, it is clear that current methods for reducing the mosquito population are inadequate to prevent dengue transmission. There is therefore an urgent need for new and innovative approaches. In this study, we propose to focus on elements of *Ae. albopictus* biology and behaviour in the field, and to evaluate the efficacy of a novel and innovative idea for control: the exploitation of “skip oviposition” (the distribution of small numbers of eggs at many sites) to disseminate minute quantities of juvenile hormone analogue by the ovipositing female; a recently published article described encouraging results against *Ae. aegypti* in Peru. In addition, we will study a novel method for age-grading mosquitoes by analysis of cuticular hydrocarbons. Finally we will run a small number of field trials to assess the efficacy of ULV treatments on field populations of both *Culex pipiens* and *Aedes aegypti*, using techniques for direct monitoring of the adult female population. A field trial of the juvenile hormone technique will be conducted against *Ae. japonicus* in Switzerland.

Approach
We propose the following approaches to address the specific aspects of the *Ae. albopictus* bionomics on which we decide to focus because considered instrumental for improving control approaches (i.e. larval bionomics and adult dispersal capacity):

For the larval bionomic studies, we will select a priori few breeding site “types” (e.g. used tires, drain-holes, small containers), reproduce them under semi-field conditions in Rome, and evaluate their relative adult productivity by mean of ad hoc designed “emerging traps”, starting from known number of larvae per site. Experiments will be carried out in different phases the reproductive season and immediately after the diapauses. Once identified the most productive “types” of breeding sites under semi-field controlled conditions, we will monitor the different relative frequencies of these in few restricted areas in Rome. The results of the study will be published and serve as basis for the identification of the most relevant targets for larval control interventions in other infested areas in Europe. If possible, the newly designed “emerging traps” will be exploited to evaluate the efficacy of antilarval treatments against *Ae. albopictus* and *Ae. japonicus*, by liaising with larvicidal campaigns in Italy and Switzerland. Protocols for their potential application in these frameworks will be developed.

For the adult dispersal study, two complementary mark-release approaches will be carried out in Rome (or other Italian infested areas), with particular reference to possible hot-spots for virus transmission (e.g. hospitals, touristic areas): 1- Release of *Ae. albopictus* females fed with blood containing rubidium (Rb) and detection of by Atomic Absorption Spectrophotometry (AAS, available at IP) of marked eggs in ovitraps. This approach will allow to estimate the range of
dispersal per single gonotrophic cycle and the duration of gonothrophic cycle; 2- Mark-Release-Recapture (MRR) with sticky-traps. This approach allows to estimate the flight range for n-days after release, and mosquito density and survival in the study area. UNIROMA1 has already carried out preliminary MRR experiments in Rome and in northern Italy, whose results indicate that females can travel up to 290 m in only 3 days (manuscripts in preparation). This may suggest the need of treating by adulticides a larger than expected area around a possible infected human case, in order to minimize the chances of transmission. The same approach would be applied to study Ae. japonicus, dispersal in Switzerland, if co-founding will be available.

We will assess the operational value and the effect of Mosquito Growth-Regulator Transfer (MGR-T) among oviposition sites via ovipositing *Ae. albopictus* females. We will initially apply the same approach recently develop for *Ae. aegypti* in the main cemetery of Rome (a highly infested area, where other control approaches have failed to have any impact, AdT, personal communication). If successful, we will replicate the approach on larger and/or ecologically differentiated field sites in Rome, and eventually evaluate the effect of the approach on adult population densities. The approach will be also tested as a proof of principle on Ae. japonicus in Switzerland. We expect this approach could allow to overcome the major problem to treat the most common small containers, where these species are known to breed, changing the perspective to decrease adult densities in urban areas. Moreover, we will test in Rome the efficacy of fogging and/or UV fogging of chemical and/or growth-regulator compounds, as an emergency approach to target populations of potential mosquito vectors (i.e. *Ae. albopictus* and *Cx pipiens*) in case of virus transmission in an European area.

When evaluating the efficacies of the above approaches, we will rely on standard approaches (including adult collections with BG sentinel traps before and after interventions), but we will also develop more powerful approaches to evaluate the success of a control intervention. First, we will try to increase the efficacy of existing traps for adult collections (e.g. BG sentinel traps, sticky traps) by testing the effects of attractants on their collection capacity. Second, we will develop an age-grading approach based on near-infrared spectroscopy analysis of cuticular composition, as recently developed for *Anopheles gambiae*. Initially, different age groups from laboratory reared mosquitoes (whose cuticular composition is likely to be altered by the artificial breeding conditions) will be tested and, after optimization of the protocol, the analyses will be extended on adults emerged from natural breeding sites collected by “emerging traps” (see above) and kept under semi-natural conditions for different day-intervals. Controls will be also carried out on field collected females by comparing results of near-infrared analysis with parous and nulliparous rates. The same approach will be extended to *Ae. japonicus* in collaboration with IPZ. If successful, as for An. gambiae, this approach will allow an easy and effective assessment of the efficacy of different interventions, which will be tested to monitor the control activities developed in the framework of the project, and beyond.

**Work breakdown**

**TASKS YEAR 1**

- Task1.3.n: Development and optimization of *Ae. albopictus* “emerging traps”.
- Task1.3.n: Evaluation of attractants to increase *Ae. albopictus* adult rate of capture by sticky-traps and/or BG-sentinel traps.
- Task 1.3.n: *Ae. albopictus* MRR experiment carried out in a 500 m-radius area in Rome.
- Task1.3.n: Preliminary assessment of operational value and effect of MGR-T via ovipositing *Ae. albopictus* females in small area in Rome’s cemetery.
- Task1.3.n: Preliminary near-infrared spectroscopy analysis of *Anopheles gambiae* and *Ae. albopictus* cuticular composition.

**TASKS YEAR 1**

- Task1.3.n: Testing rate of *Ae. albopictus* adult emergence from different “types” of breeding sites in Rome, from known numbers of larvae and pupae.
- Task1.3.n: Evaluation of attractants to increase *Ae. albopictus* adult rate of capture by sticky-traps and/or BG-sentinel traps.
- Task1.3.n: *Ae. albopictus* MRR experiments replicated in a different ecological setting in Rome (or other sites in Italy) with optimised collections methods (see Task...).
- Task1.3.n: Assessment of effect MGR-T among oviposition sites via ovipositing *Ae. albopictus* females in larger area(s) in Rome.
- Task1.3.n: Near-infrared spectroscopy analysis extended to different age-groups of laboratory reared *Ae. albopictus*.
- Task1.3.n: Assessment of efficacy of adulticide treatments fogging and/or UV fogging on *Ae. albopictus* population densities in a selected area in Rome.
TASKS YEAR 1

- Task1.3.n: Testing rate of *Ae. albopictus* adult emergence from different “types” of breeding sites in Rome, from natural breeding sites. Comparison with larval and/or pupal indexes.
- Task1.3.n: *Ae. albopictus* MRR experiment out in Italy (*Ae. albopictus*) and/or Switzerland (*Ae. japonicus*) (if co-funding made available).
- Task1.3.n: Assessment of effect of MGR-T among oviposition sites via ovipositing *Ae. albopictus* females in other areas in Rome or Italy.
- Task1.3.n: Near-infrared spectroscopy analysis extended to different *Ae. albopictus* age-groups reared under semi-natural conditions in Rome, during different phases of reproductive season.
- Task1.3.n: Preliminary near-infrared spectroscopy analysis of cuticular composition of *Ae. japonicus* age-groups reared under laboratory conditions.
- Task1.3.n: Assessment of efficacy of adulticide treatments fogging and/or UV fogging on *Ae. albopictus* population densities and mean age in a selected area in Rome.

Contingency plan

We do not expect any significant risk for studies on *Ae. albopictus* larval bionomics and adult dispersal capacity. Although we don’t have direct evidence that the MGR-T developed for *Ae. aegypti* will be effective for *Ae. albopictus*, the very similar skip-oviposition behaviour of the two species strongly support the potential of this approach on *Ae. albopictus*. However, if this will turn out not to be effective after the first small-scale trials (years 1-2), in the following years, we will devote the resources presently foreseen for the large scale implementation of this approach, on an optimization of adulticides methods (e.g. fogging and/or UV-fogging).

We are quite confident that the age-grading approach developed for *An. gambiae* could be applied to *Ae. albopictus* (*Ae. japonicus*), but if results from first experiments will not be successful, we will devote our effort toward the development of other, more expensive and time-consuming, age-grading approaches based on molecular markers (e.g. see CBD-WP).

Milestones

MILESTONES YEAR 1

ML2.3.1: “Emerging traps” to measure rate of *Ae. albopictus* adult emergence are designed to adapt to different types of breeding sites. Means of verification: different prototypes are designed and assembled.

ML2.3.2: Proof of principle of efficacy of MGR-T by *Ae. albopictus* females among oviposition sites. Means of verification: significant larval and pupal lethality obtained in sentinel sites in a 200 sqm area in Rome’s cemetery.

ML2.3.3: Implementation of age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from *An. gambiae* and *Ae. albopictus* lab samples.

MILESTONES YEAR 2

ML2.3.4: “Emerging traps” to measure rate of *Ae. albopictus* adult emergence are tested under controlled conditions. Means of verification: evaluation of performance, i.e. number of collected adults / known number of pupae.

ML2.3.5: *Ae. albopictus* active dispersal capacity in different eco-climatic conditions in Rome. Means of verification: results of MRR analysed and Mean Distance Travelled assessed.

ML2.3.6: Implementation of *Ae. albopictus* age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups.

ML2.3.7: Assessment of fogging and/or UV fogging efficacy against *Ae. albopictus*. Means of verification: significant
reduction in *Ae. albopictus* adult densities in treated versus untreated areas.

**MILESTONES YEAR 3**

ML2.3.8: Confirmation of large-scale efficacy of MGR-T by *Ae. albopictus* females among oviposition sites. Means of verification: significant larval and pupal lethality observed in sentinel sites in different ecological urban settings.

ML2.3.9: Finalization *Ae. albopictus* age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups compared nulliparous/parous rates.

ML2.3.10: Assessment of large-scale efficacy of fogging and/or UV fogging against *Ae. albopictus*. Means of verification: significant reduction in both adult densities and mean age of *Ae. albopictus* populations in treated versus untreated areas.

**MILESTONES YEAR 4**

ML2.3.11: Identification of most significant urban *Ae. albopictus* breeding site “types”. Means of verification: evaluation of most productive and most frequent “types” in an area in Rome.

ML2.3.12: Assessment of large-scale efficacy of MGR-T. Means of verification: significant reduction in adult *Ae. albopictus* population densities in treated versus untreated areas.

ML2.3.13: Implementation of *Ae. japonicus* age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups.

**Deliverables**

D2.3.1: *Ae. albopictus* “emerging-traps” prototypes designed and assembled (M12).

D2.3.2: Efficacy of fogging and/or UV fogging on *Ae. albopictus* and *Culex pipiens* adult densities populations assessed. (M24).

D2.3.3: *Ae. albopictus* “emerging-traps” performance assessed (M24).

D2.3.4: *Ae. albopictus* mean Distance Travelled in urban areas assessed (M36).

D2.3.5: Age-grading method for *Ae. albopictus* standardised (M36).

D2.3.6: Age-grading method for *Ae. japonicus* proved as possible (M48).

D2.3.7: Most important targets for *Ae. albopictus* larval control in urban areas identified (M48).

D2.3.8: Large-scale efficacy of MGR-T on *Ae. albopictus* densities assessed (M48).

D2.3.9: Large-scale efficacy of fogging and/or UV fogging on mean age of *Ae. albopictus* populations assessed (M48).
Objectives

The aim of this WP is to develop, optimize and evaluate effective tools for sand fly integrated control methods. Special attention is paid to protection of dogs which serve as zoonotic reservoir of Leishmania infantum. The general aim is to protect dogs from sand fly bites using spot-on repellents and dog collars. The evaluation of success of control programs will be monitored by investigating sand fly population densities, antibody levels to L. donovani/infantum in dogs and reduction of new Leishmania cases in humans and dogs in protected areas. For evaluation of vector-host contact and estimation the risk of Leishmania transmission we will also develop a novel tool based on host antibodies recognizing vector saliva components.

Description of work and role of participants

Approach

The developed approach will include aspects related to both control of the Sand Fly Vector and the Leishmania Reservoir as detailed in the work breakdown below.

Work breakdown:

1.1. Impact of topical application of novel insecticides and repellents to dogs (Insecticides in dogs). New chemicals and/or formulations developed in the market or under evaluation in Italy, Spain and Turkey, will be tested experimentally on dogs for the anti-feeding and toxic effect against colonized sand flies.

1.2. Effect of Insecticide Treated bedNets (ITNs) on leishmaniasis transmission to humans. The ITN method was previously proven as effective against L. tropica transmission in other parts of Turkey. Here we are planning to extend the field trials with ITNs from small to medium scale. The study will be done in an area where both sand fly populations and cutaneous leishmaniasis are abundant (Cukurova Plain, Turkey). The main aims of these trials are to study the effect of ITNs on leishmaniasis transmission, develop effective and safe (ecologically sound) strategy of integrated vector control and strengthen the vector control components of general health services in the area. Epidemiological studies and questionnaires will also be carried out in field conditions with adequate amount of human populations to evaluate the community education and participation in vector control programs and help the primary health care system to deliver sustainable disease control measures.

1.3. Insecticide resistance of sand flies. Laboratory experiments on susceptibility of adult sand flies to insecticides will be done by two different methods: susceptibility tests by WHO standard kits against mosquitoes and susceptibility WHO tests by topical application; HUESRL, ISS and ISCIII have long-term experience in both methods. These experiments will establish the baseline susceptibility level before commencing a program of anti-vector measures with insecticide; will detect any change in the susceptibility level of sand fly populations at different intervals or assess the effect on the susceptibility of a sand fly population of insecticides used in agriculture in areas where no residual insecticides have been used against vectors. Results will be available for possible risk analysis models and will provide a standard method for all Mediterranean and European countries in terms of insecticide selection.

1.4. Anti-saliva antibodies as a tool for monitoring sand fly-host contact. Sera of Beagle dogs experimentally bitten by P. perniciosus are available in partner CUNI, sequences of the most abundant salivary transcripts are available at GenBank. Proteomic methods (2D electrophoresis), Western blotting and mass spectrometry will be used for characterization of salivary antigens. Selected P. perniciosus antigens will be prepared using various expression systems and used as antigens in ELISA with experimental dog sera. Optimized method will be used for screening of dog exposure in the field. Each dog screened will be monitored once per month during the transmission season in order to observe anti-sand fly antibodies dynamics. Dog sera collected prior to the current project are available from partners of this consortium. New sera will be collected during the project.

2.1. Anti-infectiousness efficacy of new drug/immunotherapeutic regimens in dogs. ISS and ISCIII partners are regularly involved in multicentre clinical trials for anti-Leishmania drug regimens in dogs, through dedicated veterinary networks. As common efficacy assessments are performed with the objective to detect clinical and parasitological efficacy of tested products, the aim of this project is to complement such studies with the evaluation of efficacy in reducing infectiousness of treated-dog’s to sand flies. Xenodiagnostic procedures using colonized sand fly vectors will be used to test dogs enrolled under drug trials, keeping findings under the intellectual property of this project. Combinations of currently marketed
drugs and immunotherapeutics under development could be put into the study protocol.

**TASKS YEAR 1**

Task 2.4.1 (CUNI, ISS, UoC, IHMT, ISCIII, HUESRL, EGE): Survey of novel products under development to be evaluated as insecticide repellent against sand fly bites on dogs; identification of study sites and collection of background epidemiological data on human CL for the implementation of ITNs-based control approach; setting-up laboratory standard methodologies to monitor emergence of insecticide resistance of wild caught sand flies; identification of major salivary antigens of \textit{P. perniciosus}.

Task 2.4.2 (CUNI, ISS, UoC, IHMT, ISCIII, HUESRL, EGE): Survey on available marketed drugs for CL therapy; survey on novel immunotherapeutic products under development for dog treatment; design of treatment protocols for clinical trials in naturally Leishmania-infected owned dogs.

**TASKS SUBSEQUENT YEARS**

Task 2.4.1: Laboratory and field application and evaluation of insecticides repellents against sand fly bites in dogs; efficacy evaluation of ITNs application for the control of human CL; assessment of susceptibility to insecticides of European populations of sand flies; characterization and production of recombinant \textit{Phlebotomus perniciosus} salivary antigens for serological assays; serological detection of antibodies against \textit{P. perniciosus} salivary antigens in field canine populations.

Task 2.4.2: Efficacy evaluation by xenodiagnosis of the infectiousness potential of dogs treated with different drug/immunotherapeutic regimens.

**Contingency plan**

Partners are experienced in control of vectors and PhBD and most data will be collected simultaneously by various partners. During the development of the ELISA test for measuring vector-host contact, simultaneous investigation of three different systems (Pichia, \textit{E. coli}) will be carried out to reduce the risk of failure. Moreover, since several candidate antigens have been identified in preliminary tests, the risk that none will be successful is very low.

**Milestones**

ML2.4.1.1 Identification of novel biocides for dog protection against sand flies – Means of verification: Comparative insecticide/anti-feeding performances with available products.

ML2.4.1.2 Assessment of ITNs protective efficacy against human CL – Means of verification: Comparative CL incidences with appropriate control arms.

ML2.4.1.3 Determination of insecticide susceptibility to different sand fly species/populations – Means of verification: Comparative susceptibility testing with appropriate insecticide-sensitive standard laboratory colonies.

ML2.4.1.4 Availability of salivary recombinant antigen(s) from \textit{P. perniciosus} for serology testing – Means of verification: Comparative performance with native crude salivary antigen.

ML2.4.1.5 Application of ELISA-salivary recombinant antigen in field dogs – Mean of verification: Appropriateness of results as compared to the entomological \textit{P. perniciosus} situation in the study site.

ML2.4.2 Xenodiagnosis results from different groups of drug/immunotherapeutic-treated dogs – Means of verification: Comparative infectiousness results with appropriate control groups.

**Deliverables**

D2.4.1. Report on the establishment of laboratory standard methodologies to monitor emergence of insecticide resistance of wild caught sand flies (M12).

D2.4.2. Peer-reviewed publication on the efficacy data of ITNs against cutaneous leishmaniasis transmission (M36).

D2.4.3. Publicly available database and review publication on insecticide and repellent activity against sand flies, including possible resistance, a peer-reviewed publication on novel products assayed (M48).

D2.4.4. Peer-reviewed publication on salivary antigens of \textit{P. perniciosus} and dynamics of anti-saliva antibodies in experimentally bitten dogs (M24).

D2.4.5. Peer-reviewed publication on salivary recombinant antigen(s) from \textit{P. perniciosus} for serology testing (M48).

D2.4.6. Publicly available database of canine prevalence by territory of antibodies to salivary recombinant antigen(s) from \textit{P. perniciosus} (M48).

D2.4.7. Publicly available database of xenodiagnosis results in groups of dogs treated with different drug regiments, a set of peer-reviewed publications presenting the obtained results (M36).
Objectives

The objectives of this WP are to:

1. Identify insecticides and repellents and techniques of application effective for vector control at laboratory level.
2. To develop and standardize Culicoides control methods at field level in Europe according to each epidemiological situation.
3. To assess the use of netting as protection measures against Culicoides.
4. To model the impact of vector control on R0 for Culicoides borne infections using seasonal vector population models built in WP1.
5. To model the level of preventive vaccination cover needed to keep R0 below 1 in different parts of EU, using the R0 framework developed in WP1.
6. To model the combined impact of different vaccination covers and vector control efforts on R0 while taking into account the seasonal, geographical and inter annual meteorological variation within EU.

Description of work and role of participants

Background

Most common insecticidal products authorized in the EU for use in domestic animals are based on pyrethroids. The products are used topically as pour-on solutions, which provide efficacy for at least 4-8 weeks. Other insecticides are used for dipping or spraying. To date, few attempts have been conducted to apply chemical control of Culicoides spp. in an area-wide approach and there is currently no veterinary product on the European market authorized for the control of Culicoides. Studies reporting the control of Culicoides spp. in field conditions by using pyrethroids, organophosphate and ivermectines are scarce. Repellents based on plant derived products and insecticide- or repellent-impregnated nets are also used for reducing Culicoides biting rates. However, there are still no conclusive studies of the impact of these control measures on the reduction of BTV transmission and this WP is focused in their assessment.

The independent or combined impact of vaccination and vector control on $R_0$ will vary seasonally, geographically and between years with different climate conditions. EU member states are presently not able to determine the necessary protective levels of vaccination cover, vector control efforts, or movement restrictions based on objective calculations of $R_0$ or derived indicators for each country or ecosystem. Calculations of $R_0$ for within- and between-herd spread will allow stakeholders and member states to adjust the intensity of preventive strategies as well as outbreak control measures to the predicted level of transmission in each country or ecosystem at various meteorological conditions. Simulation spread models simulating virus transmission within-herds and between-herds are on the cutting edge for developing optimal prevention and control strategies. Sensitivity and elasticity analyses on the developed models allow identification of key parameters that mostly affects the model predictions. This work package will develop a set of specific scenarios for Culicoides-borne infections and use these to compare predictions from different spread models (WP1.3 and models developed outside the present project). This is state of the art for identifying variability and reliability of the different models fitted to outbreak data.

Approach

The partners participating in this WP will conduct coordinated research at laboratory and field level for developing standardized control methods for Culicoides. Testing of insecticides and repellents at laboratory level will be conducted using WHO protocols that would assure robustness of the tests. Plant derived insecticides and repellents will be especially considered at this point. A coordinated protocol will be adopted for implementation of Culicoides control at field level. The main aim will be to reduce the rate of biting of Culicoides on animals. This approach will be adapted to the epidemiological situation of each country, considering the biocology of the major vector species in the area.

Sensitivity and elasticity analyses will be conducted on each of the developed models to identify key parameters affecting the outputs. Key parameters need to be identified with a higher precision, and will be reported to the projects in WP1.1 and WP1.2 in an iterative process with these WPs. A set of representative outbreak scenarios will be developed for various
geographical areas, seasons and meteorology including average weather conditions and 90% extremes and fixed distributions for model parameter values. This set of outbreak scenarios will be used for running the different models and will form the basis of the model compassion. The identified spatial and temporal levels of vaccination and vector control that are necessary to keep $R_0$ below 1 will be presented as guidelines for control of Culicoides borne diseases in Europe.

Work breakdown:

TASKS YEAR 1
- Task 2.5.1: Development of a coordinated protocol for testing available insecticides and repellents (1,12,13,14,16,17).
- Task 2.5.2: Evaluate the efficacy of using different netting on stables for decreasing Culicoides biting rates (12,13,16,17).
- Task 2.5.3: Develop of set of scenarios and initial parameter estimates for modelling vector control (11,15,17).

TASKS YEAR 2
- Task 2.5.4: Evaluation of insecticides and repellent in field conditions (12,13,14,16,17).
- Task 2.5.5: Develop of set of scenarios and parameter estimates for $R_0$ model comparisons (11,15,17).

TASKS YEAR 3
- Task 2.5.6: Repetition of field evaluation of insecticides and repellents (12,13,14,16,17).
- Task 2.5.7: Model impact of vector control on vector populations (11,15).
- Task 2.5.8: Model impact of vaccinations cover on $R_0$ (11,12,15).

TASKS YEAR 4
- Task 2.5.9: Simulate combination of vaccination cover, stand still and vector control (12,15).
- Task 2.5.10: Comparing predictions from different spread models (confidence in predictions) (12,15).
- Task 2.5.11: Developing spatio-temporal specific recommendations for prevention and control (11,12,13,15).
- Task 2.5.12: Evaluation of the effects of insecticides and repellents on non-targeted arthropods and other species of special relevance (13,14,16,17).
- Task 2.5.13: Finalize models with all up-dated parameters estimated in WP 1 and in previous tasks (1,11,14,15,17).

Contingency plan

Vector control will success if repellent/insecticide molecules, doses and persistence applied either to animals and screens are able to reduce the biting rate of Culicoides on animals, and hence, virus transmission. The aim is to assess this in the field, if this cannot be achieved, alternative trials by using animals in controlled conditions and by using rearing/field collected Culicoides will be carried out. Modelling vector density, $R_0$ and control effort requires vector population models, spread models and quantitative estimates of control outputs. These are all produced by WP1. If reliable vector density models cannot be developed, reported field data for vector density may be used to generate distributions for vector density. Other researchers are working with modelling and control of Culicoides-borne diseases and their result will be incorporated and adjusted to the specific outbreak scenarios if additional data are needed. Lacking data for some parameters will increase the probability intervals of the predictions, but will not prevent modelling.

Milestones

MILESTONES YEAR 1
ML2.5.1: Development of a coordinated protocol for the testing of available insecticides and repellents for Culicoides control. Identification of insecticides/repellents effective for Culicoides control. Means of verification: Deliverable 2.5.1
ML2.5.2: Identification of the most adequate insecticides and repellents for Culicoides control. Means of verification: Deliverable 2.5.1
ML2.5.3: Assessment of the most adequate methodology for application of insecticides at field level: netting, application on animals, application on target devices, and application in stables. Means of verification: Deliverable 2.5.1
ML2.5.4: Development of a coordinated protocol for the assessment of the efficacy of selected insecticides and repellents in field conditions. Means of verification: Deliverable 2.5.1
ML2.5.5: Set of spatially and temporally defined scenarios and initial parameter estimates for modelling vector control.
MILESTONES YEAR 2
ML2.5.6: Design of strategies for reduction of virus transmission by Culicoides spp. by using insecticides and repellents. Means of verification: Deliverable 2.5.2
ML2.5.7: Set of spatially and temporally specific scenarios and parameter estimates for R₀ model comparisons. Means of verification: Deliverable 2.5.2

MILESTONES YEAR 3
ML2.5.8: Confirmation of the efficacy of repellents and insecticides at field level. Means of verification: Deliverable 2.5.3
ML2.5.9: Predicting and mapping potential seasonal impact of vector control in EU. Means of verification: Deliverable 2.5.3
ML2.5.10: Predicting and mapping potential seasonal impact of various vaccination covers in EU. Means of verification: Deliverable 2.5.3

MILESTONES YEAR 4
ML 2.5.11: Predicting and mapping potential seasonal impact of combinations of vaccination stand still and vector control in EU. Means of verification: Deliverable 2.5.4
ML 2.5.12: R₀-models comparison and recommendations for prevention and control. Means of verification: Deliverable 2.5.4
ML2.5.13: Assessment of the impact of the application of insecticides and repellents on non-targeted arthropods. Means of verification. Deliverable 2.5.5.

Deliverables
D2.5.1: Reporting potential strategies for vector control and final scenarios for modelling vector control (M12).
D2.5.2: Reporting results from first field evaluation of vector control and final scenarios for modelling R₀ (M24).
D2.5.3: Reporting final field evaluation of vector control. First models results of vector control and of vaccination (M36).
D2.5.4: Spatio-temporal specific overall recommendations for prevention and control and confidence of predictions/recommendations (M48).
D2.5.5: Assessment of the effect of the use of insecticides and repellents on non-targeted arthropods and other species of special relevance. Final recommendations on insecticide and repellents use for vector control (M48).
The aim of this work package is to develop and apply methods and models for the three phases in the emergence and spread of VBD (Introduction, Establishment and spatial and temporal Spread) and to gauge the effectiveness of (new) strategies and methods of control and intervention, all taking into account environmental, land cover and land use characteristics. We aim to achieve this by interacting closely with the vector, data and public health teams in both joint research and as consultants, and by merging approaches from statistical modelling, process-based modelling and agent-based computer modelling.

### Description of work and role of participants

3.1 **Quantifying introduction risk for vectors and VBD in Europe.** This is an important but severely understudied area of research. Progress on quantitative methodology has long been hampered by scarcity of data, but in recent years this situation has changed, making the topic now ripe for exploration. Introduction risk is highly vector-dependent and therefore differs for the various species of interest. There are differences in quantifying the risk of the introduction of a vector species and the risk of subsequently introducing a VBD that this vector can transmit. The pathways along which vector and VBD arrive may be very different. Introduction has of course a component of chance that is difficult to quantify. As a proxy, however, analysis of networks of transportation between specific locations, analysis of wind patterns, and the analysis of bird migration routes and volume, provide ways to quantify risk. The relevance of various pathways of introduction will be highly vector species and VBD dependent, but we aim to provide methods that are generically applicable for distinct classes of vectors and pathogens/parasites. We aim to systematically address these topics notably for the introduction of the vectors *Ae. albopictus* and *Ae. aegypti*, and for the introduction of the VBD AHSV, CCHF, *Leishmania tropica*, WNV, DENv and CHIKv, working closely with the vector groups and the data-management team (WP4.2).

3.2 **Spatio-temporal R0-risk maps for the establishment of VBD (and some specified vectors) in Europe.** Methodology to create spatial R0-risk maps has been developed within the EDEN project for Leishmania and blue-tongue virus. Notably for leishmaniasis, an approach has been developed that merges process-based, individual-infection, modelling of R0 with remote-sensing based statistical modelling of the spatial abundance of the relevant vector species. In this way we are able to link extrinsic environmental and landscape factors to intrinsic infection and life-history factors that all influence establishment of VBDs. The methodology needs to be adapted to the specific VBD in EDENext for which such an analysis has not yet been done. We also need two essential methodological developments. The first is to scale-up the method from a regional scale surrounding a field site, where detailed data are available, to a much larger country and European scale. This brings scaling problems for the remote sensing prediction methods for vector abundance, and biological problems where several life-history and individual-level epidemiological parameters are concerned because these cannot be assumed constant over larger areas as they are influenced by climatic and other factors. The second essential extension is to move the method into the temporal domain by introducing seasonal effects on ingredients of R0, notably vector abundance, host presence and individual-level parameters. This poses challenges for both the remote sensing and the R0 approaches but initial solutions have been found that could be further developed. We aim to address these topics for the vector teams studying Culicoides, sandflies, mosquitoes and ticks, and the VBD they carry.

3.3 **Models for the spread and persistence of vectors and VBD in a heterogeneous European landscape.** Modelling the spread of vectors is notoriously difficult for two main reasons. First, the rate of spread is heavily influenced by the shape of the dispersal kernel, in particular by its tail that represents rare long-distance dispersal events. This tail is hard to establish experimentally, because of the logistic constraints of mark-recapture experiments that only work over relatively short distances, as the chances of recapture over long-distances become close to zero. Second, the spread is influenced by the structure and composition of the landscape through which it takes place. Therefore assuming an isotropic and homogeneous spread is often unrealistic. One approach to overcome these difficulties used in a number of invasion ecology case studies is to derive those parameters from the analysis of invasion using space-time geo-statistics that relate dispersal rates to landscape features, or to infer dispersal kernel functions using inverse modeling. Because of computational constrains, these approaches are at present limited to models with a relatively low number of parameters, resulting in a simplification that makes them hard to interpret biologically.

Two approaches are proposed to improve the current state-of-the-art in spread modelling. First, we aim to look at the intrinsic permeability of the landscape to VBD spread through the detailed analysis of indicators of landscape and eco-
climatic spatial heterogeneity quantified at different spatial scales. The underlying assumption is that the bigger the difference in environmental conditions between adjacent pixels, the more difficult it is for an environmentally sensitive disease to move from one pixel to the next; differences between pixels will be established through wavelet analysis, a technique that lends itself to scaling up or down, thus allowing multi-scale analysis of the probability of vector or disease spread. Second, we aim to carry out virtual experiments in which the spread of vectors is modelled through an heterogeneous landscape using known life-history parameters (e.g. growth rate, carrying capacity, dispersal curves, long-distance introduction) that may vary according to local conditions. Those simulated invasion will then be used as training data for space-time statistical analysis in order to identify how the later tools allow reliable inference of the original parameters.

Both approaches can be developed independently at first, and can then be applied to study the spread of vectors studied in the vector work packages.

For persistence we will regard several issues. For the rodent carriers of diseases that also affect humans there are similar issues, but a metapopulation using spatial networks and percolation has been developed recently to explain outbreaks of plague in rodents. This will be extended in close collaboration with the rodent group to obtain insight into the observed differences in persistence threshold of rodent-borne infectious agents in different species and different parts of Europe. In particular, we will study the dynamics of PUUV in voles using data from Finland and Central Europe. For mosquitoes we will investigate, with the mosquito team, the role of overwintering mosquitoes in the maintenance of WNV, and the interplay with arriving migrants. Similar questions of overwintering and persistence are relevant for the Culicoides team and BTV.

3.4 Population-effectiveness of control and intervention of vectors and VBD in Europe. Possibilities for control and intervention depend upon the current levels of understanding of the different vectors and diseases and, in the case of emerging diseases, will depend upon the phase of arrival, establishment and spread that has been reached. This work package involves close collaboration between the modelling team and the vector groups at a very early stage, and continuous interaction with the public health teams. We will seek to discover which type of control is feasible in which phase; how feasible measures could be optimally employed; what the efficacy is at the population level; and the amount of control effort needed. The public health experts will help to determine the precise interpretations of the words ‘optimal’, ‘efficacy’ and ‘effort’ and will help to prioritize control and intervention for the various vector-VBD-host combinations. In VBD one can aim control at fundamentally different parts of the system (the landscape, the vectors, the animal reservoir or the disease directly) and public health authorities will play a role in deciding which parts of the system to target with maximum likelihood of public acceptance and success.

The (local) value of $R_0$ is a crude indicator of the control effort required to reduce directly-transmitted infections in a well-mixed host population. In the case of a vector-VBD-host system in a heterogeneous landscape new methods have to be developed to relate $R_0$ to effort, and local estimates will have to be averaged over larger spatial scales, taking into account the variation through spatial and temporal environmental heterogeneity (which in turn affects the ability or willingness of both vectors and hosts to move through the landscape). In addition, the simple relations between $R_0$ and control effort needed break down when control is targeted at specific parts of the system, as will be the rule in multiple vector/multiple host species VBD systems. We will use, and further develop, a next-generation matrix approach to examine which parts of such multiple vector/host system should be targeted for effective control. This idea is based on the same principles as $R_0$, but leads to the so-called type-reproduction number $\mathcal{T}$, that quantifies targeted control effort.

**TASKS YEAR 1**

- **Task 3.1:** Establish a data base of remotely sensed satellite data for the other tasks within this WP. Many data layers will be inherited from EDEN, but the MODIS temporal Fourier series is continually being added to and so new imagery can be produced each year. New imagery may also be available from European sources (ESA) and will need to be examined for its relevance to EDENext’s objectives.
- **Task 3.2:** Scale-up the combined high/low remote sensing analysis and next-generation matrix based $R_0$ method of characterising establishment risk from a small spatial region with relatively detailed vector sampling and environmental/land cover data, to a much wider region where fewer details are available. This will be done for sandflies and Leishmania in dogs with the PhBD team. The methodology developed for sandflies and Leishmania in EDEN can also be applied to the other vectors and VBD.
- **Task 3.3:** Thoroughly review and compare existing methods and models for describing the dynamics of spatio-temporal spread of vectors, and derive a spread model simulation framework.
- **Task 3.4:** Review the current situation within Europe of both vectors and diseases that pose or are causing a significant Public Health threat. Examine VBDs on the fringes of Europe that are moving in the direction of Europe (e.g. CCHF), or that commonly occur in travellers returning from abroad (e.g. malaria, Chikungunya). Hold one meeting/workshop with the Public Health members of EDENext to identify critical gaps in knowledge, to orient the work for year 2.
- **Task 3.5:** Organise a modelling workshop to bring together the modellers from all vector, public health and data teams.
The aim is to exchange knowledge, identify specific and generic modelling and data needs, foster cross-team collaboration, divide labour and plan activities. Activities under this heading in each subsequent year may involve either workshops or video-conferencing.

- **Task 3.6:** Identify with the vector, data and public health teams which vector species and VBD are the most relevant to assess introduction risk for. Review relevant introduction pathways and available data, Review the existing methods of assessment.
- **Task 3.7:** Task in service mode. Consultancy on process-based mathematical modelling, agent-based modelling, remote sensing techniques, statistical analysis of remotely-sensed data, mapping of $R_0$.

### TASKS SUBSEQUENT YEARS

- **Task 3.8** Update temporal Fourier MODIS database and process the time series (2001 – 2010) for signs of significant changes in key variables that are likely to favour the Introduction, Establishment or Spread of those diseases modelled inter alia under Task 3.4. This task will involve continuous updating of the image archives with MODIS and other data throughout the project lifetime. Final identification of areas of significant change; cautious forward prediction of areas of likely future changes, and therefore disease risks.
- **Task 3.9** Task in service mode. Based on the data collected on field sites common to various VBD and vectors (rodents, ticks) in a standardized fashion, investigate relations between the abundance, habitat suitability, and the key elements of VBD and environmental factors.
- **Task 3.10** Simulate spread in heterogeneous landscape under various conditions and for various types of vector, sample the results, and analyse them using inverse modelling. Apply the outcome of the analysis to a number of existing space-time vector distribution data sets.
- **Task 3.11** Review the literature on indicators of landscape permeability, and identify permeability and heterogeneity metrics. Quantify the relationship between those metrics and heterogeneity and rates of spread according to different VBD.
- **Task 3.12** Create a series of statistical models of vectors and diseases identified during year 1 as causing a significant Public Health threat. Examine ways in which such risk maps can be used by Public Health services to inform, rather than alarm, members of the public, and to inform front-line Public Health services (e.g. the General Practitioner community) of potential disease risks. Empirical relationships drawn from analysis carried at previous steps can be used to produce maps indicating which areas are most sensitive, and to feed models that can be in turn tested for scenarios of introduction and to evaluate the risk for Establishment and Spread.
- **Task 3.13** Integrated R0-mapping for periodic vector populations.
- **Task 3.14** Studying persistence mechanisms of VBD, including overwintering and dynamics in networks and/or metapopulations of hosts.
- **Task 3.15** Integrated R0-mapping under long-term environmental change scenarios.
- **Task 3.16** Recruit Public Health and other services to test the predictions of some of the models developed in years 1 and 2, e.g. with survey questionnaires to veterinarians and/or GPs; with targeted sero-surveys of intermediate hosts or of humans; or with targeted entomological surveys (e.g. in areas found to have changed ‘significantly’ under task 3.1) to look for vectors in new places. Examine how GPs, veterinarians and others have used any risk map or other predictions from the Modelling team in the previous years.
- **Task 3.17** Based on knowledge drawn in WP3.1 on risk of introduction and scenarios of change, results of the previous steps can be used to examine where conditions are most favourable for Introduction, Establishment, and Spread of vectors and VBD.
- **Task 3.18** Develop integrated generic spread models merging process-based, agent-based and remote-sensing approaches. Specific vectors and VBD will be used to guide the development, where the choice will be subject to data availability. Candidates to guide development are Aedes mosquitoes and their VBD.
- **Task 3.19** Make the concept of type-reproduction number T ready for practical use to assess effectiveness of intervention and control.
- **Task 3.20** Use models, $R_0$ and T to gauge the effectiveness of various intervention and control measures.
- **Task 3.21** Workshop or video conference of Modelling and Public Health teams to examine the impact of the results from the former team on the latter’s perception and use of predictions (maps, models, control suggestions etc.). Fine tuning of model outputs to bridge any gaps identified during the workshop.
- **Task 3.22** Predicting spread for various vectors and VBD.
- **Task 3.23** Writing scientific papers, contributions to scientific papers for other teams, and preparing PhD theses.
Contingency plan

We have learned from the experience of the EDEN project that one has to be flexible when data from a specific partner for a given generic development do not become available in time or are, usually due to (often field collection) problems beyond the control of the vector team, of poor quality. Generic development of tools in all parts of the work package can be done with several vector groups and VBD to guide us. We will communicate very frequently with all WP leaders to ensure that potential problems with either the availability and/or quality of data are identified in a timely fashion. When there are data problems for a specific partner for whom we work on a very specific modelling task, then deliverables for this task will have to be postponed (when data are delayed), or additional work, for example, using proxy data or performing sensitivity and uncertainty analysis, will be carried out. Because we envisage many requests by the vector and public health teams for support by the modelling team, we will ensure to flexibly switch between tasks when temporary data problems are encountered.

Milestones

ML3.1 Statistical analysis of data sampled from the simulated spread models outputs allow quantifying the original parameters used in the simulations (inverse modelling). This milestone depends on virtual experiments and hence does not depend on third party data, or on the availability of field collections – Means of verification. Quantitative statistical analysis identifies the correct parameters and simulation conditions.

ML3.2 Landscape heterogeneity indices are indicative of their permeability to the spread of VBD. This step will require using space-time empirical data on VBD spread from partners of the project – Means of verification. Statistical analysis of heterogeneity indices against i) simulated spread, and ii) empirical spread data of selected VBD showing a predictive power of those indices on the rate of spread.

ML3.3 Review of recent previous work on EDENext’s target diseases to identify the current state of knowledge of each, including the involvement of Public Health services in contributing to this knowledge base; and their understanding of, and their perception of the utility of, risk maps – Means of verification. A completed comprehensive review document, possibly for publication in an abbreviated form.

ML3.4 EDENext modelling-interaction workshop (several of these will be organised) – Means of verification. A brief report of the meeting, outlining the attendants, the program, the methods and problems discussed, an inventory of modelling needs for the various teams and a list of concrete plans and collaborative arrangements.

ML3.5 Models of spread that merge process-based, agent-based and remote sensing methods are constructed – Means of verification. A technical description of the integrated approach for an example vector species.

ML3.6 Public Health-Modelling-interaction workshop (several of these will be organised) – Means of verification. A brief report of the meeting, outlining the attendants, the program, the problems discussed, an inventory of threats relevant for introduction risk, an inventory of problems with model predictions, surveillance-related issues and preferences for prediction of intervention and control.

ML3.7 R0-integration for mapping scaled-up to country level and beyond – Means of verification. Publication that outlines the method and a first application.

Deliverables

D3.1 Review of the literature on spread models in heterogeneous landscape, and various environmental conditions, including those documented by remote sensing, and establishment of a modelling framework (M12).

D3.2 Report on the first EDENext modelling workshop (M 12).

D3.3 Technical report on R0-integration at country-level scale (M12).

D3.4 Report on the first Public health-modelling workshop (M12).

D3.5 Review of introduction pathways and methods of assessment, from literature (M18).

D3.6 Review of landscape permeability (M18).


D3.8 Report on second EDENext modelling workshop (M24).

D3.9 Report on second Public health-Modelling workshop (M30).

D3.10 Report on spread model simulations and statistical analysis of space-time sampled data (M36).

D3.11 Review on indicators of landscape heterogeneity and quantitative analysis of their relationship to rates of spread (M36).


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<td>D3.15</td>
<td>Two extended summaries of PhD theses on VBD modelling methodology with applications (M48).</td>
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Workpackage number | WP4.1
---|---
Starting date or starting event | M0

**Workpackage title** | DMT Service Component
---|---
**Activity type** | RTD

**Participant number** | 46
---|---
**Person-months** | 47

### Objectives
The objectives of the EDENext DMT service component are to:

- Develop and strengthen the data management ICT infrastructure established under EDEN.
- Acquire, transform, harmonise and update PAN-European spatial data sets of particular interest to the spatial epidemiology of vector-borne diseases.
- Develop spatial information systems to disseminate EDENext outputs and which establish the link with other spatial information systems such as ECDC E3 and VBORNET.
- Provide GIS and spatial data management training to EDENext partners.

### Description of work and role of participants

#### Background
The EDENext DMT Service Component is founded on using the experience of 5 years of providing data management and web archive functions for the EDEN project (www.edendatasite.com). The EDEN data site currently represents the state of the art in delivering data and related services to a broad network of partners involved in a specific set of research tasks and was recently (2009) earmarked by ECDC as an ideal basis to mirror their E3 initiative.

Given the valuable function its site has performed for EDEN, it is proposed to provide a similar service for EDENext, but with significantly wider remit. There are a number of possibilities for providing an enhanced service. These include:

- The spatial data archive will be further extended and particular attention will be given to (a) the development of data layers upon request by EDENext partners, (b) issues related to the longer term update of data layers, and (c) extension East to include new areas covered on an ad-hoc basis.
- The EDEN site was provided primarily for its members, and attracted those largely specialist users who found the site using search engines. Few specific efforts were made to collaborate with other EU funded projects and networks to incorporate information they produced, or to allow them access to public domain data acquired for EDEN. This is a major opportunity to improve the service provided.
- The training opportunities offered during EDEN were rudimentary. Here a structured GIS and spatial analysis training plan is proposed based on annual workshops and the development of distance learning tools.

#### Approach
This WP will be coordinated by Dr William Wint from Euro-AEGIS/ERGO with support from Euro-AEGIS ERGO staff and Euro-AEGIS/Avia-GIS staff. The following general approach will be developed respectively related to the objectives mentioned above:

**Data infrastructure:** Improvement of the ICT software infrastructure to ease access, and of the database structure to ease data selection, viewing and single click data access. Based on detailed use cases ICT improvements will be implemented. The EDENext DMT website will include the following parts: (a) a Spatial Data Query and Retrieval part, (b) a Training part, (c) a Science and Publication Directory part (d) a Link to VBORNET and E3 part, (e) a Links to WWW Resources part, and (e) an EDENext PhD part.

**Data acquisition:** Data mining to select and acquire area-wide spatial data sets as required, mostly through internet and based on the extensive worldwide networks of DMT. These data include (a) public domain data identified by DMT and EDENext partners, (b) specific data layers requested by EDENext partners and (c) data sets generated by EDENext partners. As part of this process data will be standardized and transformed to fit the needs of EDENext in particular and spatial epidemiological studies in general. In addition metadata sets will be compiled according to EDENext Inspire compatible standards and where necessary help and tutorial files will be made available.

**Information systems:** These will aim at disseminating spatial data and results from EDENext based on three main axes: (a) The queryable spatial Science and Publications Directory (SPD) to promote scientific collaborations in Europe using Google maps will further improved; (b) The Spatial geo-Explorer tool which enables to view and query the EDENext spatial data sets will be further improved to include commonly agreed new functions; (c) Links will be established with two major ECDC networks: VBORNET and E3.
Training: Establishment of a network of specialists from each WP and the organization of an annual workshop with a subsequent follow-up through distance learning (DL). In addition to DMT staff trainers from other WPs will also be encouraged to contribute. Workshops will be organized in June/July in Antwerp (Belgium) or Oxford (UK) for up to twenty participants who participate at their own expenses. Topics for exercises will address relevant EDEN objectives and will be jointly defined at the first workshop. It will include topics addressed in by the DMT research component in WP4.2. Particular attention will be given to the EDENext PhD network.

Work breakdown:
Most tasks from the EDENext DMT Service Component will be repeated each year.

TASKS YEAR 1
- Task 4.1.01: Improvement of DMT ICT infrastructure to strengthen safety and ease of access through the development and implementation of use cases.
- Task 4.1.02: Improvement of the DMT database structure to ease the selection and single click access to spatial data sets through the development and implementation of use cases.
- Task 4.1.03: Data mining, standardization and harmonization. Development of metadata as well as help files and tutorials as required.
- Task 4.1.04: Further development of the Queryable Science and Publications Directory Tool to include all relevant papers published by EDEN and EDENext partners.
- Task 4.1.05: Further development of the Spatial geo-Explorer Tool to include new spatial data sets and improved spatial query functionalities.
- Task 4.1.06: Establishing links and ensuring compatibility with the ECDC networks VBORNET and E3.
- Task 4.1.07: First three day workshop on GIS and spatial analysis (20 participants).
- Task 4.1.08: First distance learning follow-up course (20 participants).
- Task 4.1.09: Development and maintenance of the EDENext PhD website.

TASKS YEAR 2
- Task 4.1.10: Maintenance and further development of the DMT ICT infrastructure.
- Task 4.1.11: Maintenance and further development of the DMT database.
- Task 4.1.12: Data mining, standardization and harmonization. Development of metadata as well as help files and tutorials as required.
- Task 4.1.13: Maintenance and update of the Queryable Science and Publications Directory Tool to include all relevant papers published by EDEN and EDENext partners.
- Task 4.1.14: Maintenance and update of the Spatial geo-Explorer Tool to include new spatial data sets and improved spatial query functionalities.
- Task 4.1.15: Maintenance and further development of the links with the ECDC networks VBORNET and E3.
- Task 4.1.16: Annual three day workshop on GIS and spatial analysis (20 participants).
- Task 4.1.17: Annual distance learning follow-up course (20 participants).
- Task 4.1.18: Further development and maintenance of the EDENext PhD website.

TASKS YEAR 3
- Task 4.1.19: Maintenance and further development of the DMT ICT infrastructure.
- Task 4.1.20: Maintenance and further development of the DMT database.
- Task 4.1.21: Data mining, standardization and harmonization. Development of metadata as well as help files and tutorials as required.
- Task 4.1.22: Maintenance and update of the Queryable Science and Publications Directory Tool to include all relevant papers published by EDEN and EDENext partners.
- Task 4.1.23: Maintenance and update of the Spatial geo-Explorer Tool to include new spatial data sets and improved spatial query functionalities.
- Task 4.1.24: Maintenance and further development of the links with the ECDC networks VBORNET and E3.
- Task 4.1.25: Annual three day workshop on GIS and spatial analysis (20 participants).
- Task 4.1.26: Annual distance learning follow-up course (20 participants).
- Task 4.1.27: Further development and maintenance of the EDENext PhD website.

TASKS YEAR 4
- Task 4.1.28: Maintenance and further development of the DMT ICT infrastructure.
• Task 4.1.29: Maintenance and further development of the DMT database.
• Task 4.1.30: Data mining, standardization and harmonization. Development of metadata as well as help files and tutorials as required.
• Task 4.1.31: Maintenance and update of the Queryable Science and Publications Directory Tool to include all relevant papers published by EDEN and EDENext partners.
• Task 4.1.32: Maintenance and update of the Spatial geo-Explorer Tool to include new spatial data sets and improved spatial query functionalities.
• Task 4.1.33: Maintenance and further development of the links with the ECDC networks VBORNET and E3.
• Task 4.1.34: Last three day workshop on GIS and spatial analysis (20 participants).
• Task 4.1.35: Last distance learning follow-up course (20 participants).
• Task 4.1.36: Further development and maintenance of the EDENext PhD website.

Contingency plan

Data infrastructure: No particular risks identified except for hardware failure which may render access to the website impossible. To anticipate this all data will be rigorously back-upped and archived to mitigate the impact of hardware failure.

Data acquisition: The most likely barrier to success is failure to obtain timely responses and involvement from project partners. To anticipate this particular attention will be given to pro-actively seek inputs from EDENext partners at each EDENext AGM and during workshop/DL courses.

Information systems: Whilst we don’t anticipate major problems with the development of the SPD and Spatial geo-Explorer, the links with external information systems depends on their availability and the will of ECDC to continue its participation. This is mainly the case for the ECDC E3 network who is still at the concept stage.

Training: The success of this component is mainly depending on the will of EDENext partners to select GIS focal points who are willing and have the funds to participate to the annual training events. In addition attracting trainers from other EDENext groups outside DMT will contribute to improve the quality of these events. To anticipate this particular attention will be given to pro-actively seek inputs from EDENext partners at each EDENext AGM and during workshop/DL courses.

Milestones
The same set of milestones apply each year.

ML4.1.01 Information regarding specific data requirements is available from partners at AGM. Means of verification: list of data requirements posted on DMT website after each AGM.
ML4.1.02 Selected EDEN partners are willing to contribute as trainers to DMT first workshop. Means of verification: list of trainers posted on DMT website two months prior to each workshop.
ML4.1.03 EDEN partners select participants who are willing to participate to the proposed training cycle. Means of verification: list of workshop attendants posted on DMT website one month prior to each workshop.
ML4.1.04 Training materials are available to successfully conduct workshop. Means of verification: training material is posted on DMT website one week prior to each workshop.
ML4.1.05 Training materials are available to successfully conduct distance learning course. Means of verification: training material is posted on DMT website one week prior to start each distance learning course.

Deliverables
D4.1.01 First technical report on DMT infrastructure and content (M12).
D4.1.02 DVD with Spatial geo-Explorer and SPD to be distributed at AGM (M12).
D4.1.03 First technical report on training activities and developed training materials (M12).
D4.1.04 Second technical report on DMT infrastructure and content (M24).
D4.1.05 Updated DVD with Spatial geo-Explorer and SPD to be distributed at AGM (M24).
D4.1.06 Second technical report on training activities and developed training materials (M24).
D4.1.07 Third technical report on DMT infrastructure and content (M36).
D4.1.08 Updated DVD with Spatial geo-Explorer and SPD to be distributed at AGM (M36).
D4.1.09 Third technical report on training activities and developed training materials (M36).
D4.1.10 Last technical report on DMT infrastructure and content (M48).
<table>
<thead>
<tr>
<th>D4.1.11</th>
<th>Final DVD with Spatial geo-Explorer and SPD to be distributed at AGM (M48).</th>
</tr>
</thead>
<tbody>
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<td>D4.1.12</td>
<td>Last technical report on training activities and developed training materials (M48).</td>
</tr>
<tr>
<td>Workpackage number</td>
<td>WP4.2</td>
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<td>--------------------</td>
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<td><strong>Activity type</strong></td>
<td>RTD</td>
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<td><strong>Participant number</strong></td>
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<tr>
<td><strong>Person-months</strong></td>
<td>47</td>
</tr>
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</table>

**Objectives**
The objectives of the DMT research component are to:
- Develop area-wide (Pan-EU) host distribution/biodiversity maps and models.
- Develop fourth generation wind spread models for midge-borne diseases based on the experience of DMT and in close collaboration with the MOD (spread-component) and CBD groups.

**Description of work and role of participants**

**Background**
Given confirmed expertise EDENext DMT partners will focus on the two main research topics mentioned in the objectives.

**Host distribution.** It is axiomatic that the availability of disease and vector hosts affects the distribution of both vector and disease, and that a number of host species might be involved in disease transmission, for example, as primary hosts, (wildlife) reservoirs, or hosts of the vectors. A knowledge of host numbers is also required as the denominator needed to quantify disease occurrence in terms of incidence or prevalence. EDENext partners will therefore need access to host distribution data in order to properly evaluate disease risk and to assess both actual and potential vector distributions. There is thus a strong case for acquiring standardised and consistent information about host and denominators in formats that are appropriate for both the Integration and Vector groups.

Specifically, the following currently existing data gaps will be addressed:
- Human population numbers. Though available from regular census, these data are rarely in the public domain at an appropriate resolution, and will require substantial effort to acquire, and standardize for the whole project area;
- Domesticated livestock, including pets: Most European countries conduct agricultural surveys, but the data are not widely available in the public domain at anything below province level, which is not sufficient for disease risk or vector distribution assessments. Information about dogs is patchy and inconsistent.
- Vector and reservoir wildlife hosts: Primarily large or small mammals and birds, there is a large range of potential or actual hosts for the EDENext diseases. Whilst the ranges of most wildlife species are known in Europe, the variation in abundance is much less certain, as demonstrated by the data collected for Tick and Rodent borne disease hosts during the EDEN project.

**Wind spread models.** It has been shown that in temperate Europe wind is a driving factor of the spread of midge transmitted bluetongue virus (BTV). While currently available wind spread models correctly predict the observed spatial and temporal distribution of cases, results also indicate that other factors might influence the disease transmission such as: topography, land cover patterns and whether the vector is capable of survival to bite new hosts after wind dispersal.

Specifically, the following knowledge gaps will be addressed:
- Quantification of the relationship between topography and disease transmission.
- Assessment of the impact of habitat/landscape at 'touch down' on Culicoides survival.
- Integration of the obtained results in the existing predictive wind spread model for BTV.

**Approach**
This WP will be coordinated by Dr Guy Hendrickx from Euro-AEGIS/Avia-GIS with support from Euro-AEGIS/Avia-GIS staff, Euro-AEGIS/ERGO staff and FLI staff, as well as in close collaboration respectively with the MOD (low-resolution component) group, MOD (spread-component) group and CBD group.

**Host distribution.** The proposed work will be implemented in a three phases:
1. A detailed assessment of the requirements of each Integrated and Vector Group. These will almost certainly include human and livestock populations, as well as dogs, and deer, wild boar and selected rodents, and some bird species.
2. A wide ranging search for data available for each host species identified in phase 1, using sources from the
Wind spread models. The proposed work will be part of a PhD project and implemented in three phases:

1. Epidemiological analyses of the recent (2006-2009) BTV8 and BTV1 epidemics in temperate Europe have shown that changes in topography reduce the speed of the spread of the disease, but does not preclude disease spread. It is assumed that changes in topography induce wind turbulence, which in turn will induce Culicoides drop-down. This is anticipated to increase the risk of drop down of possibly infected midges and therefore leads to a higher case morbidity, given the presence of host and suitable habitat. In order to fully investigate this, high resolution wind data will be used to quantitatively estimate the wind turbulences induced by topography. This data will be cross-referenced with estimations of case data and where available with vector abundance data. Given this, thresholds will be defined when topography induces higher transmission and the reduction in speed of disease spread will be established. This will be investigated using data from the 2006 and 2007 BTV8 outbreaks in the Ruhr area in Germany, and from the 2008 BTV1 outbreak South-West from the Massif Central in France. These data are available to DMT.

2. A second series of factors that slow down BTV spread are related to the transmission risk at ‘drop down’, i.e. host availability and habitat condition. Host availability is already taken into account into the model but preliminary research has shown that land cover patterns are also important for vector establishment. It was shown that a combination of forest and pasture patches is favouring the establishment of BTV outbreaks. The same has been observed from traps placed along transects located between farms and forest. This relationship will be quantified. Land cover patterns will be estimated using landscape metrics. These metrics will be used in a spatio-temporal analysis. After statistical analysis the highest impact metrics will be retrieved. This will be investigated using data from the 2006 and 2007 BTV8 outbreaks in the central part of The Netherlands. These data are available to DMT.

3. The current predictive model predicts both the local autonomous spread as well as the medium-distance wind spread. This model will be further extended to include the impact of topography during the wind dispersal and the possible risk of establishment after landing. The potential of this model regarding the introduction, establishment and spread of other midge-borne viruses will be assessed.

Work breakdown:

**TASKS YEAR 1**
- Task 4.2.01: Assessment of the requirements from EDENext partners regarding area-wide host distribution data. A complete list of all host distribution requirements by all EDENext partners will be established during the first months of the project.
- Task 4.2.02: Establishment of a database and distribution maps collating all available information on the distribution of selected priority hosts in Europe. Based on the established list and available data a distinction will be made between first and second priority hosts. During this year priority will be given to first priority hosts.
- Task 4.2.03: Analysis of the “impact of slope” on the establishment and spread of midge-borne BTV outbreaks using data from the 2006 and 2007 BTV8 outbreaks in the Ruhr area in Germany, and from the 2008 BTV1 outbreak South-West from the Massif Central in France.

**TASKS YEAR 2**
- Task 4.2.04: Development of distribution and biodiversity models for first priority hosts. This work will include contributions to relevant spatial analysis studies initiated by other EDENext groups.
- Task 4.2.05: Consolidation of the host distribution database and maps with focus on second priority hosts.
- Task 4.2.06: Analysis of the “landscape factors” affecting BTV transmission risk at ‘drop down’ using data from the literature, available data through EDEN and from EDENext partners and through establishing collaborations with existing networks: e.g. VBORNET – Vector distribution, IUCN – Wildlife distribution, FAO – Livestock distribution. Aspects of host populations that might affect disease transmission, such as age and sex ratios will be included in the data searches. Attempts may also be made to locate indicators of movement that might be relevant to disease introductions and spread.

3. Where host or disease denominator information required by the Vector and Integrations groups is found to be unavailable, patchy or incomplete, it will be necessary to fill the gaps in a number of different ways: (a) to produce statistical distribution models; (b) to construct and map habitat suitability datasets or (c) to compile proxy indices of such parameters as biodiversity.

The statistical methods used will be based on a number of long established distribution modelling methods such as regression trees, or logistic and multivariate regression methods, all widely used to produce disease, host and vector distribution maps, possibly using zoned analyses and error estimation techniques based either on the application of bootstrapping or repeated modelling using covariate parameters determined by the statistical variability of the parameter values as determined by the modelling process. The outputs will therefore include not only aspects of host distributions, but also quantified indication of the reliability of the distribution models produced.
2006 and 2007 BTV8 outbreaks in the central part of The Netherlands.

TASKS YEAR 3

- Task 4.2.07: Development of distribution and biodiversity models for second priority hosts. This work will include contributions to relevant spatial analysis studies initiated by other EDENext groups.
- Task 4.2.08: Consolidation of the host distribution database and maps.
- Task 4.2.09: Integration of the “slope” and “landscape” factors in the predictive BTV-spread model.

TASKS YEAR 4

- Task 4.2.10: Publication of relevant host distribution and biodiversity model outputs. At this stage it is not possible to detail this more. It will also include contributions to papers initiated by other EDENext groups.
- Task 4.2.11: Publication of the results of the “slope factor” study.
- Task 4.2.12: Publication of the results of the “landscape factor” study.
- Task 4.2.13: Publication of the improved BTV-spread model.

Contingency plan

Host distribution. The most likely barrier to success is failure to obtain timely responses and involvement from project partners. To anticipate this particular attention will be given to pro-actively seek inputs from EDENext partners at each EDENext AGM and during the workshops and DL courses organized as part of WP4.1.

Furthermore this part of WP4.2 will also be highly dependent on the availability of external information resources. To anticipate data gaps the DMT networks will be further extended to include data source overlaps.

Wind spread models. All necessary BTV outbreak data are available to DMT prior to the start of EDENext through existing collaboration networks. In this study two additional types of data will be requested: vector presence and abundance data and landscape data of the areas under study. Contacts will be established and collaborations will be proposed to teams which operate(d) in the areas under study. If raw data are not made available, published results will be used.

Milestones

ML4.2.01: Information regarding specific data requirements is available from partners at AGM. Means of verification: list of data requirements posted on DMT website after each AGM.
ML4.2.02: High resolution wind data are processed to prepare for the “impact of slope” study. Means of verification: data posted on DMT website.
ML4.2.03: Vector data are available to prepare for “impact of slope” and “landscape factor” studies. Means of verification: collaboration agreements with research partners.
ML4.2.04: Landcover data are available at sufficient resolution (15m) in pilot area in The Netherlands to prepare for “landscape factor” study. Means of verification: collaboration agreement with research partner.
ML4.2.05: Technical reports are available in the right format to prepare for publication of results in the last year. Means of verification: Deliverables year 1-2-3.

Deliverables

D4.2.01: Technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts (M12).
D4.2.02: Technical report on the results of the “slope factor” study (M12).
D4.2.03: Updated technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts (M24).
D4.2.04: Technical report on distribution and biodiversity models of selected first priority hosts (M24).
D4.2.05: Technical report on the results of the “landscape factor” study (M24).
D4.2.06: Updated technical report on the available host distribution and biodiversity data in Europe for selected first and second priority hosts (M36).
D4.2.07: Technical report on distribution and biodiversity models of selected second priority hosts (M36).
D4.2.08: Technical report on the improved wind-spread model (M36).
D4.2.09: Relevant host distribution/biodiversity papers (M48).
D4.2.10: Slope factor paper (M48).
D4.2.11: Landscape factor paper (M48).
D4.2.12: Improved BTV-spread model paper (M48).
Workpackage number | WP5.1
---|---
Workpackage title | PH VBD Definition
Starting date or starting event | M0
Activity type | RTD
Participant number | FLI | SINE | RKI
Person-months | 18 | 4 | 12

**Objectives**

The objectives of this work package are to:

1. Define public health (PH) with particular reference to the different vector groups addressed by EDENext.
2. Clarify the role of PH in the framework of existing or emerging human and veterinary vector-borne disease (VBD) threats in Europe.

**Description of work and role of participants**

**Background**

Due to environmental and economic changes, emerging diseases with zoonotic potential will be an increasing challenge for PH in Europe. The risks and the consequences triggered by vector-borne diseases for public health in Europe are just starting to emerge in public awareness. This is clearly shown by recent events such as Chikungunya in Italy and the spread of CCHF in Europe. Whilst all agree on the importance of this topic on PH in future, this has as yet not clearly been defined. It is therefore considered essential to develop within EDENext a commonly shared definition of PH with particular reference to VBDs.

The baseline for all PH activities is to develop a common and generally accepted understanding (leading to definitions) of public health issues within the consortium so that all partners speak the same language. Such a basis will be essential to reveal vector-borne disease associated PH risks and attempt to qualify and perhaps even quantify them (see also WP 5.2 and 5.3).

**Approach**

To achieve the objectives of this WP a stepwise approach will be adopted. First an in-depth literature review will be conducted with focus on the interface between PH and emerging VBD treats. Particular attention will be given to the current position of national and international (WHO, OIE, FAO, ECDC, EFSA) public-health organisations and networks (VBORNET). Based on this review a draft white paper will be prepared, which will be discussed with the EDENext SC and AG members. During this process various versions of the draft document will be circulated within the EDENext vector groups to comment on vector specific issues.

This WP will be coordinated by FLI with inputs from SINE and RKI. The EDEN SC, AG and project partners will provide comments on document outputs.

**Work breakdown:**

**TASKS YEAR 1**

- Task 5.1.1: Literature review of PH in VBD.
- Task 5.1.2: First draft White Paper on PH in VBD.
- Task 5.1.3: Discussion first draft White Paper at mid-term SC meeting.
- Task 5.1.4: Second draft White Paper and circulation to EDENext partners for comments.

**TASKS SUBSEQUENT YEARS**

- Task 5.1.5: Third draft White Paper and discussion with AG at first EDENext annual meeting (AGM).
- Task 5.1.6: Final version of PH White Paper.

Work in WP 5.1 will be coordinated by FLI with additional inputs from SINE and RKI. The EDENext SC, AG and consortium partners will comment on report drafts and give expert input on particular VBD.
<table>
<thead>
<tr>
<th>Contingency plan</th>
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<tbody>
<tr>
<td>Both literature review and first draft White Paper on PH rely on direct inputs from PH-group partners. No problems are anticipated in that perspective.</td>
</tr>
<tr>
<td>Once the first draft has been produced the subsequent versions will heavily depend on inputs from other EDENext partners.</td>
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<tr>
<td>o To ensure the inputs by the SC and AG are provided, time will be allocated for discussion as part of the agenda of respectively the mid-term SC meeting and AGM.</td>
</tr>
<tr>
<td>o To ensure inputs are provided by other EDENext partners, partners from institutions with particular back-ground on PH related issues, will be contacted personally.</td>
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<thead>
<tr>
<th>Milestones</th>
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<tr>
<td>ML5.1.1: PH literature review is available. Means of verification: Publication on EDENext website.</td>
</tr>
<tr>
<td>ML5.1.2: Draft PH White Paper is available prior to mid-term EDEN SC meeting. Means of verification: Publication on EDENext website.</td>
</tr>
<tr>
<td>ML5.1.3: Draft PH White Paper is available prior to AGM. Means of verification: Publication on EDENext website.</td>
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<tr>
<th>Deliverables</th>
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<tbody>
<tr>
<td>D5.1.1: PH White Paper on VBD (M18).</td>
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</table>
Objectives
The objectives of this work package are to

1. Study the risk perception of stakeholders for two selected VBDs (CCHF and NE) of particular importance to PH in five representative EU countries.
2. Identify which information on risk communication is considered useful, helpful and adequate both by the public and PH professionals within the examined countries.
3. Formulate recommendations for the European Commission and the risk managers in the Member States on adequate communication of the implications of vector-borne diseases in the context of climate change for public health.

Background
PH agencies are confronted to the necessity of an adequate response in regard to risk communication. Due to the complexity of the diseases and the interdependence of international PH systems, involving governmental as well as non-governmental agencies and bodies, a sensible approach forward can only be by a participatory approach that includes all key players in the field of PH. In order to come up with a robust risk communication strategy for Europe, we have to take into account public risk perceptions in regard to vector-borne diseases. What does the public know about the diseases? What is their perception of the risk? Which diseases were already identified as relevant? What does the public know about actual preventative measures in regard to vector-borne diseases? What are considered to be sensible and relevant channels for risk communication? Etc. All these kind of questions have to be addressed before a risk communication strategy can be developed. Hence, a risk perception study in regard to vectors of human and veterinary infections, so far lacking, is a necessary pre-condition for an adequate risk communication approach.

Risk communication research has clearly shown that as long as political decisions on health risks are based on sound science knowledge, where knowledge gaps or limitations are equally addressed, the public will go along with it. Therefore, risk assessment of the identified risk factors and furthermore, a urgently needed harmonization and standardization in regard to diagnostic tools in the field is another prerequisite for the development of a risk communication strategy on vector-borne diseases.

Approach
A social scientific risk perception & risk communication study on EDENext diseases will be performed within WP5.2 that will focus on the risk perception of, knowledge about, behaviour in regard to, information behaviour/information expectations in regard to emerging diseases of EDENext context.

Knowledge about the risk perception of the public and concerned stakeholders will not only contribute to the improvement and consolidation of the knowledge base, but will also profoundly constitute an excellent basis for robust, adequate, and meaningful risk communication.

The risk perception of the public will be assessed by conducting interviews under standardised conditions with actors at the macro-, meso- and micro-level. The following actors will be involved:

- **Macro-level**: Public (Health) Authorities, concerned ministries of five selected Member States,
- **Meso-level**: Farming Organisation (NFU, etc.), Consumer Associations, non-governmental veterinary and medical societies of selected Member States, such as the European Public Health Alliance (EPHA) or the Federation of Veterinarians of Europe (FVE),
- **Micro-level**: focus groups with the public.

In total about 50-60 (10-12 per country) interviews will be conducted in the five selected countries on the macro- and meso-level and three focus group surveys with about 8-10 attendees each in the five selected countries will be carried out on the micro-level. National peculiarities in the management of existing and emerging diseases, institutional arrangements on VBD, best practice in regard to risk communication will be examined.
Work breakdown:

TASKS YEAR 1

Task 5.2.1: To examine existing relevant literature on risk perception on risk communication (12 Mon)

Task 5.2.2: Macro-, meso- and micro-level: To develop and agree upon guidelines for conducting the interviews with the stakeholders (6-12 Mon)

Task 5.2.3: Macro- and meso-level: In-depth interviews with stakeholders will be conducted within in the first of five selected countries (12-18 Mon)

Task 5.2.4: Micro-level: Conduct three focus groups interviews (about 8-10 attendees each) within the first of the five selected countries (12-18 Mon)

TASKS SUBSEQUENT YEARS

Task 5.2.5: Macro- and meso-level: In-depth interviews with stakeholders will be conducted within in the second and third of five selected countries (18-30 Mon)

Task 5.2.6: Micro-level: Conduct three focus groups (about 8-10 attendees each) within the second and third of the five selected countries (18-30 Mon)

Task 5.2.7: Macro- and meso-level: In-depth interviews with stakeholders will be conducted within in the forth and fifth of five selected countries (30-42 Mon)

Task 5.2.8: Micro-level: Conduct three focus groups interviews (about 8-10 attendees each) within the forth and fifth of the five selected countries (30-42 Mon)

Task 5.2.9: Analysis of the interviews of the macro and meso-group by country and between countries (12-48 Mon)

Task 5.2.10: Intra- and inter-focus group analysis per country and comparative analysis between countries (36-48 Mon)

WP 5.2 will be coordinated and performed by SINE with inputs from FLI and RKI. The EDEN SC, AGM and project partners will comment on draft interview guidelines and assist in identifying concerned interviewees within the selected countries.

Contingency plan

The success of this work package will be evaluated at an internal review after 18 months by the three PH participants taking into account the availability and accessibility of the involved actors and the standardized interview procedure itself.

In case that not enough interviewees agree to be interviewed, the EDENext Steering Committee and the Advisory Group will be consulted for advice.

Milestones

ML5.2.1 Internal review after 18 months carried out by the three PH participants. Results are compiled in a report. Means of verification: Publication on EDENext website.

M 5.2.2: First 10-12 interviews with stakeholders (macro- and meso-level completed (M12)

M 5.2.3: First three focus group surveys in the first country conducted (M12)

M 5.2.4: Next 20-24 interviews with stakeholders (macro- and meso-level) completed (M24)

M 5.2.5: Next six three focus group surveys in another two countries conducted (M24)

M 5.2.6: Last 20-24 interviews with stakeholders (macro- and meso-level) completed (M36)

M 5.2.7: Last six three focus group surveys in another two countries conducted (M36)

Deliverables

D 5.2.1: Relevant literature on risk perception and risk communication examined. Report on EDENext website (M12)

D 5.2.2: Guidelines for conducting the interviews with the stakeholders are developed (M12)

D 5.2.3: Comparative report on the risk perception of stakeholders, based on the analysis of the interviews results, completed (M48)

D 5.2.4: Comparative report on the risk perception of the public, based on the analysis of the focus groups, completed (M48)

D 5.2.5: Scientific publication of the results in international journals (scientific, social scientific and PH specific) (M48)

| Workpackage number | WP5.3 | Starting date or starting event | M6 |
Workpackage title | PH VBD Risk Communication and Control Strategy
---|---
Activity type | RTD
Participant number | FLI SINE RKI
Person-months | 18 6 12

**Objectives**
- Compile already existing risk assessments and conduct of a meta-risk assessment for VBD based on the new results obtained in the vertical VBD WPs with special emphasis on CCHF and Hanta viruses
- Standardize and harmonize diagnostic techniques tools for VBD in European laboratories outside of the consortium by involvement of ENIVD
- Development of information material for the public and for professionals and distribution of this material through adequate channels

**Description of work and role of participants**

**Background**
Several risk assessments on VBDs have been conducted in the past. These assessments have primarily addressed issues like the likelihood of the introduction, spread and perpetuation of VBDs in a new environment and only to a lesser extent identified risks and consequences (including their magnitude) posed by outbreaks of emerging diseases to public health (Heyman et al 2006, Maltezou et al. 2009). This includes that PH issues in regard to risk perception and communication strategies have not been part of such assessments. Based on the knowledge obtained in WP 5.2, meta-risk assessments are missing which not only compile and update the data from existing risk assessments, but also include risk communication and control strategies by informing the and seeking the collaboration of the public so that e.g. effective personal risk minimization measures can be introduced.

Since the last couple of years the infection with Hanta and CCHF viruses has received considerable scientific and public attention. Hanta viruses are causing increasing numbers of cases in several areas in Europe which has prompted better awareness of the physicians and perhaps led to a better clinical detection of cases. Also for CCHF the recent outbreak in Turkey and a case in Greece put a focus on this highly pathogenic disease. As stressed above serious risk assessments for both diseases considering the introduced PH measures are missing or at best deleterious. In particular the risk for visitors entering the endemic areas has hardly been addressed and how such risks could be controlled by appropriate information of these travellers on personal protective measures. Moreover, based on the serious analysis of the reported cases in the coming years it should be possible to describe an improved risk analysis for people staying in the endemic areas for a certain time.

A risk communication and control strategy for these two diseases will therefore be developed that will be more than just (professional) PR, but will be based on actual and solid knowledge about risk perception and information behaviour in regard to vector-borne diseases of relevant societal groups gathered in WP 5.2. This applied knowledge will lead to the development of comprehensive and scientifically sound brochures for CCHF and Hanta viruses for the information of the general public, including messages and recommendations for how to behave in case of outbreak situations. Similarly, science based leaflets on these two vector-borne infections will be provided for the information of professionals in the field of public and animal health.

There are many open questions in regard to the surveillance of VBD in many, if not most countries/areas in Europe. This is due to missing technical capacities and funding for such studies but frequently also to the lack of recommendations for diagnostic methods and tools (leading to standardisation) and for biosafety requirements and quality control. The European ‘Network for Imported Virus diseases (ENIVD)’ which is coordinated by RKI (Prof. M. Niedrig, EDENext partner 40) is a private initiative of directors of well recognized diagnostic and research laboratories. ENIVD collaborates closely with ECDC, WHO and CDC. ENIVD members provide mutual help in the exchange of diagnostic samples, i.e. sera, viruses, methods, and information. ENIVD intends to identify laboratories, capable and willing to perform rapid diagnostics (<24h) of an acute case, suspected to be infected with a viral haemorrhagic fever caused e.g. by CCHF and hanta viruses.

*Paul Heyman, Antti Vaheeri and the ENIVD members* **Situation of Hantavirus Infections and Haemorrhagic fever with Renal Syndrome in European Countries as of December 2006. Eurosurveillance 2008;13(28)**

There will be three approaches to meet these objectives:

- Already existing risk assessments for VBD will be compiled and compared in regard to the identification and definition of risk factors. Special emphasis will be laid on CCHF as a TBD and Hanta viruses as VBDs. Based on these assessments and the expertise in the vertical VBD WPs a meta-risk assessment will be carried out. In this context an intensive collaboration with other players such as the EpiSouth\(^3\), EpiNorth\(^4\) and the ECDC funded VBORNET consortia will be sought as well as with other nationally or EU funded research consortia/groups (such as Arbozoonet). Other actors will be ECDC, EFSA (BIOHAZ panel) and EMEA.

- Standardize and harmonize among participants diagnostic tools by involvement of ENIVD. EDENext will take advantage of ENIVD by channelling the diagnostic expertise obtained in the vertical WPs on VBD to external surveillance laboratories in areas supposedly at risk. This activity will be carried out in close collaboration with the ROINBO and TBD groups, who develop and standardize their diagnostic methodologies for their activities. The here proposed activity will go beyond these activities by transferring knowledge via technical workshops and by written technical recommendations to interested local diagnostic laboratories from all over Europe.

- Prepare information material (leaflets and brochures which will be also put on the Internet) for the public and for professionals in English language and make them available to national stakeholders, public authorities, via the internet and NGOs for translation and distribution. Farming Organisation (NFU, etc.), Consumer Associations, non-governmental veterinary and medical societies of selected Member States, such as the European Public Health Alliance (EPHA) or the Federation of Veterinarians of Europe (FVE).

**Work breakdown:**

**TASKS YEAR 1**

- Task 5.3.1: Analysis of already existing risk communication material and comparison with the results of the risk perception/risk communication study (M0-6)
- Task 5.3.2: Targeted risk assessment workshops on CCHF and Hanta viruses in endemic areas together with representatives and scientific experts from these regions in two expert meetings (M6-12)

**TASKS SUBSEQUENT YEARS**

- Task 5.3.3: Collect the data for the present state of the art diagnostic for Hanta and CCHF infections. Therefore arrange a close collaboration with the ENIVD network for the evaluation of the diagnostic quality and preparedness by European laboratories M12-30
- Task 5.3.4: Provide advice for the best diagnostic approach for the acute and convalescent Hanta and CCHF diagnostic for Europe and Turkey M24-48
- Task 5.3.5: Analyse the existing knowledge of local physicians for the CCHF and Hantavirus infections in endemic areas (Turkey for CCHF, South-western Germany for Hanta-viruses (areas proposed -- to be confirmed later)), also considering differential diagnostics of other diseases. This will be performed by carrying out a questionnaire study. M24-30
- Task 5.3.6: Analysis of the diagnostic capacities and quality for Hanta and CCHF in all European countries including Turkey by questionnaire M30-42.
- Task 5.3.7: Implementation of risk perception and risk communication knowledge (WP 5.2) within information leaflets and brochures (both in English language as model for copy right free external translations) based on sound science knowledge and communicated in plain, basic language (factual, straight forward, regular and appropriate to the risk in simple, clear, comprehensible and understandable messages) M30-42
- Task 5.3.8: Distribution of leaflets by public (health) authorities and departments, ministries, medical and veterinary associations, farming associations, consumer associations. M30-48

WP 5.3 will be coordinated and performed by RKI with inputs from sine and FLI.

**Contingency plan**

The success of this WP depends on the collaboration of the PH WP with the EDENext ROINBO and TBD groups on the one side and on the willingness and contributions by external partners/interviewees on the other. While difficulties in the

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3 http://www.episouth.org/

4 http://www.epinorth.org/
interaction with the latter externals must be dealt with individually, the inter WP-interactions are at least facilitated by the fact that FLI is contributing to all three groups and can act as a sort of ‘transformation belt’.

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<tr>
<td>M5.3.1: Already existing risk assessments compiled and analysed in regard to risk perception / risk communication (M6)</td>
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<tr>
<td>M5.3.2: Two targeted risk assessment workshops on CCHF and on Hanta viruses in endemic areas together with representatives and scientific experts will be conducted (M12)</td>
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<td>M5.3.4: Questionaire study on the diagnostic capacities and quality for Hanta and CCHF in all European countries including Turkey completed. M24</td>
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<tr>
<td>M5.3.5: Collection of the data for the present state of the art for the diagnosis of Hanta and CCHF infections completed. M30</td>
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<td>M5.3.6: Questionaire study on the existing knowledge of local physicians for the CCHF and Hantavirus infections in two endemic areas conducted. M30</td>
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<td>M5.3.7: Recommendations for the best diagnostic approaches for the acute and convalescent Hanta and CCHF diagnostic for Europe and Turkey are elaborated. M36</td>
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<td>M5.3.8: Leaflets and brochures implementing risk perception and risk communication knowledge (WP 5.2) for the public as well as for professionals have been worked out M42</td>
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<tr>
<td>M5.3.9: Distribution of leaflets and/or brochures by public (health) authorities and departments, ministries, medical and veterinary associations, farming associations, consumer associations and via internet on EDENext website. Start M42</td>
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<tr>
<td>D5.3.1: Report on already existing risk assessments for CCHF and Hantavirus infections ‘meta-analysis’ M12</td>
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<td>D5.3.2: Harmonized CCHF and Hanta virus diagnostic protocols the diagnostic laboratories (incl. involved ENIVD laboratories). Report to Steering committee and publication on EDENext website. M24</td>
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<tr>
<td>D5.3.3: Collection of the data for the present state of the art for the diagnosis of Hanta and CCHF infections completed. M30</td>
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<tr>
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### Workpackage number
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### Workpackage title
| Coordination |

### Activity type
| MGT |

### Participant number
| 1 |

### Person-months
| 110 |

#### Objectives
The objectives of this work package are to:
1. Ensure the efficient management of the project so that it meets its objectives.
2. Networking and liaison within the consortium.
3. Promotion of international partnerships.
4. Promote the dissemination of project results.

#### Description of work and role of participants

##### Approach
To enable the efficient coordination of EDENext, the project has been divided in five VBD groups (TBD, RBD, MBD, PhBD, CBD) and three Integration groups (MOD, DMT, PH). Each group is led by a group leader and its deputy, which funnel all communication between EDENext partners and the Project Coordinator. All group leaders and their deputies are members of the EDENext steering committee (SC). When necessary, some members of the advisory group (AG) may be invited to SC, for inputs on specific questions.

The coordination structure of EDENext and its governing bodies are detailed in section 2.1 (Consortium governance and management). The coordinator ensures the scientific coordination of the project in collaboration with the SC chairman. The scientific strategy is revised at each annual general meeting with inputs from the AG. The AG is also consulted for the design and implementation of large-scale research activities involving several countries.

The coordinator supervises the management of EDENext which is achieved, on a daily basis, by a full-time administrative and financial officer. All scientific coordination and management tasks are supported by the project secretariat.

The coordinator is in charge of liaison with EU and of representing EDENext in international workshops and events. An internal peer-review system, with numbering of manuscripts, will be established to validate by the steering committee all scientific publications released under EDENext.

The presentation of scientific results will be central to all annual meetings, to which representatives from the advisory group, as well as projects and networks related to EDENext will be invited.

##### Work breakdown:

**TASKS YEAR 1**
- Task 6.01: Establishment and maintenance of an efficient Management Structure and Plan.
- Task 6.02: Establishment and maintenance of EDENext website, leaflet and poster.
- Task 6.03: Establishment and maintenance of the internal peer review system and abstract reporting.
- Task 6.04: Representing EDENext on ad-hoc basis in international workshops and events.
- Task 6.05: Organization of the Kick-Off Meeting (KOM).
- Task 6.06: Organization of three annual Steering Committee (SC) meetings.
- Task 6.07: Compilation and submission of the periodic activity and management reports.

**TASKS YEAR 2**
- Task 6.08: Organization of the annual general meeting (AGM).
- Task 6.09: Organization of three annual SC meetings.
- Task 6.10: Compilation and submission of the periodic activity and management reports.
### TASKS YEAR 3
- Task 6.11: Organization of the annual Project meeting (AGM).
- Task 6.12: Organization of three annual SC meetings.
- Task 6.13: Compilation and submission of the periodic activity and management reports.

### TASKS YEAR 4
- Task 6.14: Organization of the annual Project meeting (AGM).
- Task 6.15: Organization of three annual Steering Committee (SC) meetings.
- Task 6.16: Compilation and submission of the periodic activity and management reports.

### Contingency plan
The large number of partners of a project such as EDENext is a management risk. To mitigate this risk the project has been divided in a series of vertical and horizontal groups. Each group member reports to its group leader, and group leaders report to the coordinator. The project thus de facto operates as a cluster of integrated research projects.

To mitigate the risk of a link missing in this chain of command, each Group Leader is supported by a Deputy. To ensure that the information is shared both have been actively involved in the preparation of EDENext and both are entitled to participate to the SC meetings.

To ensure timely delivery of contributions for the annual reports the same chain of command will be followed. The Coordinator provides the Group Leaders with templates adapted to each Group two months prior to the delivery date of the periodic activity report, the Group Leaders compile the respective inputs of their Group members and transfer Group reports to the Coordinator, who compiles the periodic activity for submission to Brussels. Detailed procedures will be described in the Management Plan.

### Milestones
The same set of milestones applies each year.
- ML6.01: Contributions to the periodic activity report are available from each Group each year.
- ML6.02: Annual meetings are attended by $\geq 100$ scientists involved in EDENext, including $\geq 20$ PhD students.
- ML6.03: The frequency of SC is maintained each year.
- ML6.04: No payment delay $\geq 6$ months is observed because of coordination / management issues.

### Deliverables
**YEAR 1**
- D6.01: EDENext management plan (M1).
- D6.02: EDENext website, leaflet and poster (M2 + timely updates).
- D6.03: EDENext KOM (= first AGM) report (M3).
- D6.04: EDENext SC meeting reports for the first year (M3-6-9).
- D6.05: EDENext first scientific and financial report (M12).

**YEAR 2**
- D6.06: EDENext second AGM report (M15).
- D6.07: EDENext SC Meeting reports for the second year (M15-18-21).
- D6.08: EDENext second scientific and financial report (M24).

**YEAR 3**
- D6.09: EDENext third AGM report (M27).
- D6.10: EDENext SC Meeting reports for the third year (M27-30-33).
- D6.11: EDENext third scientific and financial report (M36).

**YEAR 4**
- D6.14: EDENext fourth scientific and financial report (M48).
- D6.15: Proceedings of the EDENext International Conference (M48).
### 1.3.3.5  Staff effort

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A detailed Milestone list is given per Work Package

WP1.1.1
ML 1.1.1: First meeting to define field and laboratory protocols. Means of verification: a document agreed and signed in by all partners.

ML 1.1.2: Definition of collection sites. Means of verification: collection site database (Q1)

ML 1.1.3: All molecular, serological and experimental protocols standardized and optimized in participating laboratories: adoption of contingency methods if necessary. Means of verification: reports to coordinator (Q12)

ML 1.1.4: End of first year of tick and host sampling: evaluation of sampling sites. Means of verification: sample database.

ML 1.1.5: End of second year of tick and host sampling: evaluation of sampling sites and decision to extend sampling into third year to fill gaps. Means of verification: sample database.

ML 1.1.6: Genotyping of I. ricinus populations completed; population genetics analysis; comparison with blood meal analysis; comparison of micro- and macro-geographic studies. Means of verification: results in tick database; genetic analysis completed.

ML 1.1.7: Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers.

WP1.1.2
ML1.2.1: End of first year of tick and host sampling: evaluation of sampling sites. Means of verification: sample database (Q12)
ML1.2.2: End of second year of tick and host sampling: evaluation of sampling sites and decision to extend sampling into third year to fill gaps. Means of verification: sample database (Q24)
ML1.2.3: Mapping of the occurrence and geographical distribution of Hyalomma marginatum and other CCHF vector competent ticks in eastern and southeastern Europe complete. Means of verification: map available (Q36)
ML1.2.4: End of first year of development of CCHF test kits: re-evaluate approach if necessary. Means of verification: report to coordinator. (Q12)
ML1.2.5: Development and validation of a population dynamics model applied to Hyalomma spp. Means of verification: model available (Q42)
ML1.2.6: Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers (possibly from Q18 on depending on results).

WP1.2
ML 1.2.1: Schedule of collections and sampling protocol decided and available,. 1st annual report.
ML 1.2.2: First generation distribution maps. 1st annual report.
ML 1.2.3: Database constructed of existing data on community diversity and PUUV prevalence. 1st annual report
ML 1.2.4: Field experiments for virus survival designed and initiated. 2nd annual report.
ML 1.2.5: Immunogenetic field material collection accomplished. 2nd annual report.
ML 1.2.6: Immunogenetic molecular data available. 3rd annual report.
ML 1.2.7: Cross experiments and quant. PCR for spill over studies started. 2nd annual report
ML 1.2.8: Landscape epidemiological genetic field material collected. 2nd annual report
ML 1.2.9: Serial collection made of excreta from individually marked voles in field, and first quant. PCR analyses. 2nd annual report
ML 1.2.10: Field material and data base ready for Ro modelling. 2nd annual report
ML 1.2.11. All field materials collected and analyses in process. 3rd annual report

WP 1.3
ML1.3.1: Detection of WNV shedding in seropositive Coots, Crows and migratory passerines without detectable viraemia. Laboratory verification
ML1.3.2: Isolation of virus from male mosquitoes. Laboratory verification
ML1.3.3: Detection of WNV in mammals or frogs. Laboratory confirmation
ML1.3.4: Analysis of data from micro-climate stations.

WP1.4
ML1.4.1.1 Reference diagnostic laboratories for human PhBD identified and consensus protocols established - Means of verification: Appropriateness of structures and efficiency evaluation of reference laboratories.
ML1.4.1.2 Database of human leishmaniasis cases and infecting agents established - Means of verification: Appropriateness of data input verified.
ML1.4.1.3 Centralized system for Phlebovirus isolation established - Means of verification: Efficiency of sample collection and analysis.
ML1.4.2. Study areas identified and entomological collections performed - Means of verification: Representative samples of sand fly populations collected.
ML1.4.3. Experimental vector/parasite interaction studies performed - Means of verification: Appropriateness of methodology employed.
ML1.4.4. Reference diagnostic laboratories for canine leishmaniasis identified and consensus protocols established. - Means of verification: Appropriateness of structures and efficiency evaluation of reference laboratories.
ML 1.4.4.1 Database of canine leishmaniasis cases and infecting agents established - Means of verification: Appropriateness of data input verified.
ML 1.4.4.2 Development of a non-invasive method for Leishmania infections in dog - Means of verification: Comparative performance with standard assays.

WP1.5
ML1.5.1: Preliminary investigation of incursion routes. Means of verification: Deliverable D1.5.1.
ML1.5.2: Membrane feeding assessment of C. imicola. Means of verification: Deliverable D1.5.1.
ML1.5.3: Field collection of Culicoides and standardisation of detection systems.
ML1.5.4: Collaborative assessment of drop trapping techniques. Means of verification: Deliverable D1.5.1.
ML1.5.5 Develop phenological models for European Culicoides integrate static vector predictions into R0 frameworks Means of verification: Deliverable D1.5.1.
ML1.5.6: Carry out assessment of incursion routes. Means of verification: Deliverable D1.5.2.
ML1.5.7: Membrane feeding assessment of C. obsoletus group. Means of verification: Deliverable D1.5.2.
ML1.5.8: Initiate studies of oogenesis. Means of verification: Deliverable D1.5.2.
ML1.5.9: Assess laboratory vector competence of C. imicola. Means of verification: Deliverable D1.5.2.
ML1.5.10: Continue field collection of Culicoides for screening via optimised protocols. Means of verification: Deliverable D1.5.2.
ML1.5.11: Carry out initial drop trap comparison study. Means of verification: Deliverable D1.5.2.
ML1.5.12: Develop biological population models for European Culicoides and integrate seasonal vector predictions into R0 frameworks: Means of verification: Deliverable D1.5.2.
ML1.5.13: Initiate age grading studies. Means of verification: Deliverable D1.5.3.
ML1.5.14: Assess laboratory vector competence of C. obsoletus group. Means of verification: Deliverable D1.5.3
ML1.5.15: Identification of receptors which may play a role in the transmission and characterization of factor(s) present in Culicoides saliva that could interfere with the host Dendritic cells biology- Means of verification: Deliverable D1.5.3.
ML1.5.16: Continue to assess oogenesis at constant temperatures. Means of verification: Deliverable D1.5.3.
ML1.5.17: Assess survival of Culicoides under laboratory conditions. Means of verification: Deliverable D1.5.3
ML1.5.18: Continue field collection of Culicoides for screening via optimised protocols. Means of verification: Deliverable D1.5.3.
ML1.5.19: Carry out second year of drop trap comparison study. Means of verification: Deliverable D1.5.3.
ML1.5.20: Finalise phenological and population models and outputs for BTV and Culicoides spread.
ML1.5.21: Complete age grading and oogenesis studies. Means of verification: Deliverable D1.5.3.
ML1.5.22: Complete assessment of laboratory vector competence of C. obsoletus group. Means of verification: Deliverable D1.5.3.
ML1.5.23: Complete field collection of Culicoides for screening via optimised protocols. Means of verification: Deliverable D1.5.3.
ML1.5.24: Complete drop trap comparison study. Means of verification: Deliverable D1.5.3.
ML1.5.25: Complete R0 risk maps Means of verification: Deliverable D1.5.3.

WP2.1
ML 2.1.1: First meeting to define field and laboratory protocols. Means of verification: a document agreed and signed in by all partners.
ML 2.1.3: Submission of manuscripts for publications in peer reviewed journals. Means of verification: scientific papers.

WP2.2
ML2.2.1. Monitoring network established and study sites selected. 1st annual report.
ML2.2.2. First year collection done.1st annual report.
ML2.2.3. First year analyses done. 1st and 2nd annual report
ML 2.2.4. Evaluation of the first year. Internal report, 1st and 2nd annual reports
ML 2.2.5,6,and 7. Completion of tasks in the following years. Annual reports.

WP2.3
ML2.3.1: "Emerging traps" to measure rate of Ae. albopictus adult emergence are designed to adapt to different types of breeding sites. Means of verification: different prototypes are designed and assembled.
ML2.3.2: Proof of principle of efficacy of MGR-T by Ae. albopictus females among oviposition sites. Means of verification: significant larval and pupal lethality obtained in sentinel sites in a 200 sqm area in Rome's cemetery.
ML2.3.3: Implementation of age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from An. gambiae and Ae. albopictus lab samples.
ML2.3.4: "Emerging traps" to measure rate of Ae. albopictus adult emergence are tested under controlled conditions. Means of verification: evaluation of performance, i.e. number of collected adults / known number of pupae.

ML2.3.5: Ae. albopictus active dispersal capacity in different eco-climatic conditions in Rome. Means of verification: results of MRR analysed and Mean Distance Travelled assessed.

ML2.3.6: Implementation of Ae. albopictus age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups.

ML2.3.7: Assessment of fogging and/or UV fogging efficacy against Ae. albopictus. Means of verification: significant reduction in Ae. albopictus adult densities in treated versus untreated areas.

ML2.3.8: Confirmation of large-scale efficacy of MGR-T by Ae. albopictus females among oviposition sites. Means of verification: significant larval and pupal lethality observed in sentinel sites in different ecological urban settings.

ML2.3.9: Finalization Ae. albopictus age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups compared nulliparous/parous rates.

ML2.3.10: Assessment of large-scale efficacy of fogging and/or UV fogging against Ae. albopictus. Means of verification: significant reduction in both adult densities and mean age of Ae. albopictus populations in treated versus untreated areas.

ML2.3.11: Identification of most significant urban Ae. albopictus breeding site "types". Means of verification: evaluation of most productive and most frequent "types" in an area in Rome.

ML2.3.12: Assessment of large-scale efficacy of MGR-T. Means of verification: significant reduction in adult Ae. albopictus population densities in treated versus untreated areas.

ML2.3.13: Implementation of Ae. japonicus age-grading approach. Means of verification: near-infrared spectroscopy profiles obtained from different age-groups.

WP2.4

ML2.4.1.1 Identification of novel biocides for dog protection against sand flies - Means of verification: Comparative insecticide/anti-feeding performances with available products.

ML2.4.1.2 Assessment of ITNs protective efficacy against human CL - Means of verification: Comparative CL incidences with appropriate control arms.

ML2.4.1.3 Determination of insecticide susceptibility to different sand fly species/populations - Means of verification: Comparative susceptibility testing with appropriate insecticide-sensitive standard laboratory colonies.

ML2.4.1.4 Availability of salivary recombinant antigen(s) from P. perniciosus for serology testing - Means of verification: Comparative performance with native crude salivary antigen.

ML2.4.1.5 Application of ELISA-salivary recombinant antigen in field dogs - Mean of verification: Appropriateness of results as compared to the entomological P. perniciosus situation in the study site.

ML2.4.2 Xenodiagnosis results from different groups of drug/immunotherapeutic-treated dogs - Means of verification: Comparative infectiousness results with appropriate control groups.

WP2.5

ML2.5.1: Development of a coordinated protocol for the testing of available insecticides and repellents for Culicoides control. Identification of insecticides/repellents effective for Culicoides control. Means of verification: Deliverable 2.5.1
ML2.5.2: Identification of the most adequate insecticides and repellents for Culicoides control. Means of verification: Deliverable 2.5.1
ML2.5.3: Assessment of the most adequate methodology for application of insecticides at field level: netting, application on animals, application on target devices, and application in stables. Means of verification: Deliverable 2.5.1
ML2.5.4: Development of a coordinated protocol for the assessment of the efficacy of selected insecticides and repellents in field conditions. Means of verification: Deliverable 2.5.1
ML2.5.5: Set of spatially and temporally defined scenarios and initial parameter estimates for modelling vector control. Means of verification: Deliverable 2.5.1
ML2.5.6: Design of strategies for reduction of virus transmission by Culicoides spp. by using insecticides and repellents. Means of verification: Deliverable 2.5.2
ML2.5.7: Set of spatially and temporally specific scenarios and parameter estimates for R0 model comparisons. Means of verification: Deliverable 2.5.2
ML2.5.8: Confirmation of the efficacy of repellents and insecticides at field level. Means of verification: Deliverable 2.5.3
ML2.5.9: Predicting and mapping potential seasonal impact of vector control in EU. Means of verification: Deliverable 2.5.3
ML2.5.10: Predicting and mapping potential seasonal impact of various vaccination covers in EU. Means of verification: Deliverable 2.5.3
ML2.5.11: Predicting and mapping potential seasonal impact of combinations of vaccination stand still and vector control in EU. Means of verification: Deliverable 2.5.4
ML2.5.12: R0-models comparison and recommendations for prevention and control. Means of verification: Deliverable 2.5.4
ML2.5.13: Assessment of the impact of the application of insecticides and repellents on non-targeted arthropods. Means of verification: Deliverable 2.5.5.

WP3
ML3.1 Statistical analysis of data sampled from the simulated spread models outputs allow quantifying the original parameters used in the simulations (inverse modelling). This milestone depends on virtual experiments and hence does not depend on third party data, or on the availability of field collections - Means of verification. Quantitative statistical analysis identifies the correct parameters and simulation conditions.
ML3.2 Landscape heterogeneity indices are indicative of their permeability to the spread of VBD. This step will require using space-time empirical data on VBD spread from partners of the project - Means of verification. Statistical analysis of heterogeneity indices against i) simulated spread, and ii) empirical spread data of selected VBD showing a predictive power of those indices on the rate of spread.
ML3.3 Review of recent previous work on EDENext's target diseases to identify the current state of knowledge of each, including the involvement of Public Health services in contributing to this knowledge base, and their understanding of, and their perception of the utility of, risk maps - Means of verification. A completed comprehensive review document, possibly for publication in an abbreviated form.
ML3.4 EDENext modelling-interaction workshop (several of these will be organised) - Means of verification. A brief report of the meeting, outlining the attendants, the program, the methods and problems discussed, an inventory of modelling needs for the various teams and a list of concrete plans and collaborative arrangements.
ML3.5 Models of spread that merge process-based, agent-based and remote sensing methods are constructed - Means of verification. A technical description of the integrated approach for an example vector species.

ML3.6 Public Health-Modelling-interaction workshop (several of these will be organised) - Means of verification. A brief report of the meeting, outlining the attendants, the program, the problems discussed, an inventory of threats relevant for introduction risk, an inventory of problems with model predictions, surveillance-related issues and preferences for prediction of intervention and control.

ML3.7 R0-integration for mapping scaled-up to country level and beyond - Means of verification. Publication that outlines the method and a first application.

WP4.1
The same set of milestones apply each year.

ML4.1.01: Information regarding specific data requirements is available from partners at AGM. Means of verification: list of data requirements posted on DMT website after each AGM.

ML4.1.02: Selected EDEN partners are willing to contribute as trainers to DMT first workshop. Means of verification: list of trainers posted on DMT website two months prior to each workshop.

ML4.1.03: EDEN partners select participants who are willing to participate to the proposed training cycle. Means of verification: list of workshop attendants posted on DMT website one month prior to each workshop.

ML4.1.04: Training materials are available to successfully conduct workshop. Means of verification: training material is posted on DMT website one week prior to each workshop.

ML4.1.05: Training materials are available to successfully conduct distance learning course. Means of verification: training material is posted on DMT website one week prior to start each distance learning course.

WP4.2
ML4.2.01: Information regarding specific data requirements is available from partners at AGM. Means of verification: list of data requirements posted on DMT website after each AGM.

ML4.2.02: High resolution wind data are processed to prepare for the "impact of slope" study. Means of verification: data posted on DMT website.

ML4.2.03: Vector data are available to prepare for "impact of slope" and "landscape factor" studies. Means of verification: collaboration agreements with research partners.

ML4.2.04: Landcover data are available at sufficient resolution (15m) in pilot area in The Netherlands to prepare for "landscape factor" study. Means of verification: collaboration agreement with research partner.

ML4.2.05: Technical reports are available in the right format to prepare for publication of results in the last year. Means of verification: Deliverables year 1-2-3.

WP5.1
ML5.1.1: PH literature review is available. Means of verification: Publication on EDENext website.

ML5.1.2: Draft PH White Paper is available prior to mid-term EDEN SC meeting. Means of verification: Publication on EDENext website.
ML5.1.3: Draft PH White Paper is available prior to AGM. Means of verification: Publication on EDENext website.

WP5.2
ML5.2.1 Internal review after 18 months carried out by the three PH participants. Results are compiled in a report. Means of verification: Publication on EDENext website.
M 5.2.2: First 10-12 interviews with stakeholders (macro- and meso-level completed (M12)
M 5.2.3: First three focus group surveys in the first country conducted (M12)
M 5.2.4: Next 20-24 interviews with stakeholders (macro- and meso-level) completed (M24)
M 5.2.5: Next six three focus group surveys in another two countries conducted (M24)
M 5.2.6: Last 20-24 interviews with stakeholders (macro- and meso-level) completed (M36)
M 5.2.7: Last six three focus group surveys in another two countries conducted (M36)

WP5.3
M5.3.1: Already existing risk assessments compiled and analysed in regard to risk perception / risk communication (M6)
M5.3.2: Two targeted risk assessment workshops on CCHF and on Hanta viruses in endemic areas together with representatives and scientific experts will be conducted (M12)
M5.3.4: Questionaire study on the diagnostic capacities and quality for Hanta and CCHF in all European countries including Turkey completed. M24
M5.3.5: Collection of the data for the present state of the art for the diagnosis of Hanta and CCHF infections completed. M30
M5.3.6: Questionaire study on the existing knowledge of local physicians for the CCHF and Hantavirus infections in two endemic areas conducted. M30
M5.3.7: Recommendations for the best diagnostic approaches for the acute and convalescent Hanta and CCHF diagnostic for Europe and Turkey are elaborated. M36
M5.3.8: Leaflets and brochures implementing risk perception and risk communication knowledge (WP 5.2) for the public as well as for professionals have been worked out M42
M5.3.9: Distribution of leaflets and/or brochures by public (health) authorities and departments, ministries, medical and veterinary associations, farming associations, consumer associations and via internet on EDENext website. Start M42

WP6
The same set of milestones applies each year.
ML6.01: Contributions to the periodic activity report are available from each Group each year.
ML6.02: Annual meetings are attended by ? 100 scientists involved in EDENext, including ? 20 PhD students.
ML6.03: The frequency of SC is maintained each year.
ML6.04: No payment delay ? 6 months is observed because of coordination / management issues.

1.3.3.7 Contingency plan

Given the very specific risks of individual Work Packages contingency plans have been included as part of each Work Package Table. At the Group and General Management Level these will
be used as a guidance throughout the project and following the procedures described in the part on Governance below.

2 Implementation

2.1 Consortium governance and management

The project structure follows that of EDEN that was so conspicuously successful, with a set of vertical vector-related activities gathered in so-called Vector Groups (VG), linked by horizontal themes (Integration Groups – IG) providing integrated technical input to all VG, thereby minimising duplication and ensuring a coordinated approach throughout the project. It is displayed on Fig.2. below.

![Figure 2 – EDENext structure](image)

2.1.1 Governance

A scheme depicting the governance structure of EDENext is given in Fig.3 on next page.

2.1.1.1 The Coordinator

The Coordinator will be the sole focal point for the Commission and the intermediary between the partners and the Commission and between the partners and general organisation of the Project and will perform all tasks assigned to it as described in the EC Contract.

The Coordinator will convene meetings of the Steering Committee (SC) at least once every six months (target: three SC each year) and will also convene meetings at any time upon written request of any partner in the case of an emergency situation.
In particular, the Coordinator will be responsible for:

- submitting reports and other deliverables to the Commission;
- the administration, preparation of minutes and provision of the SC and the chairman of the SC and follow-up of their decisions;
- the transmission of any document and information connected with the Project to and between the concerned Group leaders and the partners;
- proposing to the SC rules for the project administration and the management of the funds received from the Commission;
- withholding advance payments and transferring sums allocated among the partners as per the budget agreed in EDENext contract (annex 1);
- making proposal to the SC to suspend all or part of the Project or to terminate all of part of the EC Contract, or to request the Commission to terminate the participation of one or more partners;
- proposing to the SC, in case of default of a partner, actions including (through a request to the Commission for an audit) suggestion on any new entity to join the Project.

![Figure 3 – EDENext governance](image)

### 2.1.1.2 The Steering Committee

The Steering Committee (SC) will be composed of the coordinator of EDENext, and each leader of the five vector groups (Rodents and Insectivores, Ticks, Mosquitoes, Sand flies and Culicoides), and of the 3 integration groups (Modelling, Data Management and Public Health). In case of unavailability, group leaders will be represented by their deputy.

The SC will assess, and possibly correct, EDENext overall scientific strategy and will examine major decisions to be taken. It will meet once every 3 months (3 times a year in addition to the SC hold during the annual general meeting). When necessary, decisions will be determined by simple majority vote.
The SC will in particular be responsible for:

- making, when necessary, proposals to the partners for the review and / or amendment of terms of the EC Contract and / or the Consortium Agreement for submission to the EC;
- establishing procedures and policies for the management of the Knowledge in accordance with the Commission contractual rules;
- making, when necessary, proposals to the Commission to introduce major changes in workpackages, particularly creation, reallocation, or termination of vector groups or integration groups;
- making a proposal to the Commission to terminate the participation of one or more partners.

The SC makes his best to resolve disputes, and scientific or ethical issues.

2.1.1.3 The Advisory Group

The Advisory Group (AG) includes prominent scientists and representatives of EDENext output users: stakeholders of human and veterinary public health with respect to vectors and vector-borne diseases. The AG will include about 10 members which may be individually requested by the SC, during the annual general meeting, the SC meetings, or when specifically needed. The members will be nominated prior to the EDENext kick-off meeting and invited at least once a year to take part to some of the meetings or activities.

The members of the AG will include: representatives of international public-health agencies (WHO, ECDC, OIE, FAO, EFSA…) as well as internationally-recognized scientists in the field of vectors and vector-borne diseases. During the preparation of this proposal, formal contacts have been made with several of these agencies and prominent scientists, who have confirmed their interest in being involved in the AG.

The role of the AG is to evaluate EDENext advances and give recommendations for EDENext scientific management to reach expected outputs in general and more specifically to:

- Advise and comment on the EDENext research strategy and its implementation, specifically when large regions, or major public-health questions are covered;
- Examine EDENext advances and give recommendations for improved EDENext R&D management to reach the expected outputs;
- Be part of the internal discussions on the outputs of the ‘what-if’ scenarios based upon the various models developed during the course of EDENext prior to their dissemination at the international level for a wider, informed public discussion;
- Ensure that the tools developed by EDENext are compatible with user needs.

2.1.1.4 The Project Secretariat

The Project Secretariat (PS) will be in charge of the financial and administrative management of the Project and of providing assistance to the Coordinator, with regard to the Coordinator's day-to-day tasks, such as preparation of meetings of SC.

The PS will translate the SC decisions into daily management tasks, including operational, administrative and financial ones. The PS will assure also the usual contacts and information exchanges with the Commission. It will be designated by the Coordinator. Moreover, PS will be responsible for:

- Day-to-day coordination, project monitoring and periodic reporting (including reviews);
- Trouble shooting and applying fall-back measures where necessary;
- Guiding partners administrative requests;
• Integrating project reports;
• Financial monitoring or the project;
• support for communication, dissemination and press contact;
• Ensuring efficient communication between the consortium partners;
• Ensuring that administrative tasks are efficiently and timely fulfilled.

2.1.2 Management tools

A dedicated internal project web site will be used to co-ordinate information exchange, keep up-to-date information about the project, store project documents, and more generally, serve as a project repository for all information necessary to administrative, technical and exploitation management.

Mailing lists will be implemented to facilitate between-partner communication (e.g., network of financial officers) and organisation of specific events (workshops, etc.).

An electronic workspace will be implemented to facilitate the administrative tasks of consortium members. A collection of templates will be available for each mandatory report. The system will provide services such as the follow-up of submissions and will launch automatic reminders and warnings. Authorised partners will be able to consult all the submitted reports.

2.1.3 Management procedures

EDENext will benefit from CIRAD facilities for its financial management, including fast and secure payments after EC subvention has been received.

A Management Handbook will be prepared during the first month of the project to ensure that all participants in the EDENext have the same understanding of what is expected from them in terms of management processes and reporting.

Financial and management information will be reported at each annual general meeting (AGM). The EDENext management team will attend these AGM to meet consortium partners.

When necessary, a management item will be included in the agenda of SC meetings to present specific questions requiring a validation by the SC members.

When budget reallocation is needed (within the limit of the overall EDENext budget) to achieve the scientific tasks decided in the implementation plan, an ad-hoc procedure will be presented by the coordinator at the SC meetings. After validation by the SC, it will be proposed to consortium members.
2.2 Individual participants

2.2.1 Partner 1 – Centre de coopération internationale en recherche pour le développement (CIRAD)

2.2.1.1 Organisation

CIRAD, Montpellier, France, is the national reference laboratory for serological diagnosis of bluetongue and is in charge of the coordination of the national surveillance network for Culicoides in France since 2000 (160 traps over mainland France and Corsica, operating all year on weekly or monthly basis). Bluetongue (BT) has been studied at CIRAD since more than a decade, first on the African continent and more recently in the Mediterranean basin (France, Morocco, Tunisia and Algeria) because of the expansion of C. imicola, an afrotropical vector, into Europe and the BTV-8 outbreaks in western Europe. Cirad participates actively in communicating to the general audience on bluetongue related topics through a website http://bluetongue.cirad.fr/ and Cirad researchers participate to national and European expert committees on bluetongue. Research activities developed at Cirad on bluetongue disease focus on: (a) Virology and vaccinology with the development of new types of vaccines mainly based on the Capripoxvirus as vectors (Virology Research Unit), (b) Developing tools (molecular and morphological) to help identifying Culicoides species; assessing bionomics and vector competence of Culicoides vector species in France (Entomology Research Unit), (c) Understanding spatial and temporal dynamics of Culicoides populations; modeling R0 maps for Culicoides-borne diseases (Epidemiology Research Unit). Cirad will mostly be involved in WP1 and WP2.

2.2.1.2 Key persons involved

Catherine Cêtre-Sossah: Virologist, PhD in Biology with 10 years of experience. Since 2002, she works as a molecular biologist on emergent vector-borne diseases (Bluetongue and Rift Valley viruses) at CIRAD UMR15 Virology Research Unit, Montpellier (France). She is the coordinator of MedReoNet project, and a partner of ORBIVAC and ARBO-ZOONET, EU PF7 projects dealing with the development of new orbiviruses vaccines and Rift Valley fever virus respectively. Thomas Balenghien: Medical and veterinary entomologist, PhD in Entomology, DMV. He has 7 years of experience in medical and veterinary entomology with a strong involvement in bionomics of vector-borne diseases (Trypanosomiasis, West Nile virus, bluetongue vectors). He joined Cirad UMR15 in 2007 and since is the coordinator of the national surveillance network for Culicoides in France. Claire Garros: Medical and veterinary entomologist, PhD in Entomology. She joined Cirad UMR15 Entomology Research Unit, Montpellier (France) in 2009. She has 7 years of experience in medical and veterinary entomology with a strong involvement in systematics and bionomics of vector-borne diseases (Culicidae and Ceratopogonidae) using molecular tools. Hélène Guis: Epidemiologist, PhD in epidemiology, DVM. She has 7 years of experience in epidemiology and modelling (vector distribution and vector-borne disease transmission) on bluetongue disease. She joined Cirad UMR15 Epidemiology Research Unit, Montpellier (France) in 2009, involved in Dyn Vect project, aiming at modelling distribution and dynamics of Culicoides in Western Europe. Mathieu Epardaud: Immunologist, PhD in immunology. He was involved in cancer research since 2008, joined Cirad UMR15 Immunology Research Unit and now is mainly interested on vector insect saliva immunomodulation action (hard ticks, mosquitoes).

2.2.1.3 Material resources

CIRAD has the necessary hardware and software to develop vector competence studies, with good laboratory (BSL-2 and BSL-3) facilities that can be used for entomological work, has access to the entire entomological surveillance network in France.
2.2.2 Partner 2 – Charles University in Prague (CUNI)

2.2.2.1 Organisation

CUNI, Prague, Czech Republic, is the most renowned higher education institute in the Czech Republic and its Faculty of Science is the leading institute in biomedical research. The Dept. Parasitology consists of five laboratories. Their research activities focus on metabolism and molecular phylogenetics of parasitic Protozoa and in mechanisms of transmission and cellular, biochemical and immunological interactions between the host, parasite and the vector. Main organisms studied are trichomonads, *Giardia*, heteroxenous *coccidia*, trypanosomes of birds, *Trichobilharzia* – snail model and *Leishmania* - *Phlebotomus* model. The study of the laboratory for Vector Biology headed by prof. Petr Volf is oriented towards various aspects of *Leishmania* - sand fly relationship. The team consists of 3 professors, Petr Volf (Professor), Milena Svobodova (Assoc. Prof.), Jan Votypka (Assist. Prof.), five researchers and seven PhD students. They study mainly molecular aspects of *Leishmania* development in sand fly midgut, antigens and enzymes in sand fly saliva and immune response of bitten hosts. Members of the team participate in biochemical, immunological and molecular studies in the laboratory and well in the field research in antroponotic and zoonotic foci of *Leishmania tropica* and *L. infantum* in various Mediterranean countries, mainly Turkey, Israel and Tunisia. Eight colonies of *Phlebotomus* sand flies maintained in the insectary represent the best collection of leishmaniases vectors in the Old World. CUNI is the coordinator of PhBD subgroup. Major part of its activity will concern vector competence and *Leishmania* – vector – host interactions. CUNI will be responsible for experimental studies on susceptibility of various sand flies to *Leishmania*, effect of temperature on *Leishmania* development, immunomodulatory effect of saliva in *L. infantum* transmission and studies of anti-sand fly saliva antibodies as a tool for monitoring sand fly – host contact. Together with HUA, CUNI will be a key partner for studies on sand fly biology and control. It will participate in the field activities studies on spread of strains and hybrids of *L. donovani* complex in Mediterranean, distribution of sand fly species of subgenus Larroussius and their population genetics

2.2.2.2 Key persons involved

**Petr Volf** (Head of laboratory): Medical entomologist with a long-term experience in application of biochemical, immunological and histological methods in the study of pathogen-vector-host relationships. **Jan Votypka** (Assistant professor): medical entomologist and protozoologist, specialized in molecular phylogenetics and molecular taxonomy, with experiences in the field work on bloodsucking diptera in different countries in Europe, Middle East and Africa. **Jovana Sadlova** (Senior researcher): parasitologist and zoologist with outstanding skills in experimental infections of sand flies and mice by *Leishmania*. **Iva Rohousova** (Senior researcher): parasitologist specialized in immunomodulatory effects of sand fly saliva and in immune response of experimental animals and humans to sand fly bites. **Vit Dvorak** (Post-doc researcher) specialized in molecular taxonomy of sand flies. **Vera Volfova** (Researcher): biologist; skills in salivary antigens and enzymes of bloodsucking insects. **Michaela Vlkova** (PhD student): involved in studies on antibody response to sand fly saliva. **Veronika Seblova** (PhD student): involved in experimental infections of sand flies and in the fieldwork.

2.2.2.3 Material resources

In addition to basic parasitological equipment several electrophoretic systems (including 2-D ELFO and iBLOT), FPLC liquid chromatography (Biological SPLC), and MALDI-TOF-TOF mass spectrometry are present at the department for protein characterization. Cryobank, animal house and insectarium are available at the department; confocal microscopy and DNA sequencing servis are located on the same corridor.
2.2.3 Partner 3 – Istituto Superiore de Sanita (ISS)

2.2.3.1 Organisation

ISS, Rome, Italy, is the main research institute for public health in Italy. Its activities include research, control, training and consultation in the interest of public health protection. It is made of 7 Departments, 5 National Centers and 2 Technical Services. The Department of Infectious, Parasitic & Immunomediated Diseases (MIPI) is composed by 15 Units that cover research and control activities on viral, bacterial, fungal and parasitic infections affecting humans.

The Unit of Vector-borne Diseases & International Health is one of the two parasitology Units of the MIPI Department. Its duties include surveillance and control of major vector-borne parasitic diseases in Italy, cooperation with developing countries as well as basic research. Research in the Leishmaniasis field consists of surveillance of human and canine disease; validation of diagnostics; laboratory and field testing of drugs and vaccines; molecular Leishmania taxonomy; biology and control of phlebotomine vectors. The Unit of Viral Diseases & Attenuated Vaccines of MIPI Department investigate on the epidemiology, diagnosis and human pathogenesis of Arboviruses. Research on phlebotomine viruses led to the discovery of 3 new agents, Toscana, Arbia (Phlebovirus) and Radi virus (Vesiculovirus), along with the demonstration of Toscana virus as an agent of neurological disease in humans. Studies performed on virus/sand fly relationships demonstrated trans-ovarial and venereal transmission in the insect host.

ISS has been appointed as deputy partner of the PhBD subgroup. Major tasks of the Unit of Vector-borne Diseases & International Health will be monitoring the spreading of L. infantum in northern continental Italy, with relevance to the evaluation of novel diagnostic tools; risk assessment for the introduction in Italy of the exogenous Leishmania species; evaluation of the vector competence of indigenous sand fly species; assessment of new methods for vector and canine reservoir control.

The main task of the Unit of Viral Diseases & Attenuated Vaccines will be the centralization of monitoring activities aimed to assess the spreading of Phleboviruses in Europe, through isolation and identification of agents from sand fly samples received by partners of the PhBD group.

2.2.3.2 Key persons involved

Unit of Vector-borne Diseases & International Health - Marina Gramiccia (PhD, Biol. Sc.) is Senior Researcher, and headed the former Unit of Biochemistry of parasites, Parasitology Laboratory, for 13 years. She is specialised in the parasitological and molecular surveillance of human and canine Leishmania infections, and responsible of the Italian Leishmania Identification Centre. She is the current ISS leader in the ongoing EC integrated project EDEN (GOCE 010284).

Luigi Gradoni (PhD, Biol. Sc.) is Research Director, and headed the former Unit of Protozoology, Parasitology Laboratory, for 16 years. He is specialised in the surveillance and control of human and canine leishmaniasis through networks of medical and veterinary institutions. He is expert in laboratory and field validation of novel anti-leishmanial drugs and canine Leishmania vaccines.

Trentina Di Muccio (PhD, Biol. Sc.) is temporary Researcher with large experience in parasite culture, molecular diagnosis and characterization of Leishmania from human, animal and phlebotomine hosts. Aldo Scalone (Biol. Sc.) is a graduated technician with large experience in the standardization of serodiagnostic techniques for protozoan diseases. Stefania Orsini is a laboratory technician with large experience in animal models for anti-trypanosomatid drug assays. Cristina Khoury (Biol. Sc.) is a graduated technician with large experience in sand fly biology, colony breeding, and taxonomy. Gioia Bongiorno (PhD, Biol. Sc.) is a temporary graduated technician with large experience in field monitoring of sand flies and GIS application, colony breeding and insecticide testing. Riccardo Bianchi is a laboratory technician with large experience in sand fly colony breeding and xenodiagnosis.
Unit of Viral Diseases & Attenuated Vaccines - Maria Grazia Ciufolini (PhD, Biol. Sc.) is Senior Researcher, with great experience in the field of Arboviruses. Her research activities are mainly addressed to epidemiology, ecology, diagnosis and human pathogenesis of Phleboviruses and Flaviviruses. Cristiano Fiorentini is a laboratory technician, with large experience in diagnostic techniques for vector-borne viruses and in monitoring of imported viral diseases.

2.2.3.3 Material resources
In addition to basic parasitology, entomology and virology equipment (sterile benches; sterile hoods and rooms; optical, stereo, fluorescent and inverted microscopes; deep freezers, fridges and cold rooms; incubators and CO₂ incubators; centrifuges and ultra-centrifuges; PCR cyclers, electrophoresis systems) ISS has all the material resources needed for the project, including a BSL3 facility, sequencing, imaging and dedicated software. Parasite, virus and serum cryobanks, insectary and animal facilities are located in the MIPI Department.

2.2.4 Partner 4 – Institut de Recherche pour le Développement (IRD)

2.2.4.1 Organisation
IRD, Montpellier-Rabat, France, is a French public research institute working for the development of Southern countries, reporting to the Ministries responsible for research and overseas development. IRD is managing for more than sixty years research, consultancy and capacity building activities in Africa, the Mediterranean basin, Asia, Latin America and French overseas territories. IRD researchers address major development challenges regarding environment, sustainable development of living resources, social studies and health. The UR016 of IRD focused on biology and control of arthropods of medical interest. The research activities focus on biology, physiology, molecular phylogenetics, population genetics of the pathogens and the host vector that transmit them, both in vitro and in natura.

The study of the IRD Team will be oriented towards various aspects of the Leishmania - sand fly relationship and diversity but will primarily focused on the molecular and biological diversity of the sandfly-Leishmania couple mainly in Morocco and to analyze results in the light of what is known in France. The team consists of 2 senior researcher and 2 assistant professors, Denis Sereno (Senior researcher), Anne Laure Banuls (Senior Researcher), Christophe Ravel (Assist. Prof), Jerome Depaquit (Assist. Prof.), 1 post doc student (Souad Guernaoui), 2 PhD Students. They will be involved in the study of sandfly and Leishmania diversity in Morocco and France. Major part of the activity of the group will concern distribution of sand fly species of the subgenus Larroussius, their population genetics and the diversity of the Leishmania strain they transmit (I.e hybrids) in Mediterranean (Morocco and France).

2.2.4.2 Key persons involved
Denis SERENO (Senior Researcher): Microbiologist, specialized in molecular parasitology with experiences in cell biology, biochemistry and entomology for the study of pathogen-host relationships. Anne Laure BANULS (Senior Researcher) : Microbiologist specialized in population genetics, molecular phylogenetics and taxonomy. Jérôme DEPAQUIT (Assistant Professor): Entomologist specialized in molecular phylogenetics and taxonomy of sandfly. Christophe RAVEL (Assistant Professor): parasitologist specialized in Leishmania molecular taxonomy. Souad GUERNAOUI (Post-doc researcher) specialized in sand flies ecophysiology with heavy experiences in field work. Baptiste VERGNES (Research engineer) Molecular Biologist Elodie GAZANION (PhD Student): biologist with outstanding skills in Leishmania drug susceptibility assays and reporter gene technology development.
2.2.4.3 Material resources

In addition to basic parasitological equipment in France (sterile benches, fluorescent and inverted microscopes, incubators, PCR cyclers, CO₂ incubator) several electrophoretic systems (including 2-D ELFO and iBLOT), FPLC liquid chromatography (Biological SPLC), Cryobank, animal house and insectary are available at the IRD Center of Montpellier. In Morocco investigations will be perform at the INH(Institut National d'Hygiène) in Rabat, where CDC trap and sterile material for field studies are presents.

2.2.5 Partner 5 – National Centre for Disease Control (NCDC)

2.2.5.1 Organisation

NCDC, Tbilisi, Georgia, is a primary public health center in Georgia with several diagnostic and research laboratories. The main activities of the Center are: surveillance and control of infectious diseases through the whole territory of Georgia; development and implementation measures against epidemics; carrying out epidemiological, diagnostic, bacteriological, virological and molecular-biological investigations; coordination of the immunization program; development of methodic and normative documents on surveillance, control and prevention of diseases; collection and exchange information about infectious and non-infectious diseases inside and outside of the country; preparation and printing methodic and information materials; providing information to the governmental and international organizations.

The NCDC has a broad experience in field surveys. There are 8 laboratories functioning at NCDC: Respiratory Diseases; Zoonoses and Anaerobic Diseases; Cholera and Diarrhoeal Diseases; Plague and other diseases with natural foci; Poliomyelitis and other Enteroviruses; Viral and Rickettsial Diseases; Molecular Epidemiology, Cell Cultures Laboratories are focused on isolation and identification of causative agents, molecular typing of isolated strains and diagnostics. All isolated strains are catalogued and stored in the NCDC culture collection. The NCDC has the most comprehensive bacterial culture collection in Georgia, with some isolates more than 25 years old.

Since 2004 the project “Development of Surveillance System and Control Strategy for Leishmaniasis in Georgia” has been carrying out with the aim to investigate an active focus of visceral leishmaniasis located in the central part of the capital of Georgia – Tbilisi. During the project activities in the studied focus: prevalence and incidence rates of the disease among target group of human population as well as seroprevalence rates among pet and stray dogs were determined, diversity of sand flies population, seasonal dynamics and their feeding status were determined, sand fly species were incriminated as vectors of the disease, parasite strains are isolated and identified, parasite strains isolated from human and dog samples were cultivated and preserved.

2.2.5.2 Key persons involved

Eka Giorgobiani (Doctor of Biological Sciences), PI of the Leishmaniasis project in Georgia, background cell biology, experience in study of vector-borne diseases (focused on leishmaniasis).

Gvantsa Chanturia, senior specialist of the Department of Molecular Epidemiology, broad experience in molecular technique (trainings: Bechtel International, Tbilisi, Georgia; US AFRIMS, Bangkok, Thailand; Lawrence Livermore National Laboratory (LLNL), CA, USA). Irina Kalandadze, senior specialist of the Malaria and other Protozoonosis Department, experience in surveillance and control of vector-borne diseases (focused on malaria, leishmaniasis). Julia Manvelian, senior specialist of the Malaria and other Protozoonosis Department, broad experience in the field work (focused on malaria, leishmaniasis, tick-borne diseases). Giorgi Babuadze, PhD student, involved in study of vector-borne diseases (trainings : USAMC-AFRIMS, Bangkok, Thailand ; Walter Reed Army Institute Research Washington D.C. USA).
2.2.5.3 Material resources

Basic equipment for microbiological, immunological and molecular biology research: microscopes, centrifuges, thermostats, freezers, autoclaves, ELISA reader/washer, PCR cyclers, Genetic Analysis System.

2.2.6 Partner 6 – University of Crete (UoC)

2.2.6.1 Organisation

UoC, Heraklion, Crete, Greece, founded in 1973, is one of the best known Greek Universities for its achievements. The Laboratory of Clinical Bacteriology, Parasitology, Zoonoses and Geographical Medicine was established in 1985. It is a National Reference Center of Zoonoses and a WHO Collaborating Center for Research and Training in Mediterranean Zoonoses since February 1995 (head Prof. Y. Tselentis). The following Diagnostic and Research Units operate under the Laboratory: *Leishmania, Toxoplasma, Medical Entomology, Rickettsiae-Bartonella, Brucella, Food borne Infections, Hepatitis, Surveillance, Environmental and Water Microbiology, International Unit in Epidemiological Research and Intervention*. The Laboratory employs 53 persons (Medical Doctors, Veterinarians, Entomologist, Biologists, Technicians, Secretary) and has more than 12 PhD students.

The specific research interests of the Parasitology Unit (head Assis. Prof. Maria Antoniou) is leishmaniasis and toxoplasmosis with emphasis on epidemiology and control. Regarding leishmaniasis: Five PhD students work in the laboratory on the epidemiology of the disease in Greece and Cyprus conducting sero-epidemiological studies, isolation of parasites from patients, dogs and sandflies; study the virulence and the resistance of isolates to drugs. Work is done on diagnosis of leishmaniasis in patients and dogs using serology, PCR and culture. The studies concern Greece and Cyprus. A new focus of *L. donovani* has been discovered in Cyprus in 2006.

UoC has participated in the EDEN-Leish sub-project and now participates in the PhBD subgroup. Its main activity will be focused on studies concerning: the spread of *Leishmania infantum* into the North of Greece and the spread “of new” strains and hybrids of *L. donovani* complex in the Mediterranean by parasite isolation and typing from patients, dogs and sandflies from different parts of Greece and Cyprus; It will help in the studies of *Leishmania* vector biology and population diversity with collections of sandflies in Greece and Cyprus; Will provide data on impact of topical application of novel insecticides and repellents to dogs and *Leishmania* control in the reservoir host.

2.2.6.2 Key persons involved

**Maria Antoniou** (Assis. Prof., Head of Parasitology laboratory): Medical parasitologist with experience in epidemiological research on zoonoses, especially leishmaniasis, the biology of *Leishmania* and the development of sandfly colonies. **Pantelis Ntais** (PhD student): veterinarian experienced in the diagnosis (clinical laboratory) of leishmaniasis, isolation and culture of *Leishmania*, sandfly collections. **Apostolos Mazeris** (PhD student): veterinarian experienced in epidemiology, the diagnosis (clinical laboratory) of leishmaniasis, isolation and culture of *Leishmania*, sandfly collections. **Vassiliki Christodoulou** (PhD student): veterinarian, experienced in the diagnosis (clinical laboratory) of leishmaniasis, isolation and culture of *Leishmania*, sandfly collections and colony maintenance, biological studies of *Leishmania* with the use of Flow Cytometry, Confocal Microscope, Electronic Microscope. **Andreas Tsatsaris** (Assis. Professor, Topographer, GIS expert) collaborator of the Parasitology laboratory in relation to data analysis.
2.2.6.3 Material resources
Basic parasitological equipment (sterile benches, fluorescent and inverted microscopes, incubators, PCR cyclers, CO2 incubator, cytopsin) animal house, insectary, confocal microscopy, TEM, SEM, Flow cytometry, DNA sequencing.

2.2.7 Partner 7 – Instituto de Higiene e Medicina Tropical (IHMT)

2.2.7.1 Organisation
IHMT, Lisbon, Portugal, is a graduate school in International Health and Tropical Medicine. It is integrated in the Universidade Nova de Lisboa (UNL), developing teaching (Post-graduation and Masters courses) and scientific activities in several fields of biomedical sciences related to Tropical Medicine (Molecular Biology, Bacteriology, Parasitology, Genetics, Entomology and Immunology), in the clinic and pathology of tropical diseases and in International Health. IHMT has a wide experience in health global initiatives and in the establishment of partnerships with Africa, South America and Asia and collaborates fully with EU institutions. IHMT as also contributed to the reinforcement of global health planning actions in order to obtain rational and efficient responses to Public Health to global threats.

The Leishmaniasis Unit integrates a nationally funded research Centre (Centro de Malária e Outras Doenças Tropicais - CMDT) on development of immunological and molecular technologies. Research interests include vector and host-parasite interactions, development of tools for human and canine leishmaniasis diagnosis and molecular epidemiology. The Leishmaniasis Unit has conducted fieldwork activities in endemic areas and developed diagnosis methodologies for epidemiological studies of vector, canine and human Leishmania infection, development and validation of serological assays and novel molecular tools. Experimental canine and rodent models have been established towards immunological studies, vaccines and therapeutic assays. In this Unit, in vitro drugs susceptibility and entomological studies have been carried out.

2.2.7.2 Key persons involved
Lenea Campino: MD. PhD; Head of Leishmaniasis Unit; permanent interest in leishmaniases research, large expertise in field studies and epidemiology of canine and human Leishmania infection having contributed to the knowledge of prevalence and incidence of the leishmaniasis in the country and to the development and validation of serological assays and novel molecular tools.
Odete Afonso: MD. PhD, Entomologist. Expertise in biocology of the phlebotomine sand flies (sand flies as Leishmania vectors; phlebotomine sand flies activity in relation to climatic changes).
José Cristóvão: (lab technician) Clinical Analyst and Public Health graduated. Experience in leishmaniasis serodiagnostics, parasite cultures, microscopy and PCR.

2.2.7.3 Material resources
The IHMT possess animal facilities that allow to the use of several experimental models (mice, hamsters and dogs), an Insectary which houses a permanent P. perniciosus colony and a Cryobank for preservation of live parasite strains, DNA samples and vectors. IHMT has available parasitological and microbiological basic equipment.
2.2.8 Partner 8 – Instituto de Salud Carlos III (ISCIII)

2.2.8.1 Organisation

ISCIII, Madrid, Spain, is a national research and scientific support organization responsible for promoting biomedical and health science research. Its mission is to develop and provide the highest quality scientific-technical services to the National Healthcare System (NHS) and society in general. The Institute works closely with NHS research centres authorises institutes and cooperative research networks in order to contribute to a structuring research in the NHS. The National Centre of Microbiology (NCM), within the ISCIII, is dedicated to research of most human infectious diseases. Diagnostic of infectious agents is carried out as a service to the NHS. It is the national reference centre for zoonosis. The Department of Parasitology, within NCM, consists of six units conducting biomedical research on a range of parasitic diseases.

The Medical Entomology Unit headed by Dr. Molina is mainly focused in the study of Leishmania – sand fly relationship, the ecology of sand fly vectors of leishmaniasis and the vector control mainly studying the efficacy of insecticides against Phlebotomus perniciosus. The Unit works in close collaboration with the WHO Collaborating Centre for Leishmaniasis of the ISCIII. The team consists of two researchers, Ricardo Molina and María Isabel Jiménez, two PhD students and a technician. They study mainly the immunogenic properties of sand fly saliva, proteomics, and the impact of the global change on the spread of leishmaniasis. Part of the research group is involved in the European project EDEN (Emerging Diseases in a Changing European eNvironment), Leishmaniasis subproject. As part of this research, the group has obtained some interesting results: the prevalence of canine leishmaniasis in the central region of Spain is increasing and the patterns of distribution of the potential vectors of the disease are changing.

In EDENext ISCIII is one of the partners of PhBD subgroup. Part of its activity will concern vector competence and Leishmania – vector interactions. Our interest will be focused on experimental studies on susceptibility of sand flies to Leishmania, effect of temperature on Leishmania development, and studies of anti-sand fly saliva antibodies as a tool for monitoring sand fly-host contact. It will participate in the field studies on the potential for introduction of L. tropica into Spain, the distribution and seasonal dynamics of sand fly species of subgenus Larroussius and in studies on sand fly biology and control.

2.2.8.2 Key persons involved

Contributors from ISCIII include: Ricardo Molina, Head of the Unit, medical entomologist with a long-term experience in the application of biological methods in the study of pathogen-vector-host relationships, sand fly infections, sand fly biology, field work, and evaluation of insecticides; María Isabel Jiménez, pharmacist expert in molecular biology and proteomics of Leishmania, including HIV co-infection; Rosa Gálvez, PhD student involved in studies of the impact of the global change on the spread of leishmaniasis; and Inés Martín, PhD student involved in studies of the saliva of Phlebotomus perniciosus as source in the search of potential targets for vaccine development against Leishmania infantum.

2.2.8.3 Material resources

ISCIII has fluorescent and inverted microscopes, stereomicroscopes, incubators, CO₂ incubators, different electrophoretic systems, HPLC liquid chromatography, PCR cyclers, laminar flow cabinets (BSL-2), real time PCR, cryobank. Animal house, insectary with environmental cabinet, MALDI-TOF mass spectrometry, DNA sequencing, and confocal microscopy are available in the department or in NCM. Also is available a BSL-3 facility in which experimentation with this type of agents is carried out. There are also central services for genomic and proteomics.
2.2.9  Partner 9 – Hacettepe University, Faculty of Science (HUESRL)

2.2.9.1  Organisation

Hacettepe University, Ankara, Turkey, as one of the leading universities of Turkey, continues to contribute to social development and universal values in the fields of science, technology and art. Hacettepe University carries on its activities with 13 faculties, 9 schools, 1 conservatory, 13 institutes, and 35 research and application centers within the scope of Act No. 2809 of the Organization for Higher Education Institutions, which was enacted in 1982. The Department of Biology consists of eight divisions as Ecology, Molecular Genetic, General Biology, Zoology, Botanic, Applied Biology, Hydrobiology and Biotechnology working on different main subjects of biology. It also contains 24 main research laboratories with high technology equipments. Ecology Division was founded in 1992. Following the establishment the division started teaching and research activities the same year. The areas that have been used for education and research by the Ecology Division were reconsidered in 1999 to become an international center. Today, the center continues its research with its faculty, assistants, experts and post-graduate students whom are well trained or still training in various aspects of ecological sciences. The center consists of three different laboratories: 1) HUESRL (Ecological Science Research Laboratories), 2) EEGL (Evolutionary Ecology and Genetic Laboratory) and, 3) MFEL (Mammalian and Forest Ecology Laboratory).

The study of the HUESRL (Hacettepe University Ecological Science Research Laboratories) headed by Assoc.Prof. Bulent ALTEN is oriented towards various aspects of vector biology and ecology (particularly sand fly and mosquito), population bio-ecology, population dynamics and modeling, geometric morphometrics, molecular taxonomy of sand fly and mosquito species, evolutionary ecology of vector populations, population genetic of vector species, in particular *Phlebotomus* and *Anopheles* species, modeling and application of integrated vector control methods such as ITNs in rural and urban areas, susceptibility, resistance, bioassay tests against various insecticides. The team consists of 4 professors, Bulent ALTEN (Assoc. Prof.), Fatih M. SIMSEK (Assoc. Prof.), Murat AYTEKIN (Assoc. Prof.), Ergi Deniz OZSOY (Assoc. Prof), six researchers, five PhD students, four MSc students. Recently, they study mainly molecular taxonomy and distribution of Larroussius species, spreading of these species and population genetics of vector sand fly species in Turkey using molecular and geometric morphometric techniques. The team also is working on seasonal population dynamics of important sand fly vector species, their biting behavior and resting microhabitats. Another interest of the team is working on effects of climatologically differences on sand fly and mosquito species. Members of the team participate in taxonomic, ecological, biological and molecular studies in the laboratory and well in the field research in Turkey, Czech Republic, Algeria, Morocco, Saharan, Sri Lanka, Brazil, Greece, Kazakhstan, Iran, Syria. One colony of *Phlebotomus papatasi* has been maintained in insectary. DNA extractions of seven sand fly species (from fifteen different localities of Turkey) and nine mosquito species (from ten different localities of Turkey) collected from Turkey has been reserved in the freezers in HUESRL. The team is also member of Malaria Sub-Group of current EDEN project.

HUESRL is the member of PhBD subgroup headed by CUNI. Major part of its activity will concern sand fly biology and population diversity, and sand fly control. HUESRL will be responsible for distribution of Larroussius species, spreading of these species and population genetics of vector sand fly species using molecular and geometric morphometric techniques in field and laboratory conditions, seasonal dynamics of sand fly species in field conditions, biting behavior of sand fly species and blood identification in field and laboratory conditions, investigation of resting microhabitats in field conditions, investigation of effects of insecticide impregnated bednets (ITNs) in field conditions and investigation of insecticide resistance of sand fly species under laboratory
conditions. Together with CUNI, HUESRL will be a key partner for studies on sand fly biology and control.

2.2.9.2 Key persons involved

Bulent ALTEN (Head of Laboratory): Ecologist with a long-term experience in vector biology and ecology, taxonomy, population ecology and genetic, geometric morphometrics and creation and application of vector control programs. Fatih M. SIMSEK (Assoc. Prof): Ecologist, taxonomist, specialized in molecular phylogenetics and molecular taxonomy in the field work on mosquito and sand fly species in Turkey and Middle East, and resistance and susceptibility tests in laboratory conditions. Murat AYTEKIN (Assoc.Prof.): Zoologist, taxonomist with a long-term experience in classic, molecular and morphometric taxonomy. He is founder and head of the morphometric taxonomy Laboratory in HUESRL. Sinan KAYNAS (Senior Researcher): Biologist, ecologist with outstanding skills in experimental studies on sand fly and mosquito populations in both field and laboratory conditions, application of vector control tools in field conditions, and resistance and susceptibility tests in laboratory conditions. Asli BELEN (Post-doc researcher): Ecologist with experiences in the field and laboratory work on rearing techniques of colonies, population ecology, molecular phylogenetics, sand fly taxonomy, geometric morphometric techniques, and computer based statistical analysis. Ozge E. KASAP (PhD student): Biologist, sand fly taxonomist with outstanding skills in molecular phylogenetics ( particularly Larroussius species), population ecology and genetics of sand fly, rearing techniques of laboratory colonies, morphometric analysis, and computer based statistical analysis. Filiz GUNAY (PhD Student): Biologist with outstanding skills in rearing techniques, environmental effects on mosquito and sand fly populations in laboratory conditions, and computer based statistical analysis. Salim CALIS (Technician) with outstanding experiences in both laboratory and field conditions of sampling collection, colony rearing, application of vector control tools in field conditions, resistance and susceptibility tests in laboratory and field conditions.

2.2.9.3 Material resources

In addition to basic biological and ecological equipments (fluorescent, inverted, stereoscopic and 3D microscopes, PCR cycles, incubators, GIS equipments, field kits, conductometers, pH meters, salinity meters, CO2 traps, light traps, animal baited traps, anemometers, hygrometers and electronic thermometers, data loggers, electronic climate stations etc.), several electrophoretic systems, FPLC liquid chromatography (Biological SPLC), mass spectrometry, resistance and susceptibility laboratory with equipments, appropriate technologies for applying impregnated bed nets in field conditions are present at our department. Animal house and three different sizes of insectaries are available in the HUESRL. One of the geometric morphometry laboratories in Biology Department is located in HUESRL with 2D and 3D microscopes, high-resolution camera system and high tech computer system. Full equipment molecular biology laboratory with sequencing service is located on the same building.

2.2.10 Partner 10 – Ege University Medical School (EUMS)

2.2.10.1 Organisation

EUMS, Bornova-Izmir, Turkey. The Department of Parasitology of Ege University Medical School (EUMS-DP) has routine laboratories which are performing diagnostic examinations, as well as research laboratories working on different fields of Parasitology. The laboratory responsible for leishmaniasis, is consist of experts related to different aspects of the disease as well as vector and reservoir studies. The Department has participated in several international research projects related to basic and molecular epidemiology of human and canine Leishmaniasis, in collaboration with international scientists, supported by EU-FP6 Programs (LeishMed, LeishRisk, EDEN) and WHO
grants. The team had also completed a number of nationally funded research projects and publications related to epidemiology and molecular biology of leishmaniasis.

2.2.10.2 Key persons involved

Dr. Yusuf Ozbel, PhD is full professor in Department of Parasitology, Ege University Medical School and has extensive experience in collaborative multi-disciplinary and complex projects. His main research is focused on the vector and reservoir studies on visceral and cutaneous leishmaniasis in the regions, in Turkey, as well as development and of diagnostic tools for leishmaniasis. In addition, he is working on \textit{Leishmania-Phlebotomus} interaction and development of new molecular biological tools for the detection of \textit{Leishmania} promastigotes in vector \textit{Phlebotomus}. Dr. Ozensoy Toz is Medical Doctor and has PhD degree on Parasitology. She received basic training on canine leishmaniasis in Institute of Medicine and Tropical Hygiene, Portugal. Besides, reservoir epidemiology she is working on molecular diagnosis of leishmaniasis (ITS regions) and micro-epidemiology based on species/strain variations in Turkey. The researchers have 42 publications in peer reviewed international journals and over 50 publications in peer reviewed national journals, and gave a number of presentations at national and international scientific meetings.

2.2.10.3 Material resources

The routine and research laboratories have all basic equipments (microscopes, inverted microscopes, stereo microscopes, incubators, deep freezers, centrifuges, fluorescent microscope, laminar flows, benches) and molecular diagnostic equipments (regular and real time PCR equipment, tissue homogenisator, DNA concentrator, computerized visualization system) are present in the department.

2.2.11 Partner 11 – Centre for Ecology and Hydrology (NERC)

2.2.11.1 Organisation

NERC, Edinburgh, Scotland, UK, part of the Natural Environment Research Council (NERC), carries out large-scale and long-term research in the terrestrial, freshwater and coastal sciences to support a broad user community. We address key environmental issues through integrated monitoring, process studies and predictive modelling. The proposed project directly complements Challenges V of the CEH’s research strategy\(^5\) by quantifying the risks of exposure of ecosystems and humans to a biological threat (Challenge V) and by developing a risk-assessment framework to help us identify strategies and control measures to mitigate impacts of environmental change on human and animal health (Challenge VI). The proposed project would run parallel to existing research on UK mosquito communities and mosquito-borne pathogens, human microbial pathogens and tick-borne infections of seabirds. Within EDENext, CEH will be primarily responsible for the development of regional scale phenological and biological population model frameworks for \textit{Culicoides} vectors with which to evaluate the impacts of environmental factors and vector control measures on midge populations and BTV. CEH will help coordinate modeling activities and knowledge exchange across the \textit{Culicoides} team and ensure integration of model outputs into the \(R_0\).

2.2.11.2 Key persons involved

Dr Beth Purse is an ecological modeller within the Biodiversity programme at the Centre for Ecology and Hydrology. She has 9 years of experience in GIS, remote-sensing, modelling and

\(^5\) \text{http://www.ceh.ac.uk/science/documents/CEH\_SCIENCESTRATEGY\_2008-2013\_FINAL\_A4S.PDF}
ecology with 18 publications in peer-reviewed journals. Her research focuses on the impacts of environmental and land use changes on vectors and invasive species especially bluetongue virus (BTV). As well as demonstrating the impacts of regional climate change on the emergence of BTV, she has been involved in coordination of midge surveillance work across Europe. Recently, she applied climate envelope modelling to highlight the importance of indigenous European vectors in facilitating the spread of BT into cooler and wetter areas of Europe, necessitating the explicit consideration of these species in vector surveillance and control programmes (UK BBSRC/DEFRA project). She is experienced in the integration of ecological modelling into risk management frameworks - forecasting future impacts of climate change on distribution of BT virus for the UK Department of Trade and Industry and evaluating the potential role in BTV transmission of candidate midge vectors in Scotland for the Scottish Government. CEH are currently appointing a post-doctoral mathematical modeller to be in post by spring 2010 who will work on EDENext and whose skills are likely to include.

2.2.11.3 Material resources

CEH has the necessary hardware and software to develop and test spatio-temporal ecological models including bespoke programs for Culicoides and BTV. The NEMESIS Beowulf cluster system at CEH Edinburgh will vastly increase the potential for computationally intensive simulation modeling and increase the range of environmental and control scenarios that can be tested. Collaborative links with prospective EDENext project partners are already well developed (both within the Culicoides and Modelling project teams) as evidenced by the joint work referenced below. CEH Edinburgh also has good laboratory (non-P3) facilities that can be used for entomological work.

2.2.12 Partner 12 – Institut of Animal Health (IAH)

2.2.12.1 Organisation

IAH, Pirbright, UK. The Vector-borne disease programme (VBDP) led by Professor Philip Mellor and including Dr Simon Carpenter has a world-wide reputation at the forefront of research concerning Culicoides-borne Orbiviruses and houses the EU community reference laboratory for BTV. The Entomology and Modelling Group, led by Dr Carpenter, contains the UK vector Culicoides reference laboratory, a centre of taxonomic excellence whose outputs include the recently launched www.culicoides.net open-access internet facility. The group specialises in number of research areas including the planning, co-ordinating and running of Culicoides population surveys, using methodologies that it successfully established and coordinated at an EU scale during recent years. During the BTV-8 incursion of BTV into the UK in 2007, the group combined a similar ecozonation-based scheme with temperature-related BTV replication limits, to enable the declaration by Defra of a ‘transmission-free period’, allowing a relaxation of animal movement restrictions. This saved the UK farming industry millions of pounds in lost trade and significantly lessening the social impact of BTV. In addition, subsequent analysis allowed a date for potential BTV re-emergence in 2008 to be set7, which was used as a means of applying pressure to vaccinate during the subsequent voluntary scheme. This ultimately proved to be extremely successful, preventing the re-emergence of BTV-8 in 2008 with massive economic benefits for UK farming (estimated independently at approximately £500m and 10000 jobs). Additional areas of success within the group include the identification of efficient and novel vectors that had previously been thought to be of low epidemiological importance in transmission of BTV. This new understanding had highly significant implications for risk assessment of BTV and similar diseases in the northern Palaeartic regions, including the UK, as it clearly demonstrated, prior to the incursion in 2006, that there was potential for a BTV outbreak to occur. Finally, the group has wide experience in the application and dissemination in the field of control measures against Culicoides
both in the UK and overseas. This experience is supplemented by the position of IAH as one of only two centres worldwide maintaining fully self supporting colonies of vector *Culicoides*, enabling detailed and continuous year-round involvement in a wide range of laboratory-based vector studies.

### 2.2.12.2 Key persons involved

Dr Simon Carpenter (PhD: University of Aberdeen) has worked on *Culicoides* midges for over nine years and has published over thirty peer reviewed publications on their ecology and vector capacity. He is currently head of the entomology and modeling group and has given over 40 invited lectures during the past 3 years following the introduction of BTV into northern Europe. In addition he acts as a primary adviser to the UK government as part of the bluetongue expert group and also took part in EFSA reviews of the area. He was awarded the 2009 Rooker prize for outstanding contribution to veterinary science. Dr Anthony Wilson (PhD: Oxford University) is an IAH fellow.

### 2.2.12.3 Material resources

IAH has a biosafety level 3 laboratory to perform all the work of vector competence, with access to field collections very easily.

### 2.2.13 Partner 13 – Institut Sénégalais de la Recherche Agricole (ISRA)

#### 2.2.13.1 Organisation

ISRA, Dakar, Senegal, created in 1974, is a public and scientific institution aiming to conduct agricultural research to alleviate poverty and malnutrition. Its main fields of interest are in animal, forestry, fishery, horticulture and agriculture areas. The Laboratoire National de l’Elevage et de Recherches Veterinaires is involved in animal health and husbandry researches, specially by developing diagnostic tools and veterinary vaccines for a better surveillance of enzootic and epizootic diseases and the implementation of efficient control strategies. He developed African horse sickness vaccines used in the West African region. LNERV is the national reference laboratory for the diagnosis of the African horse sickness and currently developing competences in *Culicoides* for a better understanding of *Culicoides* borne-diseases.

#### 2.2.13.2 Key persons involved

**Momar Talla Seck**, DVM, PhD in Biology. He is researcher in Laboratoire National de l'Elevage et de Recherches vétérinaires, head of Parasitology Service and Animal Health Program coordinator. He is in charge of the research section of the “Elimination Project of Glossinae in Niayes”. **Papa Serigne Seck**, (DVM, MSc) is an epidemi-virologist currently employed at ISRA/LNERV Virology Service, Dakar (Senegal). Prior to his appointment with ISRA/LNERV, he was Technical Assistant at the World Organization for Animal Health (OIE). He joined the OIE in 2005 where he had in charge the Veterinary Critically Important Antimicrobials dossier of the FAO/OIE/WHO joint Project on Antimicrobial Resistance. He participated to the Feasibility study for establishing epimiosurveillance networks for HPAI and other TADs and Zoonoses in Africa, for The Partnership for Africa Livestock Development (ALive). **Yaya Thiongane**, DVM, PhD in virology, Head of the Laboratoire National de l’Elevage et de Recherches Vétérinaires (LNERV), head of the Microbiology laboratory. He has many years of experience in animal health with a strong involvement in viral diseases like the Rift Valley fever and African horse sickness. He coordinates the network of sentinel herds established through FAO and AIEA collaboration in three countries (Mali, Mauritania and Senegal) for the surveillance of the Rift Valley fever and transboundary animal diseases. **Jérémy Bouyer**, DVM, PhD in Biology (entomology) works currently as a researcher in Vector Ecology and Control at CI RAD, head of the vectors team of UMR15 CIRAD-INRA Control of exotic and emerging animal diseases, duty station in ISRA-
LNERV, Dakar-Hann, Sénégal. From April 2006-dec 2008. **Assane Gueye Fall**, DVM, entomologist, DEA in entomology. He involves since 2002 on bioecology of vector-borne diseases like West Nile virus vectors and Rift Valley Fever virus vectors. He had in charge the field entomological studies of the EDEN/ISRA project. He recently participates in 2008 to the entomological investigations of the 2007 African horse sickness epidemic that occurred in Senegal. **Mariame Diop**, research assistant, regional reference laboratory FAO for the Peste Porcine Africaine, the rinderpest, the African horse sickness and the avian influenza. Since 1983, she is responsible of the diagnosis and the management of the laboratory of virology. From 1990 to our days, she participates in sero-surveillance and epidemi-surveillance programs of the rinderpest and the similar diseases.

### 2.2.13.3 Material resources

ISRA is located in a country where AHSV occurred several times and is used to run vector competence animal studies, they will be involved in the setting up of the C. imicola colony in insectariums and field experiments.

### 2.2.14 Partner 14 – Centre de Reserca en Sanitat Animal (CReSA)

#### 2.2.14.1 Organisation

The CReSA Foundation, Barcelona, Spain, is a private foundation created in 1999 for conducting research in animal health. The CReSA unites the human potential for research in animal health and takes advantage of a new technologically advanced building, with level-3 biocontention (BSL3) for conducting research with all livestock species, grouping efforts and pooling new resources in this field. Research and development programs within the animal health field, diagnostics, surveillance, monitoring, and scientific advisory functions are among the main activities of our centre.

CReSA is in charge of the Entomological and Epidemiological monitoring of Bluetongue in Catalonia (NE Spain) and also perform BT research in virology and vaccinology. Focussing on the aims of the project, CReSA Entomology and Parasitology Unit has expertise in entomological research concerning the biology, vector competence, morphological and molecular diagnosis of both suspected and confirmed vectors, vector habitats and the characterization and biology of potential agents which can be used as biological control agents. The epidemiology unit has experience in risk assessment of different diseases, including the estimation of the risk of Bluetongue introduction by different pathways. The group is also working in spatio-temporal models and in the analysis of the sensitivity of surveillance systems.

#### 2.2.14.2 Key persons involved

**Nonito Pagès Martínez**, Entomologist and molecular biologist, Master in Biotechnology (Entomology). He has 6 years of experience in bioecology and molecular biology of Ceratopogonidae. In 2003 he moved from the Spanish Scientific Research High Council (Physiology and Molecular Biodiversity Unit) to CReSA. Since then he is working as a researcher at CReSA_Entomology_Parasitology_Unit where he has been participating in the research activities developed. He is responsible of the entomological surveillance on BT vectors in Catalonia (NE Spain) and research activities of the Unit, including research on BT vectors. **Francesc Muñoz Muñoz**, Entomologist, PhD in Biology (Morphological Variation). He worked for 6 years in the Zoology Unit of the Autonomous University of Barcelona (UAB) as an associate professor for Zoology lectures. Since 2007 he works as an entomologist at CReSA-Entomology and Parasitology Unit, working in systematics and bioecology of Ceratopogonidae. He is involved in the entomological surveillance on BT vectors in Catalonia (NE Spain) as well as research activities performed on BT vectors. **Sandra Talavera Forcades**, Entomologist, Master in Biology
(Entomology). She has 4 years of experience working in systematics, bioecology and biological control of Ceratopogonidae since her incorporation at CReSA. She is involved in the entomological surveillance on BT vectors in Catalonia (NE Spain) as well as research activities performed on BT vectors. **Jordi Casal**, Veterinary Epidemiologist, PhD in Veterinary Medicine and member of the European College of Veterinary Public Health. He has 25 years of experience in veterinary epidemiology. He is the head of the epidemiology unit at CReSA and Professor of Veterinary Epidemiology and Infectious diseases at the Veterinary Faculty of the Universitat Autònoma in Barcelona. **Sebastian Napp**, Veterinarian, MSc in Veterinary Epidemiology. He has been a member of the Epidemiology unit at CReSA for the last 4 years. He is working as a consultant for the Department of Agriculture of Catalonia and in risk assessment of exotic diseases.

### 2.2.14.3 Material resources

CReSA has biosafety level 3 laboratories to perform all the work relating vector competence, with easy access to known field populations of the target *Culicoides* species through the BT vector surveillance carried out. BSL3 laboratory for insect rearing including a climatic chamber with controlled Tº and RH is also available for the purposes of the project. Finally, CReSA has the necessary software and hardware to perform the epidemiological analyses.

### 2.2.15 Partner 15 – Danish Technical University (DTU)

#### 2.2.15.1 Organisation

DTU, Copenhagen, Denmark. The National Veterinary Institute at the Technical University of Denmark conducts research in infectious diseases in livestock and makes diagnoses in diseased animals. The institute gives advice to public authorities and cooperates with them on the Danish veterinary contingency plan. The institute also hosts an international research centre for veterinary epidemiology (International EpiLab). The institute is the national reference laboratory in a number of areas including both bluetongue virus and the Culicoides vectors. National Veterinary Institute DTU encompasses all infectious animal diseases in farm livestock and companion animals. The main focus is on notifiable diseases, as well as other serious infectious diseases that affect farm livestock. The institute’s research on bluetongue is centered on spatial modeling of Culicoides and bluetongue R0 aiming at predicting the optimal preventive vaccination cover, and on bluetongue diagnostics, pathogenesis and virus characterization.

#### 2.2.15.2 Key persons involved

**Anders Stockmarr**: Statistician Senior researcher PhD. The applicant is a mathematical statistician and has extensive experience within biostatistics. He is skilled within exploratory statistics and model-building for non-standard problems, and has been working with modeling disease spread and data analysis from veterinary epidemiology. **Anette Bøtner**: Virologist, DVM, PhD, head of Section for Exotic Virus Diseases. Extensive experience in diagnostic virology. More than 20 years experience with research activities regarding development of diagnostic methods, experimental pathogenesis studies and epidemiology. Responsible for the diagnostic preparedness at the Department of Virology at The National Veterinary Institute. **Lasse Dam Rasmussen**: Molecular Biologist, M. Sc., PhD in Molecular microbiology. He has 10 years of experience in molecular biology of both prokaryotes and eukaryotes. Is currently the leader of the Bluetongue Diagnostics lab in Denmark, at DTU-vet Lindholm Denmark. **René Bødker**: Epidemiologist, PhD in vector borne diseases and climate change. He is in charge of the Reference laboratory for Culicoides and the national Culicoides surveillance program. He also heads three externally funded research projects in bluetongue and other vector borne diseases in Denmark and Scandinavia. He has previously modeled malaria and filariasis in Africa, where he worked for two years.
2.2.15.3 Material resources

The DTU has the necessary hardware and software to develop models including spatial modeling of Culicoides and bluetongue $R_0$ for the prediction of the optimal preventive vaccination cover, and the equipment and the laboratory facilities to assess bluetongue diagnostics, pathogenesis and virus characterization.

2.2.16 Partner 16 – Entente Interdépartementale pour la Demoustication (EID)

2.2.16.1 Organisation

EID, Montpellier, France. Since its creation in 1958, the principal mission of the Entente Interdépartementale pour la Démoustication du Littoral Méditerranéen (EID Méditerranée) has been to reduce mosquito (Culicidae) nuisance to a tolerable level. The nuisance arises from mosquitoes breeding in the wetlands on the margins of coastal marshes and lagoons in the five departments (administrative regions) of the Languedoc-Roussillon and Provence Regions: Pyrénées-Orientales, Aude, Hérault, Gard and Bouches-du-Rhône. EID Méditerranée is equipped with a R&D laboratory (10 permanent and 10 temporary employees) studying biocides and methodological choices (effectiveness evaluation on behalf of agropharmaceutical firms for registration purposes in accordance with Directive 98/8/EC), the biology of target species, entomological monitoring carried out for arboviral disease re-emergence surveillance schemes, and unintentional impacts on the environment. The EID’s laboratory carries out numerous national and European joint projects (PNETOX, CES DIBBECO, LIFE99 ENV/F/000489, LIFE08 ENV/F/000488 starting by January 2010, FP6 EDEN project) and co-supervises PhD theses. Control strategies are based on ecological mapping and GIS tools.

Bluetongue is studied in EID Méditerranée since 2000 in the French Mediterranean basin, especially on the entomological survey network. EID is involved in the efficacy evaluation of insecticides for culicoides control using susceptibility bioassays for culicoides vs. deltamethrin and other alternative veterinary insecticides. Different ways of application are also investigated on sheep (pour on and spray). Wild population directly collected in field and Culicoides nubeculosus reared in EID’s insectarium are used in these tests. The good knowledge of the field and large experience of entomological survey and field efficacy trials allow EID to conduct expert’s evaluations on the Culicoides imicola expansion in France (Var -83 and Pyrénées-Orientales-66).

2.2.16.2 Key persons involved

Christophe Lagneau, Agronomist, is the head of R&D laboratory in EID since 1996. He has 27 years experience on insect pest control. He coordinated a LIFE-Environment project (n°LIFE99 ENV/F/000489, 1999-2003) which demonstrated a methodological approach for a sustainable management control of noxious mosquitoes in Mediterranean natural areas in a Ramsar site in Languedoc-Roussillon (France). He is coordinator of a new European project starting in January 2010 (LIFE08 ENV/F/000488). He has co-published 13 articles and several reports on mosquito control. Marie-Laure Setier-Rio, graduated in technology research in health engineering, is in charge of Bluetongue project in EID since December 2008. She has 12 years experience on entomological survey (West Nile, bluetongue). She was responsible of Quality management in EID up to 2008. She was responsible of the soil characterisation studies of mosquito breeding sites in the frame of the project LIFE99 ENV/F/000489. Roger Venail, Master in toxins and ecosystems, is involved in the bluetongue survey network since July 2008. He is in charge of the efficacy bioassays and Culicoides nubeculosus rearing. In 2005, he carried out his training in EID on diflubenzuron side effects on Simocephalus exspinosus in open field. He published 1 article in Spain.
2.2.16.3 Material resources

The EID has the facilities and competence to run the entomological surveillance network of Culicoides in the southern part of France in the identification of all the species present in France. The presence of insectariums for different insects (Aedes, Culex, Culicoides) is of major importance in such a project.

2.2.17 Partner 17 – Universitar de les Illes Balears (UIB)

2.2.17.1 Organisation

UIB, Palma, Spain. The team led by Dr. Miranda at the University of the Balearic Islands has 9 years of experience on bluetongue. The group has a broad experience on Culicoides bioecology, including spatial and temporal dynamics, breeding sites, temporal parous rate of the Culicoides species, adult’s activity and trap performance; further, taxonomy both molecular and morphological, modeling and development of Culicoides control strategies are also current research activity of the group. Recently, the group has conducted several studies on vector competence in collaboration with Dr. Venter from the Onderstepoort Veterinary Institute in South Africa. The group also includes Dr. Lucientes from the University of Zaragoza, coordinator of the National Entomological Surveillance of bluetongue vectors in Spain. All data regarding vector surveillance is centralized in the laboratories of the University of Zaragoza and the University of the Balearic Islands. In the last six years, the group has contributed to describe the actual distribution of C. imicola and other Obsoletus complex. Furthermore, we have also found the presence of C. imicola in locations where it was not previously recorded.

2.2.17.2 Key persons involved

Dr. Miguel Ángel Miranda Chueca, PhD in Applied Entomology for the last fourteen years. He pioneered the studies on Culicoides vector species of BTV during the outbreaks occurred in 2000. The UIB’s team has been collaborating for 8 years with the research team of Dr. Javier Lucientes, from the Universidad de Zaragoza (UZ) and the Centro de Investigaciones Agrarias y Teconológicas (CITA), in Aragon. The last two year he has participated as an expert for the European Food and Safety Authority (EFSA), participates in the European Project MedReoNet and the project entitled “Developing strategies for controlling Culicoides (Diptera: Ceratopogonidae) Bluetongue virus vectors” funded by the Spanish Ministry of Science for the period 2005-2008.

Dr. Javier Lucientes, DVM has been the supervisor of 11 PhD thesis dissertations and author of 187 research papers. He has participated in 76 projects financed from government institutions and companies. His research has been dedicated to ectoparasitic arthropods and diseases transmitted by them. From year 2000 he has been fully dedicated to the research of the main vectors of BTV in Spain. Carlos Calvete, DVM, has been researcher in the Spanish Scientific Research High Council (CSIC) and currently develops his research activity in the Health Animal Department of the Center of Research on Agroalimentary Technology of Aragón (CITA). His research activity has been mainly devoted to the study relationships between macroparasites and hosts populations and, also, epidemiology (host factors related to disease-risk and epidemiological models to evaluate disease control strategies) of infectious diseases in free host-populations.

Dr. Rosa Estrada Peña is researcher in the Department of Animal Health of the Zaragoza University, Spain, where her research activity has been mainly focused on the study and characterization of bioecology, identification and control of main vectors of the Blue Tongue Virus en Spain, involved in the coordination of the Culicoides sampling of the National Entomological Surveillance Program.

Dr. Claudia Paredes Esquivel, PhD in Microbiology and Parasitology on the molecular systematics and taxonomy of Anopheles species, particularly those that transmit malaria and filariasis in South East Asia. In this institution. She has been trained in different PCR-based techniques, DNA
extraction techniques, such as RFLP, Nested-PCR, DNA sequence analysis, cloning of DNA sequences, and phylogenetic studies based on DNA sequences. **Ms. Miriam Monerris** is a research assistant in the project "Entomological Vigilance of the vector species of Bluetongue in the Balearic Islands" funded by the Institute of Animal Biology (IBABSA). She participated in the project “Development of Strategies for the Control of Culicoides (Diptera:Ceratopogonidae) populations, Bluetongue vectors” and trained in the use PCR-based techniques to identify pathogens in vectors. **Mr. Ricardo del Río López**, PhD student on vector competence and control of Culicoides vector species. He has spent four weeks at CIRAD (Montpellier, France).

2.2.17.3 Material resources

The group of UIB includes several experts in different fields (entomology surveillance, modeling, identification, molecular biology, vector competence), has access to the data regarding vector surveillance.

2.2.18 Partner 18 – Institut Pasteur (IP)

2.2.18.1 Organisation

IP, Paris, France, is a non-profit private foundation dedicated to the prevention and treatment of diseases, with a major focus on infectious diseases through biomedical research, education, and public health activities. It includes a worldwide network of 30 institutes working on emerging viruses including arboviruses such as CCHFV, CHIKV and WMV. Several research units are studying arboviruses and hemorrhagic fevers including the 3 participating to EDENext: « Unité insectes et maladies infectieuses » (UIMI, Paul Reiter), « Unité de génétique moléculaire des Bunyavirus » (UGMB, Michèle Bouloy), « Unité des infections virales émergentes » (UBIVE, Noel Tordo). UBIVE is also hosting the National Reference Centre (NRC) for Viral Haemorrhagic Fevers (VHF) and a WHO Collaborative Centre (WHOCC) for VHF and Arboviruses. UGMB is heading an OIE Reference Laboratory for RVFV and CCHFV to which UBIVE is participating.

UIMI/UGMB units are located on the Paris campus and have access to many platforms (imaging, sequencing, technology for microarray, protein analysis, etc.) as well as BSL2/3 labs and A2/A3 animal facilities including insectarium. UBIVE is located in Lyon-Gerland and benefits from the BSL3/4 and A3/4 facilities.

UIMI is oriented to the epidemiology and control of mosquito-borne arboviruses. Research is focused on (1) control of Aedes aegypti by genetically modified males (RIDL) ; vertical transmission of yellow fever and West Nile virus ; (3) epidemiology of West Nile Virus (WNV) in the field ; (4) epidemiology and control of dengue in Singapore.

GMB has a long experience in research on bunyaviruses including RVFV and CCHFV. Research is mainly focused on: (1) host cell / virus interactions in vitro and in vivo by comparing pathogenic and non-pathogenic models (RVFV/clone 13 ; CCHFV/Dugbe); (2) development of vaccines against RVFV; (3) mosquitoes competence for different arboviruses like CHIKV and RVFV; (4) production of recombinant antigens for diagnosis by ELISA of arboviruses (RVFV, CCHFV) and Hantaviruses (Puumala).

UBIVE develops expertise in research, surveillance and diagnosis of Biosafety Level 4 and 3 (BSL4/3) viruses, mainly responsible for hemorrhagic fevers (Arena-, Filo-, Bunyavirus like CCHFV) or encephalitis (Henipavirus). Research is mainly focused on: (1) understanding the pathophysiology of BSL4 viruses by comparing pathogenic and non-pathogenic models at the molecular and immunological levels, and elucidating host-virus interactions in vitro and in vivo; (2) setting up animal models (from rodents to non-human primates) reproducing BSL3/4 virus infections both to study their pathophysiology or to screen the efficiency of vaccines or therapeutics. In addition, due to Natl/WHO/OIE reference centre, UBIVE is maintaining a
collection of BSL3/4 viral species (Arena, Filo, Henipa, Bunya) as well as a complete panel of reagents/methods for diagnosis and/or surveillance including serologic, antigenic and genetic tools as well as expertise in virus isolation.

Institut Pasteur is involved in various European Projects on emerging viruses: IUMI is Steering Committee member and co-ordinator of West Nile Virus sub-project of EDEN; UGMB coordinates the Arbozoonet Network (FP7) and is associated partner of ENIVD (ECDC). UBIVE is partner in Arbozoonet, RiViGene (FP6); ENIVD (ECDC) and associated partner in Euronet P4 (DG-SANCO) and Empirie (FP7).

2.2.18.2 Key persons involved

**Prof. Paul Reiter** (M), PhD, FRES, Head of UIMI, expertise in surveillance, epidemiology and control of mosquito-borne diseases, particularly dengue; WHO Panel of Experts, International Health Regulations (IHR). **Dr Michèle Bouloy** (F), PhD, Head of the UGMB, Head of OIE Ref. Laboratory for RVFV and CCHFV, expertise in molecular/cellular biology, and vaccinology against Bunyaviruses. MB is coordinating the Arbo-zoonet Network (FP7). **Dr Noël Tordo** (M), PhD, Head of the UBIVE, Director of National/WHO Ref Centres for VHF and Arboviruses, expertise in molecular/cellular biology, and antiviral strategies against emerging viruses. **Dr Philippe Marianneau** (M) PhD, Deputy-Director of the National Reference Centre for VHF, expertise in diagnosis, molecular biology, virology, animal model development and experiments on BSL4 viruses. **Dr Anna-bella Failloux** (F) PhD, is an entomologist with a large experience in vector competence experiments, particularly in BSL3 containments.

Introduce the key persons involved in the project (up to five persons per organisation), their fields of expertise, groups, and references (up to five references per organisation).

2.2.18.3 Material resources

IP hosts large collections of viral species and reagents and regularly performs QA laboratory diagnosis of arboviruses and VHF (survey or outbreaks) using antigenic, genetic methods and virus isolation. IP will dedicate diagnostic and research laboratories, animal facilities and storage capacities of the BSL2/3/4 and A2/3/4 levels necessary for conducting the work as proposed. This includes also technical staff and consumables for running these facilities.

2.2.19 Partner 19 – University of Veterinary Medicine Vienna (VETMEDUNI)

2.2.19.1 Organisation

The University of Veterinary Medicine Vienna, Austria, is the second oldest veterinary school in the world, founded in 1765 by Empress Maria Theresia. In 1996 the University moved to a new campus, which is considered one of the largest and most modern in Europe. The University has a permanent staff of 900, approximately half are scientific and half are support staff. The annual University budget amounts to 40 million Euro, and the annual income is approx. 10 million Euro. There are 2,500 registered students. The animal hospital is treating 24,000 cases per year. The University is dedicated to research, and state-of-the-art research facilities and equipment are available throughout the University including more than ten level-3 laboratory and animal facilities. The research output is close to 1,000 original Journal publications annually.

The major achievements of the group regarding mosquito-borne (flavi)viruses are:

Identification, characterization, detailed analysis and follow-up of all aspects (entomological, virological, serological, pathological, zoonotic, diagnostic, epidemiological, etc.) of *Usutu virus*, a close relative to *West Nile virus*, which emerged in Austria in 2001, and spread meanwhile to other central European countries (15 PubMed-listed publications on all aspects of *Usutu virus* infections);
Identification and characterization of a lineage 2 *West Nile virus* (WNV), which emerged in 2004 for the first time in Europe (Hungary), and spread in summer 2008 all over Hungary and to the eastern part of Austria; this virus has been affecting several different species of birds (especially birds of prey), horses, sheep and human beings; high mortality has been observed in birds, and moderate in horses; human beings developed mainly meningitis (n > 30); no human fatalities up to now. The virus has been identified in – a comparably high number of – mosquito pools, especially in *Culex* mosquitoes, indicating that this virus will stay and overwinter in Europe, as evidenced by severe outbreaks in summer 2009, too. Since this lineage 2 WNV shares only 80% nucleotide identity to the lineage 1 WNVs, which have been around in Europe for a long time, it is quite likely that this virus will significantly spread in Europe and may in the near future also be of significant public health concern. This virus infection must be monitored closely and still a lot, in particular also entomologically, has to be done → please see the proposed description of work.

Characterization of a lineage 1 WNV which emerged in Hungary in 2003 in animals and humans and which turned out to be most closely related to the WNV which was introduced in 1999 to New York – this finding may shed new light on the introduction of WNV to America; Molecular and biological characterization of *Rabensburg virus*, which turned out to be either a novel WNV (suggested lineage 3) or a novel flavivirus; Entomological and virological studies on *Tahyna virus*, a mosquito-transmitted *Orthobunyavirus*, which is endemic in central Europe and causes a human febrile illness.

2.2.19.2 *Key persons involved*

*Norbert Nowotny*, PhD (team leader), Professor of Virology, Leader of the Zoonoses & Emerging Infections Group - All aspects of virology and some of entomology. *Jolanta Kołodziejek*, MSc, Dr.tech., Senior Researcher - Molecular virology, sequencing, phylogeny. *Bernhard Seidel*, PhD, Postdoc, Entomologist - Vector ecol. & trapping. *Herbert Weissenböck*, DVM, PhD, Professor of Pathology - Neuropathology, flaviviruses, IHC, ISH. *Helga Lussy*, Laboratory Technician - Entomol. & virol. lab. Work; *Hans Homola*, Laboratory Technician - Field & lab. Work.

2.2.19.3 *Material resources*

In short, at the Institute the skills and equipment for all types of entomological, virological (both “classical” and molecular) and serological work are available including PCR, real-time PCR, nucleotide sequencer, molecular phylogeny, etc. State-of-the-art level 3 laboratories are available.

2.2.20 Partner 20 – Academy of Sciences of the Czech Republic (IVB)

2.2.20.1 *Organisation*

Institute of Vertebrate Biology, v.v.i., in Brno, Czech Republic, is a member institution of the Czech Academy of Sciences. The general research plan "Biodiversity and ecology of vertebrates: implications in conservation and sustainable management of natural populations" is aimed to yield original scientific knowledge of the biology of vertebrates with respect to genetic, species, and community diversity, population dynamics, interactions with environments in ecosystems, and associations with microbial pathogens dangerous for man and domestic animals (see http://www.ivb.cz/general-information.html). Medical Zoology Laboratory (Department) of this institute, situated in Valtice (South Moravia), was established in 1972 for the purpose of studying natural focality of infectious human diseases.

The staff (four scientists, one Ph.D. student, two technicians) have got expertise in laboratory techniques and field work as well. During the last years, significant results were achieved on the ecology of zoonotic arthropod-borne viruses and bacteria (ranging from BSL2 to BSL3+) associated with natural foci of infections (e.g., *Borrelia burgdorferi*, West Nile virus, Bhanja virus),
and about 270 scientific papers have been published from the Laboratory. The Laboratory is well equipped with ultra-freezers, centrifuges, laminar flow and biosafety boxes, liquid nitrogen containers, a freeze-drying machine, an ultrasonic homogenizer, etc. It is also equipped to carry out molecular biology studies - with a gradient thermocycler, real-time cycler, gel documentation system, etc. There is also an accredited animal room facility in the laboratory that has been certified under the Animal (Scientific Procedures) Act. All these resources will be available for EDENext.

2.2.20.2 Key persons involved

Prof. Dr. Zdenek Hubalek has been studying ecology and taxonomy of arthropod-borne viruses and bacteria pathogenic to humans since 1974. Professor in microbiology at Masaryk University in Brno. Member of the WHO Europe expert groups “Climate Change and Adaptation Strategies for Human Health” (cCASHh project, 2001-04) and “Public Health Significance of Urban Pests” (2004-06). Member of the working group “Environmental change and infectious diseases” (ECDC, 2007). He has been involved in the FP6 project EDEN (2005-10), and ECDC tender “V-borne” (2007-08: mosquito-borne viruses; tick-borne viruses; tularemia). A total of 184 ISI WoS listed publications, 2090 citations, h value of 22 (complete bibliography at http://publicationslist.org/zdenek.hubalek). Ivo Rudolf, Ph.D., a microbiologist (Ph.D. Thesis 'Study of selected tick-borne pathogens of humans' at Masaryk University defended in 2004). Since 2004 he has been working as post-doc at IVB. He has published 14 scientific papers in peer-reviewed journals. I. Rudolf has been involved in the FP6 project EDEN (2005-2010), diagnosing diverse tick-borne agents in Ixodes ricinus ticks by molecular methods (PCR, real-time PCR). He was awarded the prize “Czech and Slovak young microbiologist of 2008”. Silvie Šikutová, Ph.D., a biologist (Ph.D. Thesis "Study of selected microorganisms transmitted by haematophagous insects" defended at the Masaryk University in 2005). Since 2005, she is working as post-doc at IVB. She has published 14 scientific papers in peer-reviewed journals. S. Šikutová has been involved in the FP6 project EDEN (2005-2010), performing serological surveys.

2.2.20.3 Material resources


2.2.21 Partner 21 – Sven Istvan University, Faculty of Veterinary Science (SZIE)

2.2.21.1 Organisation

The Faculty of Veterinary Science, Budapest, is the only veterinary school in Hungary. It is a state institution supervised and financed by the Ministry of Education, and is accredited to issue the diplomas of Doctor of Veterinary Medicine (D.V.M.), and the postgraduate degree of Philosophiae Doctor (Ph.D.) in veterinary sciences. The Faculty has an uninterrupted teaching record for more than two centuries, making it thus one of the oldest veterinary schools in the world. Since 1989, in addition to a yearly enrollment of about 100 Hungarian students, international students have been continuously enrolled in the school. A full veterinary program has been instituted and is offered in English with the pre-clinical section also in German. Currently more than 600 international students from all over the world are studying veterinary medicine in Budapest. The Department of Parasitology and Zoology was established in 1929. Zoology courses focus on different aspects of general biology and taxonomical description of the animal kingdom, supplemented by study of supraindividual organisation, population dynamics and genetics, as well as evolution biology. Parasitology which consists of theoretical and practical courses is intended to familiarize the students with the essential facts and concepts of veterinary parasitology enabling them to control and prevent economical losses, parasitozooneses, and to improve animal welfare.
Besides teaching the staff has broad range of research experience over decades with epidemiological, diagnostic and treatment/control studies on parasitic diseases of domesticated and wild animals including parasitozoonoses. Majority of the research topics have been focusing on vectors and vector-borne diseases of animals, especially tick-borne diseases. The academic staff has built up several national and international scientific collaborations with institutions, scientists and international pharmaceutical companies. The department has been taking part in EDEN integrated project.

The activity of the Department of Microbiology and Infectious Diseases, Faculty of Veterinary Science, Szent Istvan University (SzIE) covers three main areas: education of microbiology and epizootiology / infectious diseases of animals to veterinary and biology students; scientific research on different fields of veterinary microbiology, and microbiology laboratory diagnostics. The research topics contain both fundamental research, technical development (of diagnostic methods) and applied research (development and testing of vaccines and anti-microbial agents). Samples for laboratory testing are obtained from the clinics and other departments of the faculty, or from other clinics, filed veterinarians and farms.

The team of the Virology Unit would participate in the research project. The group described and genetically characterized several new virus infections in Hungarian livestock, performed surveillance on important viral pathogens, and developed new molecular techniques for the quick detection and characterization of animal virus infections. A particular interest is dedicated to zoonotic and vector-borne viruses. The team is skilled with sample collection, laboratory processing (both with molecular methods, virus isolation, and serology), and analysis of the research data. Since 2003 the study group investigates the occurrence and spread of mosquito-borne flaviviruses (WNV, Usutu virus) in Hungary. Within previous and on-going research projects the team have developed close collaborations with entomologists (Department of Zoology, Hungarian Natural History Museum), with ornithologists (BirdLife Hungary) and with the nature conservation authorities (National Parks, Zoos).

2.2.21.2 Key persons involved

Prof. Dr. Róbert Farkas, PhD: veterinarian, head of the department, president of the Hungarian Society of Parasitologists. His main research topics are the arthropods of veterinary importance and vector-borne diseases. He has participated in several international and national research collaborations for more than two decades. Number of papers in peer-reviewed journals is over 80. He is the diplomat and one of the founders of the European Veterinary Parasitology College. Dr. Sándor Hornok, PhD: veterinarian, associate professor. He has research experience in immunology and molecular biology methods of tick-borne pathogens. Number of papers in peer-reviewed journals is 30. Dr. Gábor Földvári, PhD: biologist, assistant professor. He has research experience on ticks and tick-borne disease and molecular biology methods. Number of papers in peer-reviewed journals is 13. Tamas Bakonyi, DVM, PhD: associate professor; sample collection, PCR, phylogenetic studies, molecular epidemiology, publication, project management; 14 PM. Akos Hornyak, DVM, PhD: researcher veterinarian; isolation and serological characterisation of viruses, molecular diagnostics; 4 PM. Petra Forgach, DVM, PhD: junior lecturer; sample processing, molecular diagnostics; 4 PM. Miklos Rusvai, DVM, PhD: university professor; management of sample collection, publication; 2 PM. Bence Bozsa: technician; cell culturing, virus isolation, sample processing, serology; 12 PM. Adam Paller: technician; sample collection and processing; assistance in the animal experiments; 12 PM. New employee funded by the project, PhD; Post doc; mosquito collection and identification, experiment design, mosquito control experiments, data analysis, publication; 48 PM. New employee funded by the project; PhD-student; mosquito collection and identification, field experiments on mosquitoes, infection trials on birds, data analysis, publication; 24 PM.
2.2.21.3 Material resources

The department possesses microbiology laboratories equipped for the conventional microbiological techniques and for molecular microbiology methods. The department has an animal house for research involving experimental infection of animals. PCR methods for detecting tick-borne pathogens. Primers and positive controls for detecting *Anaplasma* spp., *Bartonella* spp., *Babesia* spp. and *Rickettsia* spp. Serological methods for detecting anaplasmosis and babesiosis in animals. Collections and identification keys for identification hard tick specimens. ELISA technology for detection of antibodies to tick-borne pathogens.

2.2.22 Partner 22 – The National Institute of Research and Development for Microbiology and Immunology “Cantacuzino” (NIRDMI)

2.2.22.1 Organisation

Cantacuzino National Institute for Research and Development in Microbiology and Immunology (NIRDMI), located in Bucharest, Romania, is an institution of public importance, in the coordination of the Ministry of Health, as the main technical and scientific competent body involved in the development and application of programs aiming at preventing and controlling infectious diseases. Main fields of activity are: microbiological surveillance by the National Reference Centres recognized by the Ministry of Health for diagnosis and surveillance of communicable diseases; fundamental and applied research in microbiology and immunology; production of vaccines, bacterial immuno-modulators.

The present project is involving a research team from the Vector Borne Infections, Medical Entomology, and Molecular Microbiology Laboratories in Cantacuzino NIRDMI. This team will participate in the Mosquito borne diseases subproject, with field based research to understand the enzootic transmission West Nile virus in the Danube Delta and its emergence in humans in urban areas. Besides biology of vectors studies, molecular detection of the West Nile virus in mosquito pools, and virus isolation tests will be performed. The detected virus will be sequenced and phylogenetic analysis will be performed as well.

Dr Ceianu had contributions in West Nile virus outbreaks investigation and West Nile virus surveillance in Romania starting with 1996 till present.

2.2.22.2 Key persons involved

**Dr Cornelia Ceianu** is a senior researcher in Cantacuzino NIRDMI. Starting with 1982 she worked in Cantacuzino NIRDMI in the Medical Entomology field and zoonotic surveillance of vector borne agents, in Pasteur Institute in Madagascar (2000-2001), as a Fulbright Research Fellow in Colorado State University (1998), and as an Emerging Infectious Diseases Laboratory Fellow in the Arbovirus Branch/ Vector Borne Diseases Division in CDC/Fort Collins (2003-2004). Since 2004 she is heading the diagnostic activity of arboviruses and hemorrhagic fever viruses in the National Reference Centre for Vector Borne Infections. **Dr Gabriela Oprisan** is a senior researcher in Cantacuzino Institute, working on molecular epidemiology and evolution of RNA viruses. Her postgraduate studies include stages in Pasteur Institute Paris Microbiology in Retroviruses Biology Unit (1991-92), in the Molecular Epidemiology of Enteroviruses Unit (1999-2000). **Dr Daniela Badescu, MD, PhD**, is head of the Vector Borne Infections Laboratory. Her expertise covers diagnostic and field epidemiology of vector borne diseases, and quality control in the laboratory work as well.

2.2.22.3 Material resources

A BSL3 facility is planned to be functional by the end of 2010 year, molecular biology and virology facility are in place.
2.2.23 Partner 23 – University of Roma “La Sapienza” (UNIROMA1)

2.2.23.1 Organisation

The University of Rome “Sapienza”, Rome, Italy, is the largest University in EU. The Medical Entomology group in Parasitology Unit of the Department of Public Health Sciences boasts a long lasting tradition in research on mosquito vector of human diseases, with particular reference to malaria vectors and *Aedes albopictus* and *Ae. aegypti*. The role of the group in the project will be focused on the component of the MBD-WPs related to *Ae.albopictus*, which will be coordinated by the group leader Dr. Alessandra della Torre (AdT).

2.2.23.2 Key persons involved

**Alessandra Delatorre** has a long lasting experience in mosquito vector studies. In particular, since the colonization of Rome by *Ae. albopictus*, she has carried out researches on the biology of the species in Italy, with particular attention on those behavioural aspects that affect its potential efficiency as arbovirus vector and the optimization of monitoring and control interventions. Moreover, she has developed and patented, in collaboration with Dr. P. Reiter (MBD group coordinator) a novel kind of sticky-traps, which was proved to be a valuable alternative to approaches currently used to monitor *Ae. albopictus* and *Ae. aegypti* and a very effective tool to study their biology. In the last 10 years, she has acquired managerial experience in science by participating as PI or co-PI in a series of international/national collaborative projects funded by NIH-USA, TDR-WHO, FP6-EC, and Italian Funding Agencies; presently, she is WP-coordinator in two FP7 projects funded in 2009: “MALVECBLOK: Population biology and molecular genetics of vectorial capacity in *An. gambiae*: targeting reproductive behaviour and immunity for transmission refractory interventions” and “INFRAVEC: Research capacity for the implementation of genetic control of mosquitoes”. In the frame of the latter project, she is in charge of coordinating a European multi-centre *An. gambiae* and *Ae. albopictus* stocking and rearing facility, and is contributing to the development of molecular tools for the study of population structure of *Ae. albopictus*. The late will be instrumental for having the possibility to utilise as soon as available the new molecular tools expected from INFRAVEC in the frame of the present project.

Staff participating in the proposal: PI (10%), Assistant Professor (M. Pombi, 25%), 2 Post-Docs (B. Caputo, 50%; F. Marini, 50%). 1 PhD student (to be recruited, 100% for 3 years); 1 technician (M. Calzetta, 25%).

2.2.23.3 Material resources

Relevant to the project are 4 insectaries (with T, RH and photoperiod) for mosquito rearing, one of which fully reserved for *Ae. albopictus*; incubators for small scale rearing under different T; facilities for *Ae. albopictus* outdoor rearing under semi-natural conditions during the reproductive season; binocular microscopes for mosquito dissections; access to Near-Infrared spectrometer in collaborating Department.

2.2.24 Partner 24 – University of Zurich (UZH)

2.2.24.1 Organisation

The University of Zurich (UZH) is the largest university of Switzerland, with almost three thousand professors, assistants and senior scientists performing research and teaching The Institute of Parasitology (IPZ) is effectively participating in scientific programmes, in which emphasis is given to both applied and basic research. IPZ is the Swiss reference centre for arachno-entomology as appointed by the Swiss Federal Veterinary Office, and it provides routine diagnoses of arthropods within this frame. Research on arthropods at IPZ focuses on field investigations of potential and
active insect vectors. Recently, IPZ has developed research projects on biting midges (Culicoides spp.), vectors of the bluetongue virus, fruit flies (Phortica spp.), vectors of Thelazia eye worm and invasive mosquitoes as Ae. japonicus and Ae. albopictus, vectors of Chikungunya and West Nile viruses. Research includes field ecology and molecular biology, and current developments of laboratory rearing methodologies will help to implement experimental investigations. The team will include Dr. Francis Schaffner and with this project we ask for financial support for a part of a PhD student position.

In EDENEXT, UZH will provide Ae. japonicus populations for competence studies (CHIKv and DENv) and will be in charge of field activities addressing the bionomics and population dynamics of this invasive species, and will evaluate the efficacy of innovative control strategies against invasive mosquitoes in Central Europe.

2.2.24.2 Key persons involved

**Dr Francis Schaffner**, French, PhD: medical and veterinary entomologist. He has more than 24 years of experience in surveillance, control, taxonomy, ecology of insect vectors and epidemiology of human and animal vector-borne diseases. He was during 8 years co-ordinator for the detection and control programme of invasive mosquitoes, firstly Ae albopictus, throughout France, and he participated actively to the risk assessment of West Nile and chikungunya viruses for metropolitan France. He was also involved in the former EU-funded project EDEN, initially as a scientific referent for a full partner (EID Méditerranée, France) and since his relocation to Zurich (end of 2006) as invited expert in entomology. Beside his main activity as leader of a research team on arachno-entomology, he is working as consultant within the Avia-GIS company and the Euro-AEGIS group, major activities including training and capacity building, as well as providing guidance and advice for risk assessment and management of vector-borne diseases. Thus, he has lead in 2008 the TigerMaps project for ECDC (Development of Ae albopictus risk maps) and is member of the recently created consortium who is developing for ECDC the VBORNET European Network of entomological and public health specialists on vector borne diseases. He is active in several international scientific societies and co-leader of the European Mosquito Control Association (EMCA) Ae. albopictus working group, which allows him to develop numerous contacts throughout Europe. He published more than 40 articles in peer-reviewed journals and 25 other papers, booklets, book chapters or CD-ROM, of which most are closely related to the EDENEXT project.

2.2.24.3 Material resources

IPZ will dedicate to the project its standard laboratory and computer equipment as well as two climate chambers for the rearing of laboratory colonies of mosquitoes.

2.2.25 Partner 25 – Institute of Public Health Albania (IPH)

2.2.25.1 Organisation

IPH, Tirana, Albania, is the only country coordinating center on public health in Albania aiming to protect the Albanian population from infectious agents, hazards and disability. CIDD is the national coordination center on surveillance and control of infectious diseases with more 10 reference laboratories including the Lab of virology and Entomology, where the National Reference Centre for Arboviruses and Hemorrhagic Fever viruses is established and all important infectious diseases and outbreak investigation databases. CIDD is the national center for biosafety and viral biological preparedness. CIDD is the national center on surveillance, outbreak investigation and control of CCHF and other hemorrhagic fevers. It is running three BSL-2 units and the establishment of BSL-3 is under way, equipped with PCR machines. The lab is dedicated to diagnosis of human infectious diseases caused mainly by viral diseases including arboviruses and viral hemorrhagic fever viruses,
especially CCHF virus and hantaviruses. It is also the national center for control of CCHF and has an experience on control strategies, community information and education as well as developing training packages on CCHF for medical doctors including infection control. It is coordinating the South East European network on surveillance and control of infectious diseases where a regional center is going to be established and has recently participated European Network for Imported Viral Diseases. The group has long standing collaboration with the Department of Microbiology of Aristotelian University, with national institutes in Bulgaria, Serbia, Montenegro, Romania, FYROM, Croatia, Bosnia and Herzegovina, Instituto Spalanzani and Instituto Superiore di Sanita in Italy, INVS, Paris, France and Health Protection Agency in UK.

Previous Experience relevant to the Tasks: Extensive experience in CCHF diagnosis, outbreak investigation, tick surveillance and control of CCHF. Achievements: identification of first CCHF cases in Albania, outbreak investigation and infection control guidelines, mapping for the first time the ticks and ecology and CCHF in Albania, implementation of control strategies, establishment of viral imported diseases laboratory diagnosis in Albania, Study on cytokines and on CCHF clinical course.

2.2.25.2 Key persons involved

**Ass. Prof. Silvia Bino, MD, PhD:** Ass. Prof. of Infectious Diseases, Head of CIDD department, trained in Infectious Diseases, epidemiology and public health with internationally recognized expertise in the field of diagnosis, surveillance, outbreak investigation, training and control of infectious diseases including CCHF and who established the first database of CCHF in Albania.

**Mrs. E. Velo,** PhD: Biologist, entomologist, experienced in tick identification and surveillance. **Dr N. Como,** PhD: Medical doctor specialized in infectious diseases, with a long experience in CCHF clinical diagnosis and treatment. **Mrs. M. Kota Dhimolea,** PhD: Virologist who has been working on in the field of diagnosis of CCHF and other viral imported diseases. **Dr. E. Tomini MSc:** Medical doctor epidemiologist who helped on outbreak investigation and control of CCHF and establishment of CCHF database in Albania.

2.2.25.3 Material resources

The entomology lab has oviposition traps, CDC light traps, aquatic pipettes, mini mosquitoes breeders, stereo microscopes, microscope, thermostat, mechanical aspirators, bug-dorm-1, rearing and observation cage, Fay-Price traps, chemical hood with molecular filter, etc. The collaborates with virology and molecular virology lab for performing molecular diagnostics.

2.2.26 Partner 26 – Consejo Superior de Investigaciones Científicas (CSIC)

2.2.26.1 Organisation

CSIC, Sevilla, Spain. The Higher Council of Scientific Research (http://www.csic.es) is a Gov Agency. It is the Public Organisation most important of Spain with 126. The Doñana Biological Station (http://www.ebd.csic.es/) is a public Research Institute belonging to CSIC Natural Resources Area. Originally it was devoted to the study of terrestrial ecology. Our main goal is to carry out multidisciplinary research from an evolutionary viewpoint, on the way in which biodiversity is generated, maintained and how it deteriorates, as well as the consequences of its loss and the possibilities of its conservation and restoration. During the 6th Frame Program our laboratory was a research group in the EDEN project (WNV sub-project). The staff includes 2 Titular Scientists, 1 additional contracted Doctors, 1 Pre-doctoral student and 2 Technicians.
2.2.26.2 Key persons involved

**Dr. Jordi Figuerola Borras**: Scientific Tenure. His research activities in recent years have focused on studying the mechanisms that promote and/or restrict local and long distance dispersal of plants, invertebrates and pathogens by waterfowl. Work with parasites has focused on different groups of blood parasites and pathogens, mainly Protozoa blood and West Nile virus and Influenza in wild birds. He has published over 80 articles in journals covered by SCI, 19 popular science articles, 12 book chapters and 1 book (see http://www.efd.csic.es/jordi). Since 2006 he had been project leader of 9 projects on West Nile virus, Influenza and dispersal of toxic algae by waterfowl. **Dr. Ramon C. Soriguer Escofet**: Scientific Tenure. Research topics: the biology, ecology and genetics of game species. He has also conducted numerous studies on small mammals, conservation biology of endangered species, biomedicine and parasites. He has authored over 100 scientific publications. Among them, there are 7 books and 26 book chapters. He has the scientific responsibility of a National Scientific-Technical Infrastructure. Along with Dr Figuerola share responsibilities at the current National Plan for Surveillance of West Nile of the Spanish Ministry of Agriculture. Since 2006 he had been project leader of 7 projects on West Nile virus, Avian Influenza and mosquitoes and flavivirus interactions. **Technical Assistant**: EBD (CSIC) provided to the research group with technical assistants (1-2 according to the financial availability). The senior scientists in the research group are a consolidate and multidisciplinary team. But its greatest value is the consistency of the group and the long experience of work of joint research and publications shared.

2.2.26.3 Material resources

Our Institute has all the field material and lab resources needed for this project, including GIS, Ecophysiology and Molecular Ecology Lab (http://www.efd.csic.es), Field Station (http://icts.efd.csic.es/), microscopy units, and software. Two administrative units will be very helpful for the project: the European Projects Unit and the Research Support Unit.

2.2.27 Partner 27 – Agence Française de Sécurité Sanitaire des Aliments (AFSSA)

2.2.27.1 Organisation

The French Food Safety Agency is a public and independent organization contributing, through monitoring, alert, research and research investigation, to the protection and improvement of public health, animal health and welfare, vegetal and environmental health. The Agency also evaluates health and nutrition risks and benefits, through collective expert assessments and submits policy proposals to the French Ministry of Agriculture. The Agency coordinates the Med-Vet-Net network of excellence uniting over 40 European research bodies, participates in the EPIZONE (animal diseases) and EuroFIR (food composition) networks.

The AFSSA LERPAZ laboratory, located at Maisons-Alfort, is involved in reference and research activities on zoonotic or major animal pathogens. More particularly, the Virology unit homes national reference laboratories for bluetongue (BTV), African horse sickness, foot-and-mouth viruses, and also one community reference laboratory (CRL) on equine diseases, including West Nile disease. This laboratory contributes to several European networks, such as Arbozoonet (WNV), EPIZONE (BTV,…), MED-VET-NET (hepatitis E virus).

2.2.27.2 Key persons involved

**Dr. Stéphan Zientara**: He is the Contract Manager and Head of the Virology unit for the AFSSA-LerpaZ laboratory. He has a 20 years experience in animal virology (in particular in Foot-and-Mouth Disease, bluetongue, West Nile, African horse Sickness, equine influenza, equine arteritis virus, equine herpes and equine infectious anaemia viruses). He has been involved in six European projects and is a member of several EU Scientific working-groups. He is member of the EU-FAO
research group on Foot-and-Mouth diseases, Head of the European reference laboratory on equine diseases and member of the board of the European society for veterinary Virology. He is author or co-author of 70 international publications and 130 national publications and communications. **Dr. Sylvie Lecollinet**: She is a Titular Scientist and the deputy head of the CRL on equine West Nile virus infection. She is involved in many projects on West Nile virus, in relation with its epidemiology, the development and improvement of diagnostic methods and vaccines and also pathogenicity studies.

### 2.2.27.3 Material resources

The Institute has all the material resources needed for this project, including a BSL3 facility (laboratories + animal facilities), and also facilities for viral culture, biotechnology (including several real-time PCR instruments) and immunology techniques.

### 2.2.28 Partner 28 – Danube Delta National Institute for Research (DDNI)

#### 2.2.28.1 Organisation

DDNI, Tulcea, Romania. Danube Delta National Institute for Research and Development (DDNI) was established in 1970 and it has as the main objective the performance of the fundamental and applied research in a variety of topics including (i) structure, evolution and function of the specific wetland ecosystems; (ii) monitoring of the biological diversity and environmental factors; (iii) modelling the processes that are the basis of ecosystem functioning; (iv) sustainable use of the biological natural resources (fish, vegetation, game and landscape); (v) assessment and reduction of the human impact; (vi) restoration and rehabilitation of the ecosystems that have been injured by the negative human activity; ecological restoration; (vii) ecological rehabilitation of some threatened species. Due to its expertise in the wetlands fauna’s biology and ecology, DDNI has been involved in several national and international projects. The present project is involving a research team including the Ornithology and Hunting and Game labs stuff in the Danube Delta Institute. This team will participate in the Mosquito borne diseases subproject, with field based research to understand the enzootic transmission West Nile virus in the Danube Delta and its emergence in human settlements. The team will work especially in WP 1.10 - 1.14 and will help the Cantacuzino Institute team to reach goals in the other work-packages.

#### 2.2.28.2 Key persons involved

**Dr. Kiss J. Botond** is a senior researcher in the Danube Delta National Institute for Research-Development and got his PhD degree in Biology in 1999, Iassy University, Romania. Starting with 1972 he has worked in the Danube Delta National Institute in projects regarding the biodiversity (birds, mammals), bird ectoparasites. His ornithological and parasitological researches were applied in West Nile virus research in last 5 years in EDEN project. **Marinov Mihai** is a Scientific Researcher in the Biodiversity Department in the Danube Delta National Institute, working on Ornithology and Hunting and Game laboratories. His expertise covers field techniques in ornithology and other vertebrates and habitat mapping. He graduated from the Ecological University of Bucharest (Biology Department) in 2002; PhD Student (2004-2011) in Vertebrates at the University of Bucharest (Biology Department). Since 2005 he is heading the Hunting and Game lab in the Danube Delta National Institute. Mr. Marinov had contributions in West Nile virus surveillance in last 5 years.

#### 2.2.28.3 Material resources

Field. Ships, engine boats, cars; equipment for field activities (centrifuges, pipettes, electrical generator); Office. 2 notebooks, 4 PC, printers and all software needed (i.e., CorelDraw, Arc Wiev etc). Laboratory, equipped with all necessary (centrifuges, refrigerators, freezers etc)
2.2.29 Partner 29 – Finnish Forest Research Institute (METLA)

2.2.29.1 Organisation

METLA is an independent research organisation under the Ministry of Agriculture and Forestry in Vantaa, Finland, promoting ecologically, economically and socially sustainable forestry. METLA has a permanent staff of about 800. METLA has a long and scientifically wide tradition in forest zoology, especially in mammalogy and entomology, and forest pathology. The team of Prof. Heikki Henttonen (HH) has specialized on long-term surveillance and experimental studies on rodent dynamics, and on the ecological interactions of rodent dynamics and rodent-borne pathogens and parasites world-wide. METLA coordinated robo research in EDEN, and will do so in EDENext, and is involved in all processes of this vector group research (WPs 1-2). **Haartman Institute (HI)**, adjacent to Biomedicum, is part of the Medical Faculty of University of Helsinki and has long traditions in research on zoonotic viruses. It also houses HUSLAB responsible for diagnostics of these viruses. The Viral Zoonosis Unit of HI (VZU) is widely internationally recognized and is a WHO reference lab. HI is involved in WPs 1-2.

2.2.29.2 Key persons involved

**HENTTONEN, Heikki**, (http://www.metla.fi/pp/HkHe/index-en.htm), coordinator of RBD in EDEN and EDENext, is Professor of Forest Zoology at METLA, an adjunct professor at University of Helsinki, an invited Research Associate at the Univ. of Alaska Museum in Fairbanks, and in Southwestern Museum. Univ. New Mexico. His research fields are the population ecology of small rodents, and the ecology and evolution of rodent borne parasites and pathogens. HH has published about 170 refereed international articles, and is ISI Highly Cited in Ecology/Environment Category. HH has been involved in several EU projects on rodent-borne pathogens in Europe, and in Finnish Academy and NSF-financed projects on rodent parasites in Eurasia and N America. As a board member of the European Society of Mammalogy and International Federation of Mammalogists, as well as the member of steering committee of Intl Rodent Biol Congresses and EDEN, HH has a wide international contact network which greatly helps in research of rodent-borne pathogens. HH has collaborated with AV since late 1970s. **NIEMIMAA, Jukka**, MSc, field coordinator. JN has worked 20 years in HHs team, and has an unrivalled expertise in the field methodologies in research of rodent-borne diseases around the world. **VOUTILAINEN, Liina**, PhD. LV has worked many years as the lab coordinator between the field and lab personel in Finnish robo research. She masters both the field and laboratory methods in robo research.

**VAHERI, Antti**, Prof. of Virology at HI is (co)discoverer of four hantaviruses (Puumala, Tula, Topografov, Saaremaa). His research includes hantavirus infections, other rodent-borne viral zoonoses (new arenaviruses, TBEV and Borna disease virus in rodents) and viral diagnostics. AV has 571 original publications and 131 reviews in English. AV has been cited 27566 times including 74 "Hits" (cited >100 times) and his Hirsch index is 86. AV has supervised 42 PhD theses and currently (co)supervises 18 doctoral students. Received 8 US-NIH or EU grants and was coordinator in 2 of the latter. EMBO member and since 2007. AV is the President of Intl Soc for Hantaviruses. **VAPALAHTI, Olli**, Prof. of Zoonotic Virology at HI and Vet Faculty. OV and AP are organizers of Nordic and European meetings on Viral Zoonoses. VZU is associated to the University Hospital Laboratory (led by OV) with ~10 000 samples annually. Access to 40000 archival samples from human patients suspected of viral zoonoses, and thousands of vet and wildlife samples (rodent, avian, arthropod). **PLYUSNIN, Alexander**, PhD, Docent in Virology at HI. AP is widely recognized expert in genetics of viruses, currently chair of the Bunyaviridae study group in the Intl Committee on Viral Taxonomy and member of the EU and ECDC expert panels. **SIRONEN, Tarja**, PhD works as a post-doctoral fellow at VZU, an experts on the genetics of rainbo viruses.
2.2.29.3 Material resources

METLA has a special rodent lab where e.g. the treatment of rodents to process virological samples is done before the samples are delivered to specific diagnostic analyses at HI. All samples coming from our international collaborators travel this route. METLA has the equipment for all kinds of field collection methods in robo research. Students starting robo research in other collaborative teams usually come to METLA and HI for training both in field and lab methods. HI has access to all molecular technology (including 454 pyrosequencing and microarrays) needed for virus discovery from rodents, insectivores and other zoonotic vectors. HI has an inhouse BSL-3 facility and access to another BSL-3 with animal facility at Vet Faculty of University of Helsinki.

2.2.30 Partner 30 – University of Antwerp (UA)

2.2.30.1 Organisation

UA, Antwerp, Belgium. The Evolutionary Ecology Group at the University of Antwerp studies population ecological and behavioural ecological questions in a number of mostly terrestrial vertebrate model systems (rodents, songbirds). Very often, the fundamental questions are set in an applied framework, focusing on animals that are a pest in agriculture, a reservoir for infections or key species in nature conservation. The group has teaching responsibilities at different levels, a strong research record and a drive to make its scientific knowledge available to society. It consists of 4 professors, currently 5 postdocs, about 20 PhD-students and 6 permanent technical and administrative staff.

The team has long-term experience in studying the epidemiology of rodent-borne infections including European hantaviruses, African arenaviruses, bubonic plague, leptospirosis and echinococcosis. The main question of interest is the link between the ecology of the host (spatial, temporal) and the epidemiology of infections in the host as well as the risk for humans to become infected. The team combines active field work in Europe, Africa and Central Asia, with experimental work in the lab and the use of mathematical modelling as a tool for hypothesis generating and for simulations.

2.2.30.2 Key persons involved

Prof. dr. Herwig Leirs, principal investigator, is a rodent ecologist with a long experience in the study of rodent population ecology and the ecology of rodent borne infections. He has coordinated or participated in a number of international projects, incl. EDEN. On several occasions, he acted as an expert for WHO. He also is a part-time senior researcher at the Danish Pest Infestation Lab, University of Aarhus, Denmark. Dr. Jonas Reyniers is a postdoc physicist (with experience in modelling biological systems) who recently joined the team with the aim to reinforce the mathematical modelling expertise in the team. He replaces Dr. Stephen Davis who had a very fruitful stay of several years in the team but who recently moved to a permanent position in Australia. Katrien Tersago is currently finalising her Ph.D. project (which took place in the framework of EDEN, and was highly appreciated there) on the ecology of Puumala virus (PUUV) in bank voles in Belgium. She will participate as a postdoc in the EDENext project. Benny Borremans is a PhD-student studying the phylogeography of PUUV in bank voles.

2.2.30.3 Material resources

The lab is well equipped for field work in Belgium and abroad with all kinds of field equipment, traps and vehicles. It has its own small ABSL2+ animal facility with individually ventilated cages, for experimental work. Through H. Leirs, the team has access to a the ABSL3 lab at the Danish Pest Infestation Laboratory in Denmark.
2.2.31 Partner 31 – Swedish Institute for Infectious Disease Control (SMI)

2.2.31.1 Organisation

SMI, Stockholm, Sweden. The Swedish Institute of Infectious Disease Control (SMI) is a government expert agency with the following tasks: (i) Surveillance and diagnosis of notifiable infectious diseases, including molecular and serological typing of microorganisms, (ii) Reference laboratory for clinical microbiology in Sweden and (iii) Public health related research in control of infectious diseases. In addition, scientists at SMI are involved in basic research, financed by external grants. The section VZO, headed by Prof. Lundkvist, at the Virology department, has broad experience in development of diagnostics of arthropod- and rodent-borne virus infections and has created a solid base for immunological, molecular and pathogenetic research on arthropod- and rodent-borne viruses. VZO is responsible for the diagnostics of viral zoonoses at SMI. ÅL has a wide network of international collaborators. Attributed in WP 1-2.

2.2.31.2 Key persons involved

Åke Lundkvist, PhD, Professor – Principal investigator. Gert Olsson, PhD – rodent ecologist. Maria Wahlström – microbiologist. Elina Rintala – PhD student

2.2.31.3 Material resources

BSL-3 and BSL-4 laboratories, including handling of infected animals. All needed laboratory equipment as instruments for serology, RNA extraction-robots, RT-PCR machines, and 454-sequencing.

2.2.32 Partner 32 – Institut National de Recherche Agronomique (INRA)

2.2.32.1 Organisation

In the French National Institute of Agronomical Research, the Animal Health Department has a growing investment on tick-borne diseases, with 9 scientists from 4 laboratories (Clermont-Ferrand, Nantes, Montpellier – a joint laboratory with CIRAD - and Paris). This trend has been reinforced by INRA-CIRAD joining recently in a common consortium called Agreenium, thus facilitating collaborations on tick-borne diseases, as several researchers of CIRAD are also working on that topic. At INRA, investigations are carried out on several tick-borne pathogens (Bartonella spp, Borrelia spp, Babesia spp.) and on their vector Ixodes ricinus. Research activities aim to a better understanding of the complex host-pathogen-vector-environment systems, in order to design and evaluate new control methods. The genetic and phenotypic variability of pathogens (virulence) and ticks (vector competence) are described using various molecular markers and experimental approaches. Field studies are conducted to assess the role of biotic (including domestic, wildlife fauna but also vegetal cover and landscape features) and abiotic factors on population dynamics of ticks and on the prevalence of pathogens. A modeling approach is finally developed to integrate those data in epidemiological models and evaluate the relative role of those factors, allowing to simulate the efficacy of various control methods. Within EDENext, INRA will be involved in the assessment of (1) tick dispersal among I. ricinus populations using a population genetics approach and identification of the host used by the ticks for their previous bloodmeal, (2) genetic variability of Babesia spp. and Bartonella spp., (3) I. ricinus competence for Bartonella spp. strains and identification of tick genes involved, (4) immunomodulation observed in the host following tick bite.

The CBGP (a joint research unit INRA/IRD/CIRAD/AGRO.M) carries out researches in the fields of systematics, genetics and ecology relevant to the management of populations and communities of organisms for the purposes of agriculture, public health and biodiversity. These researches seek to
elaborate the conceptual and theoretic approaches, and the tools (molecular and bioinformatic), necessary to manage interacting communities which respond to global changes, either through biological control or conservation strategies.

Within EDENext, we will develop immunogenetics, population genetics, phylogeography and phylogeny of rodents with regards to landscape epidemiology and hantavirus distributions. This concerns WP.1 (Emergence and spread): our studies will provide a better understanding of genetic factors and evolutionary forces mediating emergence and spread of hantaviruses or other rodent-borne pathogens, and WP.2 (Intervention and control): rodents and pathogens monitoring in French areas endemic for Puumala hantavirus constitutes an “early warning system” for local health authorities.

2.2.3.2 Key persons involved

**Tick Group - Olivier Plantard:** Population Geneticist, PhD in Ecology and Evolutionary Biology. He is working on the assessment of gene flow among parasites populations at various spatial scales using molecular marker such as microsatellite loci or nucleotidic sequences. Since 2007, he is working on I. ricinus as a vector of Babesia divergens to understand how the genetic functioning of tick populations (gene flow, reproductive mode…) affects the genetic structure of the parasite. **Muriel Vayssier-Taussat PhD**, senior researcher (DR) at the National Institute of Agronomic Science (INRA) in the UMR BIPAR since 2001. She is the head of the team “VECTOTIQ - Bactéries vectorisées et spécificités d’hôtes”. Her areas of interests include the physiopathology and epidemiology of Bartonella. She has isolated a new Bartonella species, i.e. Bartonella chomelii from ruminants, she has developed standardized methods to extract DNA from ticks and more recently, she used an artificial feeding technique of Ixodes ricinus ticks to prove Ixodes ricinus is a competent vector for Bartonella henselae. **Mathieu Epardaud: Immunologist, PhD** in immunology. He joined CIRAD/INRA UMR 15 Immunology Research Unit, Montpellier (France) in 2008. He has been involved in cancer research up to 2008 and is now moving towards vector-borne diseases. He is mainly interested on vector insect saliva immunomodulation action (hard ticks, mosquitoes). He has developed an original model that allows an in vitro reconstitution of the principal steps of infection. **Gwenaël Vourc’h**, veterinarian, PhD in ecology and evolutionary biology (2001), HDR (2009). She joined INRA UR346 Epidemiology Animal in Clermont-Ferrand (France) in 2003 and has been the deputy head of UR436 since 2008. Since 2003, she has been working on the identification of environmental factors that influence the acarological risk in a pasture/forest landscape as well as at a continental scale (project in the USA). Since 2005, she has been looking at the consequences of the introduction of the Siberian chipmunk in suburban forest in France on the human risk for Lyme disease. **Laurence Malandrin, PhD**; researcher in the Tick-Parasite-Host interactions group at the Veterinary School of Nantes - France (part of INRA UMR 1300 BioEPAR), working since 1999 on the biological model of an Apicomplexan parasite transmitted by *Ixodes ricinus*: *Babesia divergens* (cattle and sheep). Her focus is on Babesia divergens virulence and interactions with its two hosts, the animal erythrocyte and the tick. She conducted intra- and inter-species genetic variability studies on the closely related species B. divergens and B. capreoli, as well as vector-competence studies and experimental infections with the zoonotic species EU1. She is involved in the B. divergens genome sequencing project which started in January 2009.

**Rodent Group - Nathalie Charbonnel:** Principal investigator, immunogenetics of rodent/pathogen interactions. **Jean-François Cosson**: Researcher, population genetics and phylogeny. **Maxime Galan**: Engineer, molecular biology for neutral and immune genes. **Anne Xuereb**: Engineer, immune response analyses and molecular biology for Orthopoxvirus detection and identification. **Yannick Chaval**: Technician, rodent systematics and rodent field work
**Associated partners:** Johan Michaux (University of Liège-CBGP): Researcher, rodent/pathogen phylogeography. Serge Morand (CNRS-CIRAD): Researcher, host-pathogen interactions.

**2.2.32.3 Material resources**

Molecular biology platform enables DNA and RNA extraction, genotyping, sequencing, and gene expression. Breeding house (P2+P3-Cirad partner). ICT cluster for population genetics and phylogenetic studies, with appropriate software packages.

**2.2.33 Partner 33 – Slovak Academy of Sciences (SAS)**

**2.2.33.1 Organisation**

SAS, Bratislava, Slovakia. The Institute of Zoology is an independent entity affiliated with the Slovak Academy of Sciences (SAS), the main scientific and research institution in Slovakia. The Institute publishes research results, cooperates with scientists and other institutes of the SAS, universities in Slovakia and scientific institutions in other countries. The Section of Medical Zoology of the Institute closely co-operates with related departments in the Institute of Virology and Parasitological Institute SAS within the frame of various collaborative scientific projects on tick-borne and rodent-borne diseases. Within the SAS campus, the research staff of the Institute has access to the BSL3 animal facilities at the Institute of Virology. SAS conducts research on epidemiology of viral (TBEV), bacterial (Borrelia, Anaplasma, Ehrlichia, Rickettsia, Francisella) and protozoan (Babesia) tick-borne zoonoses, molecular diagnostics, genetic variability and phylogenetic relationships of tick-borne pathogens and physiological and molecular interactions on the tick-pathogen–host interface. Research experience in epidemiological studies of zoonotic viruses and bacteria. The Institute of Zoology is the contractor within the FP6 project EDEN (participation in the TBD group) and in the FP6 Coordination Action Project ICTTD3 and participated in the V-borne project funded by ECDC. The staff members also participate in a number bilateral projects (with institutions in the Czech Republic, Hungary, Poland, Italy, Great Britain), projects funded by the Slovak Research and Development Agency and other Slovak grant.

**2.2.33.2 Key persons involved**


2.2.33.3 Material resources


2.2.34 Partner 34 – Ludwig Maximilians Universitaet Muenchen (LMU)

2.2.34.1 Organisation

LMU, Munchen, Germany. The Institute of Comparative Tropical Medicine and Parasitology (www.tropa.vetmed.lmu.de) is an integral part of the Veterinary Faculty of the Ludwing-Maximilians-University of Munich and is – in addition to its teaching and diagnostic commitments at the University – a fully equipped research institution. The Institute has focussed its research activities for the last 24 years primarily on ticks and tick- and other arthropod-borne pathogens. The Institute is ISO - certified (DIN EN ISO 9001:2008) since 2003 for research, diagnostics, and teaching, i. e. the Staff is familiar with the laboratory procedures, safety regulations and the Quality Management (DQS). The laboratory facilities are equipped up to the BSL II including appropriate molecular technique equipment. The research work is focussed on aspects of epidemiology of ticks and tick-borne pathogens (incl. Zoonoses) and on therewith associated pathogenetic mechanisms: It includes various ticks and Babesia spp. Anaplasma phagocytophilum, Rickettsia spp., Borrelia spp., Tick-borne encephalitis virus and Bartonella spp. (TBD-level). The Institute runs in-vitro culture laboratories for tick-cells (various cell-lines) and for several TBD pathogens. ICTMP is the coordinator of a EU-Marie Curie Project and is partner of several national and international projects on ticks, tick cell cultures and TBD’s (VICCI, INTERREG IV A, EDEN (as the TBD-reference laboratory), ICTTD, VETAFRICA, Pirobras and CAPARA.

2.2.34.2 Key persons involved

Prof. Dr. Kurt Pfister: Veterinarian; Head of the Institute for Comparative Tropical Medicine and Parasitology in Munich (since 2001); Diplomate and founding member of the European Veterinary Parasitology College (EVPC); conducted research projects on the pathology and epidemiology of B. canis in dogs and A. phagocytophilum infections in cattle; 10 years experience in leading positions in the veterinary pharmaceutical industry, incl. Chief Technical Officer of Biokema SA. Prof. Dr. Lygia Passos: Veterinarian; research group leader at the Federal University of Minas Gerais, Brazil; research scientist at the Institute since 2007: epidemiological and immunological aspects of tick-borne diseases of cattle, horses and dogs; specifically with regard to Anaplasma incl. genetic analyses of isolates and in vitro cultivation. Several international collaborations, 52 scientific papers. Dr. Stefan Schumacher: Biologist; PhD on experimental parasitic infections of laboratory mice with emphasis on gene expression profiling at the Institute for Tropical Medicine in Tübingen (Germany); since 2007 in charge of the quality management system according to DIN EN ISO 9001:2000 as quality manager for the certified scopes of diagnostics, teaching and research at the Institute for Comparative Tropical Medicine and Parasitology. Dr. Cornelia Silaghi: Veterinarian: DVM on the epidemiology and genetic diversity of Anaplasma phagocytophilum and Rickettsia spp. in Ixodes ricinus; similar work on rickettsial agents in fleas; since 2008 scientific staff member at the Institute, working on ticks and tick-borne diseases with a special focus on risk analysis for domestic animals and humans and the use of bioinformatic tools for the characterisation of vector-borne pathogens. Dr. Dietmar Hamel: Veterinarian; DVM on the epidemiology of g-I helminths of chamois in Germany; since 2008 research worker at Institute of Comparative Tropical Medicine and Parasitology, since 2009: Head of Diagnostic Laboratory; special interest on arthropod-borne diseases of dogs, particularly on diseases related to migration. Dr. Zweygarth: Veterinarian;
working from 1983-1993 at the Veterinary Laboratories in Kabete, Kenya (trypanosomes). 1991 he received the Int. Felix-Wankel-Tierschutz-Award for his research on in vitro testing of resistance in trypanosomes. From 1993-2008 he worked at ORI (South Africa) with in-vitro parasite models. He got a PhD (2006) from the Utrecht University (NL) and since 2009 he is working at ICTMP. He has published 104 scientific papers.

2.2.35 Partner 35 – Fundazione Edmund Mach (FEM)

2.2.35.1 Organisation

FEM, Trento, Italy. The Edmund Mach Foundation (FEM) is a private, non-profit institute of the Autonomous Province of Trento, established in 2005 by the merging the Istituto Agrario di S. Michele all’Adige (www.iasma.it) and the Centro di Ecologia Alpina (www.cealp.it). The mission of the FEM Research and Innovation Centre (CRI) is to promote Trentino’s land-based economy through research and innovation in the fields of agriculture, food quality and safety, and environment and natural resources. Research activities in the latter area focus on human-mediated and natural processes affecting mountain ecosystem functions and services under global change scenarios. A strong interdisciplinary approach is promoted, which combines theoretical and empirical research from the smallest (nucleotide) to the highest (GIS and remote sensing) scale, and integrates basic ecological research and environmental monitoring using modelling and scenario analysis. Research in ecology and epidemiology focusses on emerging zoonotic diseases and host-parasite interactions in natural populations, with special emphasis on understanding the impact of global change on the risk of spread and introduction of new and emerging pathogens into wild and human populations inhabiting European alpine ecosystems. During the 6th Framework program, the group was a core partner of the Integrated Project of the European Community “EDEN” (Emerging Diseases in a Changing European Environment: http://www.eden-fp6project.net/) within the subproject “Tick Borne Diseases and Rodent Borne Diseases”.

FEM has extensive experience with intensive tick collection from small mammals and game animals, molecular identification and analyses of pathogens, population genetics of a variety of animal species, and remote sensing and epidemiological modelling, as illustrated by expertise of team members and publication list. The team is supported by a number of very experienced field and laboratory technicians (V Tagliapietra, F Rossi, D Arnoldi, M Girardi).

2.2.35.2 Key persons involved

Annapaola Rizzoli, DVM. PhD: coordinator of the FEM-CRI Environment and Natural Resources Area and Head of the wildlife ecology and epidemiology group (founded at the Centro di Ecologia Alpina in 1993). Scientific interests include integrating veterinary medicine with other disciplines, especially biology, epidemiology, genetics, and spatial and mathematical risk assessment modelling. Heidi Hauffe, BA (Zoology), Rh Sch, D Phil: Level 2 Researcher at the FEM-CRI. Set up the genetics laboratory at the Centro di Ecologia Alpina (now part of FEM) in 1997, and has applied population genetic theory to many alpine species; has also studied phylogenetics of tick-borne zoonoses. Extensive experience with a wide range of laboratory/field techniques. Will work closely with C. Vernesi of FEM-CRI Biodiversity Programme. Francesca Cagnacci, MSc (Biology), D Phil: level 3 Researcher at FEM-CRI. Extensive experience in behavioural ecology of vertebrate species, esp with regards wildlife and zoonotic diseases, planning large scale empirical experiments, using a range of methodologies and techniques. Roberto Rosà, PhD: Level 2 Researcher at FEM-CRI, with the Rizzoli group since 1995. Main role is development of statistical and mathematical models in epidemiology and ecology, esp models of host-parasite interactions focussed on macroparasites and vector borne diseases. Markus Neteler PhD (pending): Head of the GIS and Remote Sensing technological platform of FEM-CRI. Main research interests are
remote sensing for environmental risk assessment and epidemiological modelling, and Free Software GIS development.

2.2.35.3 Material resources

The FEM Research and Innovation Centre has all the facilities needed for this project. Two administrative unites will be very helpful for the project: the European Projects Unit (Dr Roberto Chincarini) and the Research Support Unit (Dr Roberto Maffei).

2.2.36 Partner 36 – Research Centre Borstel (RCB)

2.2.36.1 Organisation

RCB, Borstel, Germany. The research focus of the Division of Veterinary Infection Biology and Immunology at the Research Center Borstel includes:

• Establishment of effective disease surveillance mechanisms in animal health services firmly anchored on sound epidemiological analysis and efficient information and reporting systems,
• Improvement of existing and development of new molecular diagnostic tools for pathogen detection and differentiation and for epidemiological studies, iii) Vaccines for the prevention of infectious animal diseases and zoonoses, and iv) To clarify the mechanisms of the interactions between the host, vector and pathogen through the use of genomics and bioinformatics.
• Training activities include supervision of postgraduate students and organization and carrying out of international technical workshops in the area of molecular biology, diagnostics, vaccine development and bioinformatics.

Among others, the RCB is coordinating a EU-funded project dealing with development of vaccines against tick-borne disease in small ruminants ("Pirovac"), is deputy coordinator of a Marie Curie Initial Training Network (ITN) on ticks and tick-borne diseases ("Postick"), is deputy coordinator of a coordinated action dealing with arbo-viruses ("Arbo-Zoonet"; www.arbo-zoo.net) and is responsible for the Asian Component of the international consortium on ticks and tick-borne diseases (ICTTD 3).

The RCB will be contributing to investigations on vector competence and capacity with the task of identifying potential markers of vector competence and/or capacity; ticks feeding under different experimental conditions; RNA extraction, cDNA synthesis and subtractive hybridization; sequencing and identification of differentially expressed genes; analysis of correlation of differentially expressed genes with pathogen transmission; RNAi knock down of differentially expressed genes to assess role in pathogen transmission; determining the pathogen dose on the viability of the tick; assessment of differentially expressed genes to be used as a marker for the determination of the vector capacity.

2.2.36.2 Key persons involved

Prof. Ulrike Seitzer received her Diploma in Biology from the Georg-August-University Göttingen, 1987, Germany; 1995 PhD Graduation at the University of Lübeck, Germany and 2006 apl. Professor for immunology and cell biology at the University of Lübeck, Germany. Dr. Seitzer has a long experience with the immunology and molecular biology of different diseases among them infectious diseases. She has published more than 45 papers in different journals. She has an enormous technical and scientific knowledge in immunology, molecular biology, protein chemistry and clinical investigations. Currently she is senior scientist at the Division of Veterinary Infectiology and Immunology and leading a research group in charge of establishing molecular tools for pathogen detection and differentiation.
2.2.36.3 Material resources


2.2.37 Partner 37 – Innovative Diagnostics-VET (ID-VET)

2.2.37.1 Organisation

ID-VET, Montpellier, France. ID-VET’s core activity of ID-VET is the development and production of a range of Elisa reagents used by veterinary laboratories involved in surveillance programs implemented by the European community and professional organisations in the animal farming industry. Through strategic partnerships with institutional research organisations or industrialists in the veterinary field, and through its own professional experience, ID-VET innovates in the following areas:
- Development and commercialisation of reagents designed to detect emerging pathologies.
- Progress in the intrinsic performance of diagnostic tests: high discrimination between positives and negatives, sensitivity, specificity, detection level and repeatability of methods.
- Simplification of use, improvement of product robustness.

Based on this innovative strategy, and with special attention to production and quality control, ID-VET is a privileged partner of actors in the field of veterinary diagnostics. For example, ID-VET is currently a major provider of kits used in the recent European outbreak of diseases such as Blue-tongue, West-Nile, and Influenza.

2.2.37.2 Key persons involved

Philippe Pourquier, the company’s founder, has extensive experience in veterinary antigen and antibody immunodetection. He currently manages a team of 25 people, one third of which is devoted to R & D. He is very skilled technically: throughout his career in the diagnostics industry, he has developed more than 20 different ELISAs for the diagnosis of a wide range of infectious diseases. From 1992 to 2004, he was in charge of the French association of diagnostic kit producers and liaison with regulatory authorities, normalisation, and breeder associations, among others. Philippe Pourquier has also introduced ID-VET as the industrial partner in 3 FP6 research programs (FLUAID, ParatbTools and BTVAC), and a FP7 program (ORBIVAC). Loic Comtet, in charge of R&D at ID VET, and has 6 years experience in the field of ELISA development for infectious diseases. Romain Porte is a graduated technician with extensive experience in serodiagnoses and quality control.

2.2.37.3 Material resources

ID VET possesses laboratory facilities that allow for the production and purification of monoclonal antibodies (CO2 incubator, 6 80°C freezer etc.) and recombinant antigens (E. Coli and baculovirus). ID VET is equipped for the production and stabilization of large volumes of plates (OYSTER BAY Pump coating machine, large drying ovens, sealing machine etc.).

2.2.38 Partner 38 – Kafkas Universitesi (KAU)

2.2.38.1 Organisation

KAU, Kars, Turkey. Kafkas University, owing his name to Caucasus, where it is located, is governmental institution with educational and research activities. It has 5 faculties and 7 high schools with 12816 students, 468 academic and teaching staff and 385 support personnel. It is
located in far Northeast city Kars. Kafkas University plays major role in regional education and research. The University is member of the Inter-University Cooperation Program, which is formed by 14 Turkish Universities with the aim of developing regional academic and scientific network in eastern parts of Turkey. It also has connections with institutions of the bordering countries such as Georgia and Azerbaijan, which is very important example of the international collaboration for regional development of the sub-Caucasian countries. Regarding this project proposal Kafkas University can contribute on ticks survey, animal/human serosurveillance and PCR detection of the TBD pathogens in animals and ticks.

2.2.38.2 Key persons involved

Zati Vatansever, DVM, PhD, Professor of Parasitology at the Department Parasitology, Faculty of Veterinary Medicine, Kafkas University, Kars, Turkey. He has 19 years of experience in parasitology, particularly in the field of tick-borne diseases. He obtained his PhD from the University of Ankara working on the epidemiology of tropical theileriosis in Cukurova region in Turkey. As part of “Theileria annulata macroschizont-infected cells in vaccination” INCO-DEV, STD4-CT 95-0004 project, he also worked as visiting scientist for 9 months at the University of Edinburgh. Being a partner in FP7 project ARBOZOONET, Dr. Zati Vatansever currently works with collaboration of Turkish Ministry of Health on the CCHF epidemiology and particularly vector ecology He is also member of the Advisory Board for CCHF in Turkey. He is also carrying out molecular studies on the simultaneous detection of tick-borne pathogens by PCR and Reverse Line Blotting. He is member of the Turkish Society for Parasitology and an associate member of the EU Concerted Action project "Integrated Control of Ticks and Tick-borne Diseases". Atila AKCA, DVM, PhD, Associate Professor of Parasitology. Yakup Yildirim, DVM, PhD, Associate Professor of Virology. Baris Sari, DVM, PhD, Associate Professor of Parasitology. Mukremin Ozkan Aslan, Professor of Parasitology.

2.2.38.3 Material resources

Together with newly established Faculty of Medicine, Faculties of Veterinary Medicine and Natural Sciences of Kafkas University are involved in research of animal and human diseases threatening the region. Vector and wildlife ecology including migratory birds are also studied. All 3 faculties have their routine and research laboratories and also use the facilities of the central research laboratory of the University. Laboratories have insectariums and basic material for mosquito and tick breeding. There are routine parasitology and virology laboratories with serology and PCR capabilities.

2.2.39 Partner 39 – Friedrich Loeffler Institute (FLI)

2.2.39.1 Organisation

FLI, Riems, Germany. The Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health (FLI) is an independent higher federal authority affiliated with the Federal Ministry for Food, Agriculture and Consumer Protection. The FLI publishes research results, cooperates with scientists and scientific institutions in Germany and worldwide, and fulfils in the area of biorisks the tasks assigned to it by the World Organisation for Animal Health as ‘Collaborative Centre for Zoonosis in Europe’ as well as by the World Health Organisation as ‘World Reference Centre for Rabies’. FLI runs the veterinary branch of the German Zoonoses Platform, an initiative which is funded by the German Ministry for Education and Research. Four institutes (syn. depts.) are located on the Isle of Riems: Molecular Biology, Infectiology, Diagnostic Virology, and for Novel and Emerging Infectious Diseases. The FLI presently holds laboratory and animal facilities up to level L3+ (L4vet) and from 2011 on laboratories and animal housing from BSL2 to BSL4 at its headquarters on the Isle of Riems. In the zoonotic area, FLI is conducting research studies on viral zoonoses.
caused by flaviviruses (West Nile virus, Japanese encephalitis virus a.o.), influenza (avian, swine) viruses, alphaviruses (American equine encephalitis viruses), bunyaviruses (Hanta-, Rift Valley fever virus, Crimean-Congo haemorrhagic fever virus a.o.), rhabdo viruses, Herpeviruses (Hepatitis E virus), filoviruses (Marburg, Ebola viruses) and by Henipaviruses. For all these diseases, FLI functions as national reference laboratory based on the German animal disease act.

Broad range of research experience over decades with epidemiological and diagnostic studies on infectious agents ranging from BSL2 to BSL3+ (zoonotic bacteria and viruses), BSL3** (prions) and BSL3 Agriculture (e.g. FMD). Main participant (Martin H. Groschup) was heading the veterinary branch of the German TSE Research Platform during its existence 2002-2008 and is since 2009 cofounder and head of the veterinary branch of the German Zoonosis Research Platform (www.zoonosen.net), which organises and coordinates the research activities nationwide across the thematic fields of virology, bacteriology, and parasitology. Prof. Groschup is also partner in the EU funded NADIR infrastructure project and is involved in the ArboZooNet group.

2.2.39.2 Key persons involved

Prof. Dr. Martin H. Groschup (1959): Veterinarian, Board exams in veterinary microbiology and in virology. Director of the Institute of Novel and Emerging Infectious Diseases at the FLI. Assigned director of the new BSL4 facility at the FLI. Own research experience on bacterial and viral pathogens and on prions. 136 ISI Web of Science listed publications, h value of 28. Dr. Rainer Ulrich (1958): Biologist with special expertise in genetics, molecular biology and virology. Working experience in human and animal virology. Founder and leader of the network "Rodent-borne pathogens in Germany" with broad collaborations to research groups on rodent biology and microbiology, virology and parasitology research groups. Research experience for 15 years on hantaviruses. 101 ISI Web of Science listed publications, h value of 19. PD Dr. F. J. Conraths (1956): Veterinarian. Doctoral degree in virology, habilitation (PhD) in parasitology, epidemiology and animal disease control. Board exams in veterinary microbiology and parasitology. Director of the Institute of Epidemiology of the FLI. Own research experience on viral and parasitic pathogens. 115 ISI Web of Science listed publications, h value of 22.

Dr. C. Staubach, Veterinarian, Institute of Epidemiology at FLI, specialized on GIS applications. PD Dr. H. Kampen (1963): Biologist, specialized in medical entomology and parasitology. Research experience in vector biology and vector-pathogen interactions. Head of the working group 'Arthropods' at the FLI. 22 ISI Web of Science listed publications, h value of 7. Dr. U. Ziegler (1970): Veterinarian, Board exams in veterinary virology. Research experience on flaviviruses (WNF) and on prions. 12 ISI Web of Science listed publications, h value of 5.

2.2.39.3 Material resources

FLI will dedicate diagnostic and research laboratories, animal facilities and storage capacities of the BSL level necessary for conducting the work as proposed. This includes also technical staff and consumables for running these facilities. Moreover, FLI will provide computational expertise and custom designed software.

2.2.40 Partner 40 – Süddeutsches Insitute für Empirische Sozialforschung (SINE)

2.2.40.1 Organisation

Founded in 1999, sine is an independent social scientific research institute based in Munich, Germany. We have performed extensive research on risk issues in national and international context. The focus of the studies has been in recent years on public risk perception and risk communication strategies of risk management and stakeholders in the field of health, food and environmental risks. In that regard we have conducted research inter alia for the WHO, the OECD,
the International Risk Governance Council and the German Institute for Risk Assessment (BfR). Sine was involved in several European funded projects of FP 5 and FP 6, such as: “Stakeholders in Risk Communication“ (STARC, CA); “Public Perceptions of BSE and CJD risk in Europe, their interplay with media, policy initiatives and surveillance issues. Drawing the lessons for information policy” (STREP); “Promoting Food Safety through a New Integrated Risk Analysis Approach for Foods” (SAFE FOODS, IP) or within the NoE: “Prevention, Control and Management of Prion Diseases” (NeuroPrion).

In all of these international comparative projects, recommendations in regard to improved risk governance, including risk and crisis communication were formulated and best practices identified. Sine is familiar with qualitative as well as quantitative social scientific research methodology and with the organisation and moderation of expert and stakeholder workshops as well as conducting expert interviews and focus group research.

In EDENext sine will be in charge for WP 5: risk perception and risk communication in regard to vector-borne infections and how to adequately address and involve key actors of public health agencies as well as stakeholders within a PH risk control and communication strategy.

2.2.40.2 Key persons involved

Contributors from sine include: Dr. Kerstin Dressel has worked for several years in scientific research before she left the work bench to be trained as sociologist. She is co-founder and head of the sine-Institut and has conducted numerous studies for sine, in particular in the field of (international) risk research. She is an expert in risk communication, risk perception and risk governance. As former scientific secretary of the German TSE Research Platform she is experienced in communicating with decision-makers and stakeholders and at the science-public interface. Dr. Marion Müller, sociologist, has worked for many years in the field of Public Health and on questions of sociology of medicine. Dr. Patricia Pfeil, co-founder and head of sine, was trained as sociologist. She is an expert at qualitative social scientific methods.

2.2.40.3 Material resources

All proposed social scientific methods, such as in-depth-interviews, focus group research, literature research and comparative analysis, are well established within sine for many years. Due to former involvements in other scientific consortia, we are familiar with working in an environment of life science and basic research (for example, sine has been the sole social scientific partner within the NeuroPrion Network of Excellence of more than 50 science-based partners).

2.2.41 Partner 41 – Robert Koch Institute (RKI)

2.2.41.1 Organisation

The Robert Koch-Institut (Berlin, Germany) serves the Federal Ministry of Health as a central scientific institution in the field of biomedicine and is one of the most important institutions for public health issues in Germany. The RKI links risk research with political advice. Its tasks include protection against infectious diseases and analysis of the health situation in Germany. In total, approximately 800 employees of whom 370 are scientists (incl. PhD-students) are working at the RKI. There are National Reference Centres and advisory laboratories within the institute for various bacteria and viral diseases which are the central contacts for identification and control of diseases.

Since 1995 we organize the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD), which is now funded by the European Centre for Disease Prevention and Control (ECDC). The ENIVD takes actions to build up and improve laboratory diagnostic capacities in Europe with regard to development of diagnostic tests, quality control/standardization of laboratory procedures, dissemination of scientific and technical information concerning viral infections of European interest, and training of
laboratory staff. Based on four consecutive contracts funded by the European Commission (EC), our laboratory network has expanded during the last 13 years from five to 47 participating laboratory experts based at public health institutes and universities in 27 EU member states and 6 non-EU countries (Switzerland, Norway, Bosnia & Herzegovina, Turkey, Russia & Israel).

Besides the organization and coordination of the ENIVD-network and one of the advisory laboratories at the RKI (Consultant Laboratory for tick-borne encephalitis), the focus of our laboratory working group are the diagnostic as well as the research regarding pathology and treatment of flavivirus infections like Dengue-, YF-, WN, JEV- and TBE, and other emerging infections like SARS, Chikungunya fever and VHFś (e.g. Hanta- and CCHF). Since 1999, the ENIVD has performed 18 external quality assurance studies to assess the quality of serological and/or molecular diagnostics.

In EDENext RKI will be in charge of risk estimation for vector borne human viral diseases and the relevance of these diseases for public health situation in the different European countries. This risk estimation will be performed in close collaboration with the other partners and considering the view of European diagnostic laboratories to be in the first front for emerging diseases due to climate or environmental changes.

2.2.41.2 Key persons involved

Contributors from RKI include: Prof. Matthias Niedrig is Clinical Virologist (Biology/Virology) at the RKI for 14 years and Head of Laboratory since 9 years. In total, Matthias Niedrig has a professional experience in viral diagnostics of about 21 years and is coordinating the ENIVD-network successfully for 14 years. Prof. Dr. Klaus Stark, head of the department for Zoonotic and tropical infections dealing with the epidemiological investigations of such diseases in Germany and familiar with modeling of vector borne diseases.

2.2.41.3 Material resources

The RKI has necessary hardware for the access to all literature and references important for tasks. With the hub of the ENIVD we have excellent connection to the ECDC and other international PH organizations like WHO. Since we are working on the respective viruses for many years we know the stakeholders within Europe and outside to obtain the relevant information. This will enable us to collect and process the relevant information and also to distribute the outcome of this WP via congresses and web portal for all interested parties.

2.2.42 Partner 42 – University of Utrecht (FVM)

2.2.42.1 Organisation

FVM, Utrecht, Netherlands. The chair of Theoretical Epidemiology in the Faculty of Veterinary Medicine consists of one associate professor, three assistant professors, two postdocs and five PhD students. The group is closely related to a chair of veterinary epidemiology of infectious diseases of equal size. The theoretical epidemiology group broadly works on population dynamics of infectious diseases, and has three types of activity: the development of new mathematical and statistical methods, using quantitative methods to study questions in the dynamics and control of infectious disease in humans and wildlife, and applying mathematical models to obtain insight into transmission and control of animal infections. The group is focussed on mechanistic, i.e. process-based, modelling, trying to understand population phenomena by describing biological processes at the level of individuals. The group has a long history in mathematical epidemiology. Notably the theory to define and calculate the basic reproduction ratio $R_0$ has been developed over many years. The next-generation method is used today as the standard way to compute $R_0$ in epidemic models. A textbook on the mathematical epidemiology of infectious diseases was published in 2000
(Diekmann & Heesterbeek), which has quickly become a well-known reference in the epidemiology modelling literature (a new expanded edition will be available soon). Recent themes of activity are linking immune system dynamics to the transmission of infection between individuals in a population, the dynamics of infections in metapopulations of hosts (notably in wildlife populations), and the emergence of vector-borne infections in heterogeneous environments.

2.2.42.2 Key persons involved

Hans Heesterbeek is the key person who will supervise the researchers that will be employed in the project. He will also be involved in doing part of the research, in interacting with the vector groups and with the other partners in the modelling work package. He has an extensive track record in mathematical population dynamics with more than 70 collaborative research papers, both in theoretical and in biological journals (three of which in Nature and Science in the last seven years), and two books. He is one of the editors-in-chief of the journal Epidemics and editor of Proceedings of the Royal Society B.

2.2.42.3 Material resources

Modelling principles and techniques, theory and applications of thresholds, statistical techniques, computer software for infectious disease modelling, training and teaching materials for mathematical modelling in epidemiology.

2.2.43 Partner 43 – University of Oxford (UOXF)

2.2.43.1 Organisation

Oxford University’s Department of Zoology (Oxford, UK) hosts the TALA Research group that was founded by David Rogers in 1993 to examine the role of remote sensing in predicting the distribution and abundance of tsetse flies and the incidence and prevalence of tsetse-transmitted diseases. Today TALA, now part of the larger Spatial Ecology and Epidemiology Group (SEEG) within the Department of Zoology, is a recognized leader in the field of low resolution image processing and applications to a wide variety of diseases. TALA developed temporal Fourier processing techniques to capture elements of habitat seasonality in the NOAA AVHRR satellite data time series, and non-linear discriminant analysis to use the Fourier imagery to describe vector and disease distributions and abundance. This unique combination of image processing and application has now been applied to a wide range of diseases, from anthrax to West Nile Virus locally, regionally and globally. TALA has applied and developed a wide range of time series analytical techniques to examine trends in key seasonality variables across continents and to show changes in the epidemiology of a variety of vector-borne diseases through time.

The same temporal Fourier analysis skills have been applied more recently to composited MODIS data from NASA’s newer Terra and Aqua satellites. These data required the development of new algorithms to cope with the timing of the composited data within each calendar year and the resulting imagery was a major input into the activities and data archives of the EU FP6 EDEN project. They were used, for example, as descriptor variables in the risk maps produced for the EDEN partners inter alia by the Low Resolution Remote Sensing team headed by TALA.

TALA enjoys technical challenges within practical applications, from the use of administrative region rather than point data on disease occurrence to the application of risk mapping methods to describe the distribution of poverty in the Horn of Africa. Risk map production is moving towards using geo-spatial and Bayesian approaches to improve map accuracy.

Work has been carried out for a variety of agencies; DFID, DEFRA, DoH in the UK; FAO, WHO, ECDC in mainland Europe; and the INTREPID project in the USA.
TALA/SEEG results are published widely in the reviewed literature, and past and present team members have edited and written chapters for two special issues of *Advances in Parasitology* (Volumes 47 and 62 for 2000 and 2006 respectively) and contributed to a specialist book on *Spatial Analysis in Epidemiology*.

### 2.2.43.2 Key persons involved

David Rogers, University Professor of Ecology, specialises in temporal Fourier processing of satellite data and the development of discriminant analytical models to describe the distribution and abundance of vectors and diseases. He has also developed methods to detect significant changes in the Fourier seasonality variables over time. **Dr Luigi Sedda** trained as a Forester but now specialises in geo-spatial analysis of vector and disease data and the application of Bayesian techniques to modelling. **David Benz**, also part of the DMT group, carries out all the activities involved in receiving remotely sensed data from NASA and processing them into useable Fourier products.

### 2.2.43.3 Material resources

This team has the entire NASA archive of NOAA AVHRR pathfinder data (both 8km and 1km) from 1982 to 1999, and has Fourier processed them for a number of projects. The group also receives selected current Terra and Aqua satellite MODIS data (MIR, daytime LST, nighttime LST, NDVI and EVI) and produces new temporal Fourier layers for the entire time series after the end of each calendar year. All data reside on a dedicated server. The team benefits from the UK University software agreement with suppliers for the provision of ERDAS Imagine, ESRI-Arc and Mapinfo products, and also from the facilities of the UK University environment (computing and library services).

### 2.2.44 Partner 44 – Université Catholique de Louvain (UCL)

#### 2.2.44.1 Organisation

UCL, Louvain la Neuve, Belgium, is at the forefront of innovation and excellence in education and research. The university includes 3 sectors (Medical Sciences, Humanities and Social sciences, Science and Technology), 12 faculties, 21 research institutes, 3 scientific parks, 2 hospitals and 1 museum. With more than 21000 students (122 different nationalities) and 5000 members of staff including 1400 professors and 1800 researchers, UCL has local, European and international visibility. The excellence of research within the UCL results in its international radiation: nearly 600 PhD students come from the whole world; among the thousand of annually concluded contracts, more than 200 contracts of research are signed with foreign universities and companies.

The department of Geography focuses on land changes and their impact in rural and urban landscapes of temperate and tropical regions. Research is conducted both on the causes of land-use change and on their impacts on soils, ecosystems, vectors of diseases, and sustainable development. This work is conducted at local, regional and global scales. Land-cover changes are monitored using time series of remote sensing data, and field collected data, analysed using geographic information systems. We focus on both slow, fine scale land-cover conversions and fast, broad scale land-cover modifications.

The research unit focuses on the study of the etiology, distribution and risk of vector-borne and zoonotic diseases in relation to the environment. More specifically, the interactions between human and/or animal populations, the landscape, and the vectors, hosts and pathogens are studied. The analysis of remote sensing data is a prominent tool, and the department has a long experience in the field. Spatial analysis and geographic information systems are important complements to the use of remote sensing data. Statistical analysis and modelling complete the set of tools routinely used to
document the interactions outlined. The experience so far includes mosquito- and tick-borne diseases as well as zoonotic diseases, in a range of environments, including tropical ecosystems and western and eastern European settings, as was done in the EDEN project.

2.2.44.2 Key persons involved

Sophie Vanwambeke is a professor in Geography in the department of Geography in UCL since 2007. Building on her land science background, Sophie Vanwambeke specialises in the integration of landscape-level environmental aspects into various disease systems in tropical and temperate regions. She was an academic visitor at the Environmental Change Institute in Oxford University in 2007 and a Fulbright visiting scholar in the Asia-Pacific Institute of Tropical Medicine and Infectious Diseases in 2008. Interdisciplinary research is a major aspect of her experience to date, and Sophie Vanwambeke has collaborated with entomologists, epidemiologists, public health specialists, and biologists.

2.2.44.3 Material resources

The department is well equipped in computer hardware including desktop computers and data servers. This will be consolidated in the research unit for the needs of the project. The department can also access the services for intensive computing and mass data storage through the university. A number of software options for remotely sensed data processing and geographical information systems are available and routinely used. Specialised IT personnel support this infrastructure. A range of fieldwork equipment is also available.

2.2.45 Partner 45 – Université Libre de Bruxelles (ULB)

2.2.45.1 Organisation

The Biological control and Spatial Ecology Lab. (abbreviated as LUBIES, Lutte Biologique et Ecologie Spatiale) is part of the Université Libre de Bruxelles (ULB) in Brussels, Belgium. It is a complete university with seven faculties (engineering, sciences, economics and politics, law, medicine, psychology, letters and philosophy) and about 20 000 students. ULB was ranked as the fifth best francophone university by the Times Higher Education University Ranking for 2008, and the 183rd best worldwide. Within the university, the LUBIES is attached to the School of Bioengineers, which groups research units working in diverse fields of applied biological sciences (e.g., landscape ecology and urban planning, environmental sciences). The School of Bioengineers is staffed with faculty of sciences and engineering faculty. Both faculties offer the research environment and intellectual support necessary for successful research in both fundamental and applied sciences.

The researches of LUBIES deal with demographic and spatial changes in several harmful organisms such as forest, agricultural and urban insect pests and animal diseases. LUBIES focuses on the mechanisms which trigger outbreaks and epidemics, on the factors favoring their spread and persistence, and on the development of monitoring and control methods. A particular attention is given to invasive alien organisms: emerging diseases (bird flu, bovine tuberculosis, bluetongue) and exotic insects (forest and urban tree pests), and to the patterns and processes involved in their extension (global change, farming systems, trade). These processes include interactions between these organisms and their host or habitat, and with their biotic and physical environment. The methods used to approach these systems include uni-variate or multi-variate spatial statistics, spatially-explicit and spatially-realistic population models and simulations.

More specifically relevant to this proposal, LUBIES will be leading WP3.3 which aims to model the spread of vectors and VBD in a heterogeneous European Landscape. This task will be supported by LUBIES established previous experience in modeling the spread of invasive species (the horst
chestnut leafminer *Cameraria ohridella* in Germany, France, and Great-Britain, and the bark-beetle *Dendroctonus micans* in Great-Britain) and of emerging pathogens (Bovine tuberculosis in Great-Britain) in heterogeneous landscapes. In complement, LUBIES will also benefit from its participation to the project EPISTIS (2006-2010) which aims to better understand the spatial ecology of Bluetongue in Belgium and Italy at different spatial scales.

2.2.45.2 Key persons involved

**Marius Gilbert** (MG) will be the key person supervising the work of the staff employed under this project, which remains to be identified. MG holds a permanent academic position with the Belgian Fonds National de la Recherche Scientifique since 2006, hosted at the ULB, and has an established track record of publications in invasion ecology and spatial epidemiology (http://www.ulb.ac.be/sciences/lubies/mgilbert.htm).

2.2.45.3 Material resources

LUBIES has access to, and will further expand, all the necessary hardware infrastructure and electronic storage capacity required to carry out the required tasks. Software required for this task is either in the public domain, resulting from LUBIES own developments, or has already been acquired. In addition to its own computing resources, LUBIES also has access to the ULB University Computing Center facilities, with high performance computing capabilities for scientific and technical applications on its HYDRA platform (http://www.vub.ac.be/BFUCC/hydra/about.html).

2.2.46 Partner 46 – European Agro-Environmental health GIS associates EEIG (EURO-AEGIS)

2.2.46.1 Organisation

Euro-AEGIS, European Agro-Environmental health GIS associates EEIG, is a European Economical Interest Grouping (EEIG) founded in 2004 by Avia-GIS (Zoersel, Belgium) and ERGO (Oxford, UK). The general objective of Euro-AEGIS is to assist in the development of and promote GIS and RS products, applications and training in agro-environmental monitoring, disease surveillance and environmental assessment for sustainable development. The two member companies of Euro-AEGIS have a well established track record of collaboration with national governments and international agencies; GIS and remote sensing applications expertise; desk-top-publishing and website development; close contacts with the European research community.

Euro-AEGIS participated as the partner to the EDEN FP6 project “Emerging Diseases in a Changing European Environment” and was in charge of the spatial data management support for the 49 consortium members and the development of spatial information systems: http://edendatasite.com. Euro-AEGIS also was a leading partner of the ECDC funded V-borne project "Assessment of magnitude and importance of vector-borne diseases in Europe" and was awarded a one year bridging fund by ECDC to maintain the EDEN DMT assets and prepare for the development of a “European Environment and Epidemiology Network (E3)” to enhance the pan-European capacity to analyze, predict and respond to changing communicable disease patterns due to global change. Currently Avia-GIS is leading through Euro-AEGIS the ECDC funded VBORNET framework contract which aims at developing a European Network for Arthropod Vector Surveillance for Human Public Health.

In EDENext Euro-AEGIS will be in charge of further developing the spatial data archives and information systems of the consortium and will conduct research activities within the fields of (1) the wind-spread of bluetongue and (2) the spatial modeling of species biodiversity.
2.2.46.2 Key persons involved

Contributors from Avia-GIS include: Guy Hendrickx, Managing Director, specialized in spatial epidemiology, the spatial modeling of VBD’s and the development of spatial information systems for disease management; Els Ducheyne, Scientific Director, specialized in the design of spatial species distribution and arthropod windspeed models; Bart De Groot, ICT specialist, Web applications and software developer.

Contributors from ERGO include: Willy Wint, Director, specialized in spatial data acquisition and processing, and in spatial modeling of disease vectors and animal hosts; Neil Alexander with key skills in Website and data archive management, and in spatial data manipulation; and collaborator David Benz, also part of the Modelling Team, who focuses on remotely sensed data processing and management.

2.2.46.3 Material resources

Euro-AEGIS has access to, and will further expand, all the necessary hardware infrastructure and electronic storage capacity, as well as acquired software licenses and developed software applications needed to develop, establish and maintain spatial data production chains, web-archives and spatial information systems to the high standards as required by EDENext.
2.3 Consortium as a whole

The EDENext Project will be conducted by an international consortium comprising 53 registered senior research team leaders from 46 research and public health institutions in 22 countries representative from the Western, Northern, Eastern and the Southern part of the European continent, as well as two partners from Africa. In Table xxx a breakdown is given of partners per country and in Figure xxx the spatial distribution of the partner institutions is shown. EDEN partners include 40 governmental institutions, four private non-profit foundations and two SMEs.

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Table xxx – EDENext partners per country.

Figure xxx – Map of the EDENext consortium partners – The map currently shows the location of head offices of the consortium partners, in each member country (and in other countries where applicable) a series of field sites will be selected at an early stage of the project as described in Work Packages 1 and 2.

All partners have been selected due to their outstanding scientific record, existing links/activities with VBD research/networks and complementary skills needed to achieve the EDENext objectives. The EDENext consortium includes: field and laboratory entomologists,
acarologists and rodent specialists; public health specialists; modelling specialists; public and veterinary health specialists; ICT specialists. Most of which have significantly contributed to the start of the art in their field of expertise. The EDENext consortium builds further on the consortium and networks established by EDEN taking into consideration the new research challenges, the inclusion of a Culicoides Group and the withdrawal of the Malaria and Africa Groups who are part of consortia responding to other specific FP7 calls. In this process a major effort was also conducted to strengthen two weaknesses of EDEN: representation from German-speaking Europe (Germany, Austria and Switzerland) and the inclusion of dedicated Public and Veterinary Health specialist teams. In addition links with previous EDEN partners and the European VBD community will also be maintained through membership to the ECDC VBORNETHET network. In Table xxx, at the end of this part, the main Work Packages to which each partner contributes are listed.

The EDENext consortium will be coordinated by Renaud Lancelot at the Centre de Coopération Internationale en Recherche Agronomique pour le Développement (CIRAD), Montpellier, France, who has previous experience of coordination of an EU Integrated Project (EDEN) and of several other multi-partner international collaborative projects in Europe and Africa funded by the EC, ECDC and bilateral funding sources. A secretariat established in Montpellier comprising the coordinator, a financial and an executive assistant will be responsible for day to day management and coordination of the consortium. Management and coordination will reflect the decisions of the EDENext Steering Committee chaired by the elected Chairman of the SC of which the Coordinator is Secretary and comprising Leaders and Deputies of all five vector groups and three Integration Groups as shown in Table xxx below. Of the 17 partners entitled to participate to the SC meetings, 35% are women (6). All European regions are represented.

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Table xxx – Members of the EDENext SC
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2.4 Resources to be committed

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The expected impact stated in the call text is copied in the box above. To ensure EDENext will achieve this impact the structure of the project was specifically designed to achieve this impact. Each Vector Group specifically addresses research questions to improve our understanding of (1) emergence and spread of VBDs and (2) intervention and control of VBDs. In addition a major effort is also put into a better understanding of VBD risk perception and communication through PH actors, which will significantly contribute to bring research outputs to PH decision makers to the benefit of the European citizens. Thus the proposed EDENext Work Plan, Deliverables, Milestones and Contingency Plans have been specifically designed to achieve this impact.

The fact that EDENext builds further on the networks, expertise, field work oriented research and integrative research established under EDEN will have a continued impact on the European research capacity in the field of VBDs. Current major EDEN assets in this perspective are the PhD network with 60 members who conduct research in the field of VBDs, and more than 175 peer reviewed scientific papers.

In this process EDENext will not only aim at strengthening multidisciplinary research within and between the EDENext Vector and Integration Groups, but also strengthen links with other European and International initiatives.

This will include collaborations with other relevant FP6 and FP7 projects in general and in particular, as requested by EU, with the three ‘sister projects on VBDs’ under the current HEALTH and ENVIRONMENT calls:

- HEALTH.2010.2.3.3-3: Integrated disease-specific research on West Nile Virus infections, Chikungunya and/or Crimean Congo Haemorrhagic Fever. The main aim of these project(s) is to conduct research on basic virology, transmission, epidemiology and diagnostics of VBDs also addressed, from the vector perspective, in EDENext.
- HEALTH.2010.2.3.2-4: Controlling malaria by hitting the vector: New or improved Vector Control Tools. FP7-CALL-FOR-AFRICA-2010. The main aim of this project is to develop and test vector control tools adapted to malaria control. Here also both projects will benefit through sharing methods and results on a regular basis.
- ENV.2010.1.2.1-1 The effect of environmental change on the occurrence and distribution of water related vector-borne diseases in Africa. The aim of this project is to investigate how environmental change, including changing climatic conditions affect the spatial and temporal distribution and dynamics of water related vectors and VBDs in Africa. This call is very similar to the original EDEN call and therefore of particular interest to many EDENext partners, and a basis to establish collaborative links.
In addition collaborations with ECDC will be further strengthened through:

- **VBORNET – European Network for Arthropod Vector Surveillance for Human Public.** One of the main aims of the network, of particular relevance to EDENext, is to develop and maintain a centralized data base of mosquito, tick and phlebotomine vector distributions in Europe at three administrative unit levels. Collaborative links will enable to further strengthen this data base and work toward developing joint modeling approaches to produce continent wide grid based vector distribution probability maps.

- Support to the E3 initiative. The aim of this network will be to connect epidemic intelligence and infectious disease surveillance data with meteorological variables, entomological data, water quality records, air quality measures, remote sensing information, geology, population density and many other information sources using the EDEN DMT facility as an example. Through developing this collaboration the impact of EDENext will further reach beyond the VBD community to include also spatial epidemiologists dealing with non VBD infectious diseases.

It is this opportunity to expand collaborative networks and conduct multidisciplinary and multi-team research which is the main added value of a project such as EDENext. The FP7 research funding program is a unique tool which enables to achieve such results. Without EU research money such a high level and complex integration could not be achieved.

### 2.6 Dissemination and/or exploitation of project results, and management of intellectual property

The rules concerning the management of knowledge, intellectual property rights and innovation-related activities are described in detail in the Consortium Agreement. Foreground (generated knowledge) shall be the property of the partners(s) generating it. If dissemination of knowledge does not adversely affect its protection, the partners shall ensure large dissemination.

EDENext project results will be disseminated through the activities of three work packages: Coordination (WP6), Public Health (WP5) and Data Management (WP4). Dissemination targets will be the scientific community, the public health community and the general public.

#### 2.6.1 Scientific publication

Each EDENext team is responsible for publishing its scientific results in peer reviewed journals as part of achieving the EDENext objectives, preferably via the highest ranking open access journals, to ensure maximum impact in a worldwide scientific public. Within each group, Group Leaders and their Deputies will organize co-authorships and the timely publication of sub-national, national, regional and Pan-European papers as appropriate. More complex collaborative and integrative papers involving different Groups are planned at SC level.

Prior to publication all EDENext papers will be submitted by the Group Leaders or Deputies to a rapid internal review system organized by Coordination (WP6) with help from the SC. The main aim is to ensure that proposed papers conform to the EDENext standards and objectives. Once accepted a unique EDENext number will be assigned and a standard disclaimer (validated by the appropriate service of DG-Research) included in the acknowledgements. Each year a document including abstracts of all EDENext publications which are “in the
pipeline" with will be distributed at the AGM and made available as a pdf (subject to copyright) on the EDENext website.

Once published each paper will be included as part of the EDENext Science and Publications Directory which is part of the EDENext DMT website (WP4). This tool provides a georeferenced description of research data holdings and results produced by EDEN and EDENext members that allows potential collaborators to identify clearly what the EDENext community has achieved, and map the studies and data holdings, without releasing the actual data. This provides dissemination of research activities whilst retaining intellectual ownership, and was shown to be a crucial factor favoring data sharing under EDEN. The Directory will be accessible to the general public; any researcher interested in starting a research collaboration will be free to use it and contact EDENext partners based on search results.

EDENext partners will also be encouraged to participate in relevant workshops and international conferences and present EDENext work in progress results. A proposed attendance plan will be made each year by each Group as part of the workplan set out in the annual report.

An important aspect of dissemination to the scientific community will be the EDENext PhD network. This network will include all past EDEN (60), as well as EDENext, PhD students and has been seen by reviewers as one of the main assets EDEN developed for longer term impact on EU VBD research. As part of the network activities, a PhD meeting will be organized prior to each AGM at which PhD students will present ongoing work and discuss issues with peers, SC and AG members. The back-bone of the network will be a PhD website which will include personal pages for each PhD student, a PhD mailing list, information on conferences and meetings, and most importantly an extended Postdoc job offer page, which will ensure high visibility to internet search engines.

2.6.2 Data dissemination

In addition to the publication of scientific results EDENext will also devote considerable efforts to the dissemination of spatial data sets which are of particular interest to the spatial epidemiology of VBDs and other infectious diseases. This was started by the DMT (see also WP4) under EDEN, and is being supported by bridging funding from ECDC who is using the DMT web service as a basis for building their proposed European Environment and Epidemiology Network (E3).

"The aim of the ECDC-E3 network will be to connect epidemic intelligence and infectious disease surveillance data with meteorological variables, entomological data, water quality records, air quality measures, remote sensing information, geology, population density and many other information sources. Through integrating and synthesizing these data sets, disease surveillance systems will be able to incorporate and analyze environmental precursors to disease pandemics, thus preparing public health to meet the challenges of our time."

As part of EDENext, the DMT web-based service will be further strengthened (see WP4 for more details) and advertised to the international research community. In doing so particular attention will be given to data ownership. Generally speaking epidemiological data are author protected and accessible through direct contact with authors (see also the Science and Publications Directory Tool described above), and spatially descriptive data are freely accessible. In all cases users are requested to properly mention data sources.

Dissemination will be achieved through the DMT website and through a DVD which will include the main spatial data layers and time series of interest to EDENext and a customized geo-Explorer Tool an advanced spatially queryable tool to extract information for user
defined locations. Existing links with the ECDC funded networks VBORNENET and E3 will be further strengthened to ensure compatibility and added value.

2.6.3 PH Risk communication

A specific workpackage has been designed to address interactions with Public Health actors and decision makers, and which will address issues related to risk perception and risk communication (See objectives and activities of WP5). During this process a full range of actors will be involved at various levels:

- European and International agencies involved with human and veterinary public health (DG-SANCO, ECDC, EFSA, WHO-EU, OIE, FAO), European public health networks (EpiSouth, EpiNorth, VBORNENET), and the European laboratory network for viral diseases (ENIVD)
- Consumer Associations, Farming Organizations, Non-Governmental veterinary and medical societies such as the European Public Health Alliance (EPHA) or the Federation of Veterinarians of Europe (FVE).
- National Public Health Authorities.
- Focus groups representative of the general public.

In this work, particular attention will be given to clarify the factors which affect risk perception by PH stakeholders and the general public in the EU and to identify the type of information and risk communication which is considered useful, helpful and adequate by both groups. As a result recommendations will be formulated for the European Commission and the risk managers in the Member States on adequate communication of the implications of emerging VBDs in the context of environmental and economic change for PH, and the obtained results will be presented to the European Commission and the authorities of Member States concerned with PH risk communication.

In addition a series of leaflets and booklets will be prepared to inform the general public about the main VBD related issues identified by EDENext. These will be based on the past experience gained with EDEN and the ECDC funded V-borne consultancy, as well as on newly gained information through EDENext.

Two main formats will be developed and disseminated:

1. Web-based 800 word fact sheets describing the VBD issue using a FAQ format and providing relevant facts and figures. Issues will be selected in close collaboration with the ECDC funded VBORNENET and complementary to existing fact sheets. EDENext will develop these factsheets in English and French, and encourage other translations by national PH agencies.

2. Booklets in the series "Les savoirs partagés" published by CIRAD. Such booklets have already been developed successfully on different topics such as avian influenza and bluetongue. Of the former 85,000 copies were disseminated. In 50 pages of a very handy pocket format all relevant information regarding the selected disease is provided, with full color figures, diagrams and photos. A recently conducted study has shown their high

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impact in a wide range of readers in Europe and Overseas. These booklets will be published in collaboration with national and international agencies. Booklets will be produced in French and English.
## 3 Ethical issues

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**CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL**

All research activities of EDENEXT will be carried out in compliance with fundamental ethical principles, and all project participants will conform to the legislation and regulations of the countries in which studies are conducted, and to those in the European Union.

EDENEXT research will not involve the use of human embryos, fetuses, embryonic stem cells, or human fetal tissues. Genetically modified animals, non-human primates, dogs and cats will not be used.

Experiments, including human clinical samples (blood samples) or anonymous personal data, will be approved by local/national ethics committees or local authorities prior to the start of the research activities. All necessary steps will be taken to ensure confidentiality.
More specifically, for the serological CCHFV survey in humans, a specific consent form explaining the purpose, procedures, benefits, risks, discomforts, and precautions will be provided to candidates for reading and signature prior agreement to participate in research activity. All information gathered from the study will remain confidential by hiding participants’ identities from sampling to possible publication. Participants will not be paid to participate in this research project.

Regarding animal experiments in rodents and dogs, efforts will be made to use the minimum number necessary to obtain statistically sound data. All these experiments will be performed according to the 3Rs (replace, reduce, refine). All experimental animals will be supervised and inspected by veterinarians on a daily basis. All animal samplings and experiments will be approved and monitored on an on-going basis by institute ethical committees and will be performed in accordance with EU and national laws and safety provisions, including animal welfare requirements. The forthcoming new EU directive on animal welfare and experimentation will be followed, even if it had not been finally accepted when the EDENEXT starts.

For immunological and genetic studies in wildlife, we try to utilize existing materials which reduces the need for sampling of totally new extensive wildlife materials. All samplings will be done by local scientists or together with local scientists to be certainly able to follow the local laws and to avoid accidental intrusions of sites with endangered species. If sampling on endangered species is necessary, we will not sample them in a destructive way. Should protected species be sampled (in a nondestructive way), it will be done together with local scientists and only with all necessary permits from local authorities. Our wide networking and existing connections certify that local expertise is always used and local regulations are acknowledged.

All experiments involving hazardous products and infectious wild-type microbes will be performed in certified laboratory facilities, in accordance with the respective safety provisions in the countries where the research is carried out. Shipment of all clinical and animal samples will be made in accordance with the IATA regulations and national regulations using legal couriers.

EDENEXT includes work with pathogenic microbes, which fall into categories BSL-2, 3 and 4. These partners have fully certified laboratories for handling such microbes. The work will be carried out by personnel specifically trained and instructed to carry out such work.

In order to further ensure that all safety, ethics and legal provisions are met, this topic will be included as a subject for discussion at the workshop on laboratory techniques and standardization to be held at the beginning of the EDENEXT project. During this workshop, representatives of all participating laboratories will be informed of their duties and responsibilities in relation to EU policy.

Focal Point for animal ethics and samples, safety and other EU-policy related issues will be confirmed during contractual negotiations according to requirements. He has been provisionally identified as Prof. Heikki Henttonen, who formerly was also the focal point of animal ethics in the EC-funded EDEN project. He has been working since many years in the animal ethics committee of Helsinki University, and has a long-term experience on studying pathogens of wild animals around the world. He is a board member of European Society of Mammalogy, International Federation of Mammalogists, and “Rodens & Spatium” congress series, international and local expertise as well as networking on animal ethics questions is secured.

Regarding works conducted in developing countries, surveys involving animals (domestic ruminants, equids) will be designed with the official veterinary services, and samples will be made by local veterinary officers, in compliance with biosafety and biosecurity recommendations made by the World animal health organization (OIE) to its member states. Farmers and other people in the surveys will be informed of their goals and expected benefits, for scientists and local communities.
4 Gender issues

The scientific objectives of the EDENext project do not have any special gender issues. Vector-borne pathogens infect both men and women, when at equal occupational or leisure risk, although some aspects of pathology may vary with sex. There is no evidence that global change in either climate or emergent diseases is gender-specific, giving rise to any differential women's needs. The focus of this project is biological, not sociological, so enhanced understanding of gender issues falls well outside the objectives. On the other hand, the Scientific Directorate of the EDENext project is very aware of the gender imbalance amongst the senior scientific community and has sought specifically to redress this imbalance in the leadership of, and participation in, each sub-project of the work. The problem for women scientists does not lie in the number of PhD qualified female graduates (c.40% of total) or researchers (c.36% of total), but in the steep loss of women with increasing seniority; i.e. there is no shortage of female human resources, but a shortage of female leaders. This in turn results in a lack of role models for each successive generation of female graduates.

In the EDENext project we have achieved a higher than average representation by women amongst the lead researchers, both for the key national partners and the group leaders and their deputies. On average, little more than 10% of senior posts (grade A, equivalent to professor) are held by women in the Medical and Natural Sciences in the EU member and associated states for which data is available.

By comparison the representation of women at senior positions in EDENext is significantly higher and more closely reflects the proportion of women at more junior levels:

- Of the 53 registered senior team leaders, 15 are women, which amounts to 28%.
- Of the 17 members of the SC, 6 are women, which amounts to 35%.

4.1 Gender action plan

To build further on the positive record shown above the following guidelines will be followed during EDENext. All appointments associated with EDENext will be on merit and experience, but the following affirmative measures will be taken by senior management and project leaders to encourage the application, appointment and participation of women:

- Applications from women for EDENext PhD and Marie Curie funding will be promoted;
- Advertisements and notices shall state clearly that female applicants are encouraged to apply;
- Every effort will be made to achieve a 50:50 gender balance of short-listed candidates for interview. If this is not achievable, written explanations will be provided to EDENext management;
- Women will be encouraged to take leading roles in all EDENext activities;
- Records of the recruitment process will be kept for inspection and a comprehensive, up-to-date listing will be maintained of all appointments and personnel associated with EDENext, by grade, sex, disability, religious affiliation, minority group status and nationality;
- During dissemination efforts aimed at the general public and schools, EDENext will particularly target a female audience.