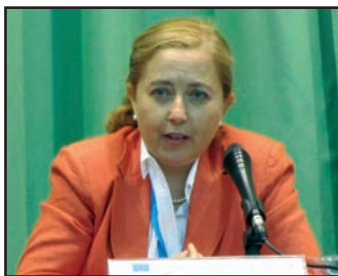




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Isabel Mínguez-Tudela

It was with great sadness that the steering committee of Arbo-Zoonet received the news that Isabel Mínguez-Tudela passed away on 16 Apr 2011, aged 55 after a long battle against cancer. Even under these adverse health conditions, she was working and fighting until the last moment for European research in animal health.

Isabel was senior scientific officer at DG Research and Innovation of the European Commission in Brussels. She was Spanish, trained as a veterinarian and obtained a PhD in Animal Virology in Madrid. She served in the field of Agriculture and Biotechnology for 20 years, managing dozens of EU research projects on animal health including BSE, avian influenza, African swine fever, arbovirus infections, swine flu, foot-and-mouth disease, rabies, and many other topics, thus also including the Arbo-Zoonet project. On behalf of the steering committee of Arbo-Zoonet I can say that Isabel was a leading scientist with a clear vision and competence, thus also being an invaluable help in successfully coordinating Arbo-Zoonet.

Her role in the development of veterinary medicine in Europe and linking it to Asia, Africa and Latin America can not be described with only a few words and will remain in our memory. Many young scientists will remember forever how she supported them to make good science and to collaborate in a fair way. Let us keep her in our hearts and give what we have learned from her to the younger generation in order to continue in her way in doing good science for a fairer world.

On behalf of the Steering Committee and all partners of the Arbo-Zoonet project

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ARTICLES

TICK-BORNE RICKETTSIAL AND EHRLICHIAL INFECTIONS

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Tick-borne rickettsioses

Tick-borne pathogenic rickettsiae are members of the genus *Rickettsia*, family *Rickettsiaceae* in the order *Rickettsiales*. They are Gram-negative, obligate, intracellular bacteria that have a life cycle which involves both an arthropod vector and a vertebrate host. They cause infections in humans, named rickettsioses which can present with an array of clinical signs and symptoms. These zoonoses are among the oldest known vector-borne diseases [1].

Rickettsiae are classified into four groups based on their biological, genetic and antigenic characteristics: the spotted fever group (SFG), typhus group, transitional group and ancestral group. Rickettsial phylogeny is based on sequence analyses of different genes, namely housekeeping genes, which are useful for distinguishing distinct strains, and genes encoding variable immunodominant outer membrane proteins that are under evolutionary pressure. The genetically-based phylogenetic analysis has substantially affected the previously proposed taxonomy of rickettsiae [2].

Vertebrate hosts are infected with tick-borne rickettsiae via direct inoculation by a feeding tick. Ticks with hard chitin are vectors and reservoirs for SFG rickettsiae. Ticks acquire SFG rickettsial species through transovarial transmission (adult female to egg) and transstadial passage (egg to larva to nymph to adult), and by horizontal acquisition during feeding on a rickettsiemic host. Most SFG rickettsiae are probably maintained in nature by all these mechanisms [3, 4].

Most of the clinical characteristics of rickettsial diseases are related to disseminate infection of the endothelium, where they grow and stimulate oxidative stress. Infection of endothelial cells at the site of tick inoculation of most SFG rickettsiae is followed by local dermal and epidermal necrosis that forms an eschar. Disseminated infection, further injury to the vascular endothelium and infiltration of perivascular mononuclear cells leads to vasodilation, an increase in fluid leakage into the interstitial space and a characteristic rash. Thus, the most prominent pathophysiological effects of rickettsial infection of endothelial cells include: an increase in vascular permeability; generalized vascular inflammation; oedema; increased leukocyte–endothelium interactions; and release of powerful vasoactive mediators that promote coagulation and pro-inflammatory cytokines [1].

SFG rickettsiae are tick transmitted and include highly pathogenic organisms, such as tick-transmitted *Rickettsia rickettsii* that cause **Rocky Mountain spotted fever (RMSF)**. *R. rickettsii* is transmitted in rural areas by *Amblyomma* and *Dermacentor* ticks [2, 3, 5]. The disease is endemic in the southeastern and Midwest United States and in parts of South America. It affects those who have exposure to tick-infested habitats, such as wooded and grassy areas. Highly lethal RMSF is characterized by headache, fever, myalgia, nausea and vomiting early in the illness; if untreated, severe disease can develop that sometimes progresses to multi-organ failure. In severe cases, hypovolaemia and hypotensive shock result in acute renal failure. If untreated, the mortality rate can be as high as 20% [1, 3, 4, 6].

Rickettsia conorii causes **Mediterranean spotted fever (MSF)** and both it and its variants (Astrakhan fever, Indian tick typhus) are transmitted by dog ticks (*Rhipicephalus sanguineus*) in urban and suburban areas. The disease is present in Europe, Africa and Asia, with the principal foci of Mediterranean and Caspian littorals [5, 7]. Clinical features include fever, constitutional symptoms, a generalized maculopapular rash, and an inoculation eschar at the site of the tick bite. Most cases are mild, but complications are not uncommon and include neurological involvements, peripheral gangrene, and respiratory distress syndrome. The overall fatality rate is ~2% [7, 8].

Rickettsia africae is transmitted by *Amblyomma* ticks and causes **African tick-bite fever (ATF)** and is endemic in large parts of rural sub-Saharan Africa and the eastern Caribbean. Cattle ticks act as reservoirs and vectors, and are locally very common on the vegetation (especially during the rainy season), are notoriously aggressive, and readily bite humans. Cases are typically acquired during agricultural work [8, 9]. The clinical presentation includes headache, neck myalgia, and one or several inoculation eschar with regional lymphadenitis, whereas a vesicular cutaneous rash and mouth blisters are seen in up to 30% of the patients. African tick bite fever is usually a self-limited, mild disease, and no fatalities have been reported to date [3]. It is also the most commonly encountered rickettsioses in travel medicine. Most patients are infected during wild game safaris and bush walks, often of short duration. African tick bite fever often occurs in clusters and may sometimes present as large outbreaks among safari tourists, military personnel, game hunters, sports participants, or school students. Risk factors include game hunting, travel during the summer season, and travel to southern Africa, where the incidence of ATF is particular high [10].

Rickettsia parkeri, transmitted by ticks of the genus *Amblyomma* has only recently been recognized as a pathogen of humans in the USA and Uruguay. It causes mild to moderate spotted fever rickettsioses. Although first identified in 1937, *R. parkeri* has been recognized as a human pathogen only since 2004, when it was isolated from an eschar on a serviceman from Virginia. Little is known about the geographic distribution of *R. parkeri* in the United States or the epidemiology of the disease it causes. *R. parkeri* may be the etiologic agent of some rickettsioses cases in southern USA that have been misdiagnosed as RMSF [2-5].

Rickettsia slovaca is transmitted by ticks of the genus *Dermacentor* and was described as an agent of tick-borne lymphadenopathy (TIBOLA). This syndrome is defined as the association of a tick bite, an inoculation eschar on the scalp, and cervical lymphadenopathy. The disease has been documented in patients in Hungary, Slovakia, France and Spain. Dermacentor ticks are active during early spring, again in autumn and even in winter in southern Europe. They frequently bite people, particularly on the scalp. Infections most likely occur in children and in patients who were bitten during the colder months of the year [1, 7, 8].

Confirmation of diagnosis is difficult during the acute phase and proper treatment is essential for rapid recovery and prevention of complications. Thus, presumptive therapy with antirickettsial drugs is recommended whenever a case of rickettsioses is suspected. The standard drug of choice is doxycycline, 200 mg daily for 3–14 days, depending on the clinical course. Most patients will improve within the first 24 h after the start of therapy. Chloramphenicol and the newer macrolides are probably good alternatives to doxycycline [10].

Agent	Disease	Tick Vector	Geographic Distribution
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever (RMSF)	<i>Dermacentor variabilis</i>	Eastern two thirds of United States and Pacific Coast
		<i>D. andersoni</i>	Rocky Mountain States
		<i>Amblyomma cajennense</i>	Central and South America
<i>Rickettsia conorii</i>	Mediterranean spotted fever (MSF)	<i>Rhipicephalus sanguineus</i>	Southern Europe, Africa, Western and Southern Asia
<i>Rickettsia africae</i>	African tick bite fever (ATF)	<i>A. hebraeum</i>	Southern Africa
		<i>A. variegatum</i>	Central, East, and West Africa, West Indies
<i>Rickettsia slovaca</i>	Tick-borne lymphadenopathy (TIBOLA)	<i>D. marginatus</i> , <i>D. reticularis</i>	Europe
<i>Rickettsia parkeri</i>	R. Parkeri rickettsiosis	<i>A. maculatum</i>	United States
		<i>A. triste</i> , <i>A. dubitatum</i>	Brazil, Uruguay, Argentina

Table 1. Epidemiology of tick-borne rickettsial infections

Ehrlichioses

Human ehrlichioses and anaplasmosis are acute febrile tick-borne diseases caused by various obligate intracellular bacteria from the genera *Ehrlichia* and *Anaplasma* (family *Anaplasmataceae*). These diseases have been known for a long time in veterinary medicine and only recently became important pathogens of humans. These tick-borne zoonoses are considered as emerging diseases. As the first case of human monocytotropic ehrlichiosis (HME) occurred in 1986, human granulocytic anaplasmosis (HGA) was described as a separate entity in 1994 and ehrlichiosis caused by *Ehrlichia ewingii* was reported in humans in 1999. The number of cases has increased due to better diagnostic techniques, better surveillance worldwide, and due to an increased number of animal reservoirs and tick vectors [11-13].

Ehrlichia chaffeensis, the etiologic agent of human monocytotropic ehrlichiosis (HME) is an emerging zoonosis that causes clinical manifestations ranging from a mild febrile illness to a fulminant disease characterized by multi-organ system failure. *E. chaffeensis* is maintained in nature through ticks and several vertebrates. The main mammalian host in the USA is the white-tailed deer, which serves as a reservoir for the bacterium, and the tick vector (*Amblyomma americanum*) becomes infected during blood meals taken from an ehrlichemic mammal. Most cases of HME have been reported from the south-central and southeastern US. A couple of hundred of cases are reported yearly to the CDC with an incidence between 2 and 4.7 per 100,000 of the population [12-14].

HME is a more severe disease than HGA with 42% of cases requiring hospitalization, and a case-fatality rate of 3%. Up to 17% of patients develop life-threatening complications, although severe disease and death are more common in immunocompromised patients, which are manifested as a multisystem disease resembling toxic or septic shock syndrome. Fever is an almost universal symptom, followed by headache, myalgia, and arthralgia. A rash is present in 10% of cases of HME and can be maculopapular or petechial. Although the clinical manifestations of HME are nonspecific, laboratory abnormalities (thrombocytopenia, leukopenia and elevated liver enzymes) provide important diagnostic clues [11, 12].

A. phagocytophilum causes human granulocytotropic anaplasmosis (HGA), previously known as human granulocytotropic ehrlichiosis (HGE). *Anaplasma phagocytophilum* is transmitted by *Ixodes sp.* ticks, which also transmit agents that cause Lyme disease and babesiosis. In North America *I. scapularis* is the principal vector of *A. phagocytophilum*. This tick species has a high affinity for biting humans. In the Northeast and Midwest part of the US, the main reservoirs are the white-footed mouse and the white-tailed deer. The number of clinical cases of human anaplasmosis has increased since the first description. Since then, almost 2700 cases have been documented in the USA. HGA is a seasonal disease since clinical cases are mostly reported during the summer and spring, since outdoor activities are predominant during these seasons [5, 12, 13].

The first confirmed HGA case in Europe was described in Slovenia in 1997 [15]. During the following years, human anaplasmosis has been reported in the Netherlands, Spain, Sweden, Norway, Croatia, Poland, Austria, Italy and France. To date nearly 100 cases have been reported in Europe [14]. The main vector of *A. phagocytophilum* is *I. ricinus*. The reservoirs in Europe are probably small mammals. Roe and red deer represent a very important host for the adult tick *I. ricinus*, a vector of *A. phagocytophilum*, and could therefore also serve as a the natural reservoir. Human cases have a seasonal distribution and occur mainly during summer, when ticks are most active [16].

HGA resembles HME. Its clinical presentation is nonspecific and usually consists of fever, headache, malaise, myalgia and/or arthralgia and is often accompanied by leukopenia, thrombocytopenia, anemia and increased activity of hepatic enzymes. Rash is uncommon, noted in less than 10% of patients. HGA tends to be a less severe illness than HME, although life-threatening complications including acute respiratory distress syndrome, acute renal failure, and hemodynamic collapse have been reported [11, 12].

Human Ehrlichia ewingii (HEE) ehrlichiosis - Ehrlichia ewingii was a canine pathogen until in 1999 a series of four human cases of *E. ewingii* infection were described. The epidemiology of HEE remains unknown due to the lack of a specific serologic assay for this organism and the absence of a dedicated reporting system for this infection. Most infections have occurred in patients with HIV, or immunosuppressed patients following organ transplantation. *Amblyomma americanum*, the primary vector for *E. chaffeensis*, is also the primary vector for *E. ewingii*. Most cases of HEE have been reported in Tennessee, Missouri, and Oklahoma in the United States. Little is known of the clinical spectrum of HEE due to the paucity of reported cases [13]. Symptoms appear to be similar to those described for HME and HGA. Despite the fact that the majority of HEE infections have been in immunocompromised hosts, the clinical manifestations appear to be milder. Findings of leukopenia, thrombocytopenia, and abnormal liver function tests are variably present [14].

Agent	Disease	Tick Vector	Geographic Distribution	Vertebrate Hosts
<i>Ehrlichia chaffeensis</i>	Human monocytotropic ehrlichiosis (HME)	<i>Amblyomma americanum</i> , <i>Dermacentor variabilis</i> , <i>Ixodes pacificus</i>	Southeastern and South-Central United States, California	White-tailed deer
<i>Ehrlichia ewingii</i>	Ehrlichiosis ewingii (HEE)	<i>A. americanum</i>	Southeastern and South-Central United States, California	White-tailed deer
<i>Anaplasma phagocytophilum</i>	Human granulocytotropic anaplasmosis (HGA)	<i>I. scapularis</i>	Human granulocytotropic anaplasmosis (HGA)	White-footed deer mouse, white-tailed deer
		<i>I. pacificus</i>	Pacific coastal United States	Squirrels, wood rats
		<i>I. ricinus</i>	Europe	Red deer, roe deer, horses, dogs, cattle, sheep, small mammals, wild boar

Table 2. Epidemiology of tick-borne ehrlichioses and anaplasmosis

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Most patients with HME or HGA respond well to tetracycline if administered early in illness. Doxycycline is preferred over tetracycline because it has fewer side effects and better patient tolerance. Doxycycline remains the treatment of choice in pediatric patients, despite the risk of dental discoloration in this age group. This drug is bacteriostatic in its activity against rickettsial organisms. Pregnant patients with ehrlichial infection represent a particular challenge, as doxycycline is contraindicated. In this population, as well as in patients with a specific contraindication to doxycycline, rifampin may be substituted [12].

There is a steady increase in incidence of tick-borne rickettsial and ehrlichial infections in several parts of the world. Some of these diseases are considered as emerging diseases in human medicine.

Various factors have contributed to the emergence of these tick-borne illnesses, including better awareness by physicians; better diagnostic tools, including modern techniques in molecular biology; changes in the environment with the expansion of the animal reservoirs; and the growth of susceptible human populations.



ARBO-ZOONET ANNUAL MEETING 2010

RABAT, MOROCCO, 22.-24. NOVEMBER 2010

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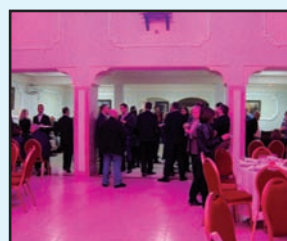
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The annual meeting 2010 of Arbo-zoonet project was held from November 22 to 24 in Rabat, Morocco. The purpose of this meeting was to review the activities carried out on Rift Valley fever virus, West Nile virus, Crimean-Congo hemorrhagic fever virus and related viruses and to link with other networks and International organisations. Thus participants from OIE, ECDC and WHO as well as representatives from other scientific networks, such as EpiSouth, EDENext, CCH Fever, and EuroWestNile attended the meeting.

The two-and-half day meeting was devoted to presentations and discussions on presentations by the participants of Arbo-zoonet and to open discussions with colleagues from international organisations and other networks. A significant number of young researchers present their work to an attentive audience followed by interesting discussions. Current scientific developments in the field were Intensive discussions on took place during the meeting in Rabat.

Abstracts and presentations of the meeting can be accessed and downloaded from the Arbo-Zoonet download site at www.arbo-zoo.net.



Programme of the Arbo-Zoonet Annual Meeting

Monday 22nd November 2010

Morning session 9h- 12h15

9h-9h05	MICHÈLE BOULOY: Introduction
9h05-9h30	Opening by PROF. OUAFAA FASSI FIHRI, Institut Agronomique et Veterinaire Hassan II, Rabat, Morocco: 'Research on West Nile virus in Morocco'
9h30-9h50	ANTONIO PETRINI, Representative of OIE: Laboratory Twinning
9h50-10h10	KATRIN LEITMEYER, Representative of ECDC: Introduction to ECDC & Relations to European Networks
10h10-10h30	PIERRE FORMENTY, Representative of WHO: Remapping Rift Valley fever outbreaks in Africa and the Middle East
11h-11h15	JOHANNA KABADANIAN/NADIA KHELEF: Project relevant information from Brussels
11h15-11h35	RENAUD LANCELOT, Representative of Edenext
11h35-11h55	PHILIPPE BARBOZA, Representative of EpiSouth
11h55-12h15	ANTONIO TENERIO, Representative of EuroWestNile

Afternoon session 15h-17h30 Chaired by Richard Elliott and Michèle Bouloy Epidemiology (I)

15h-15h15	PAOLO ALMEIDA: "Mosquito Surveys For West Nile and other Flaviviruses in The Algarve, Portugal in 2009-2010"
15h15-15h30	AYSEN GARGILI: "Bacterial Pathogens in Human-Biting Ticks; is there an underestimated problem?"
15h30-15h45	HARUN ALBAYARAK: "Complete genome sequences and phylogenetic analysis of Israel West Nile Virus"
15h45-16h	SADEGH CHINIKAR: "Important experiences and informations about Crimean Congo Haemorrhagic Fever in recent decade in Iran"
11h15-11h35	RENAUD LANCELOT, Representative of Edenext
11h35-11h55	PHILIPPE BARBOZA, Representative of EpiSouth
11h55-12h15	ANTONIO TENERIO, Representative of EuroWestNile

Afternoon session 15h-17h30 Chaired by Richard Elliott and Michèle Bouloy Epidemiology (I)

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15h30-15h45	HARUN ALBAYARAK: "Complete genome sequences and phylogenetic analysis of Israel West Nile Virus"
15h45-16h	SADEGH CHINIKAR: "Important experiences and informations about Crimean Congo Haemorrhagic Fever in recent decade in Iran"

Genetic variability

- 16h30-16h45 FELICITY BURT: "Identification of natural reassortants of Crimean-Congo Haemorrhagic Fever Virus in Southern Africa"
- 16h45- 17h
Virus isolates, 1944 – 2010" JANUSZ PAWESKA: "Phylogenetic analysis of Rift Valley Fever Virus isolates, 1944 – 2010"
- 17h-17h15 NICK JOHNSON: "Current status of West Nile Virus phylogeny"
- 17h15-17h30 MARIETJIE VENTER: "Detection of the first highly neuroinvasive lineage 1 West Nile Virus strain in South Africa through sentinal surveillance in horses"

Tuesday 23rd November 2010

Morning session 9h- 12h45 Chaired by Noel Tordo and Tony Fooks Pathogenesis

- 9h-9h15 SARA AKERSTROM: "In vivo bioluminescence imaging of Rift Valley Fever Virus in mice"
- 9h15-9h30 BEN HAXTON: "Characterisation of cytokines within the central nervous system in response to a neuroinvasive virus"
- 9h30-9h45 HELEN KARLBERG: "Caspase-dependent induction of apoptosis during infection and CCHFV np serves as a substrate for caspase mediated cleavage"
- 9h45-10h KAREN MANSFIELD: "Studies on Flavivirus Pathogenesis"
- 10h-10h15 RAQUEL RODRIGUES: "Crimean-Congo hemorrhagic fever virus infects human hepatocytes and induces IL-8" secretion
- 10h15-10h30 FRIEDEMANN WEBER: "Contribution of ISG20 to the interferon response against of Bunyaviruses"
- 11h-11h15 JEAN JACQUES PANTHIER: "Host genetics control of Rift Valley Fever infection"
- 11h15-11h30 DAVID WALLACE: "Development of an infection model for RVF in 6-month old sheep and dose evaluation of the M35/74 challenge strain of virus"
- 11h30-11h45 CÉLINE BAHUON: "Construction and characterization of the infectious clone of the highly virulent WNV strain is-98-st1"

Vaccines

- 11h45-12h HANI BOSHRRA: "Ubiquitination of Rift valley fever virus nucleoprotein creates a potent alternative to glycoprotein-based DNA vaccines"
- 12h-12h15 RICHARD ELLIOTT: "Creation of a recombinant Rift Valley Fever Virus Containing a two-segmented genome"
- 12h15-12h30 BEN BRENNAN: "Assessing the reassortment potential of a two-segmented Rift Valley Fever Virus"
- 12h30-12h45 ROB MOORMAN: "Rift Valley fever virus immunity provided by a paramyxovirus vaccine vector"

Afternoon session 14h15-17h30 chaired by Jabbar Ahmed and Janusz Paweska Epidemiology (II)

- 14h30-14h45 DAREM TABBAA: "Preparedness and response to Congo Crimean Hamorrhagic Fever in Syria" 9
- 14h45-15h DANIEL RUZEK: "Search on Arboviruses in Ghana (plan of the project)"

- 15h-15h15 VÉRONIQUE CHEVALIER: “West Nile in Europe: sizing and comparison of West Nile virus surveillance in a changing epidemiological context”
- 15h15-15h30 PHILIPPE BARBOZA: “Crimean–Congo Haemorrhagic Fever Virus in Mediterranean and Balkans countries from 2002 to 2008” and “West Nile Outbreak in the Mediterranean region, autumn 2010”
- 15h30-15h45 MATTHIAS NIEDRIG: “Rodents as Sentinels for the Prevalence of Tick-Borne Encephalitis Virus?”
- Diagnostics**
- 15h45-16h JOELLE DE VRIESE: “Development of NS1 capture Elisa as an early viral detection tool for West Nile Virus (WNV) infected target birds”
- 16h-16h15 MEIK DILCHER: “Pyrosequencing of viral genomes”
- 16h15-16h30 CHARMAINE VAN EEDEN: “Shuni virus: a cause for neurological disease in horses in South Africa”
- 17h-17h15 CLAUDIA FILIPPONE: “High density DNA resequencing microarrays for the diagnosis/discovery of highly pathogenic viruses: application to Crimean Congo Hemorrhagic Fever Virus outbreaks”
- 17h15-17h30 PETRUS JANSEN VAN VUREN: “The 2010 Rift Valley Fever outbreak in Humans in South Africa: a laboratory perspective”
- 17h30-17h45 DEWALD ZAAJMAN: “Development of a differential diagnostic macroarray-based assay for neurological and febrile infections in Africa”

Wednesday 24th November 2010

Morning session chaired by Franco Ruggeri

- 9h-9h15 PAOLO CALISTRI: Arbo-Zoonet Webmapping application
- 9h-12h Workpackage leaders and General discussion

Posters

- NURIA BUSQUETS : “Experimental West Nile Virus infection in European falcons”
- JOLYON MEDLOCK : “Ecological & entomological approaches to informing public health policy and risk assessments on emerging vector-borne zoonoses”
- MARINA MONINI : “Cloning and expression of the West Nile Virus envelope protein E”
- MAARTEN HOEK : “Risk of introducing Rift Valley Fever virus into the Netherlands”
- EGIL FISHER : “Modeling prevention and control of Rift Valley Fever epidemics in the Netherlands”
- JACQUELINE WEYER : “An overview of human Crimean-Congo Haemorrhagic Fever cases in South Africa, 1981-2010”



LINKING TO INTERNATIONAL ORGANIZATIONS

WHO: Remapping Rift Valley fever outbreaks in Africa and the Middle East

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Rift Valley Fever (RVF), is a viral zoonosis that primarily affects animals but that also has the capacity to infect humans. Infection can cause severe disease in both domestic animals (cattle, sheep, goat, and camels are amplifier hosts during major outbreaks) and humans. Vaccines for animals are available and experimental vaccines have been developed for humans. RVF is endemic throughout sub-Saharan Africa; the disease has occasionally spread to Egypt, Saudi Arabia and Yemen. The major mode of transmission to humans is direct contact with infected animal blood or organs, but the virus can also be transmitted by mosquito bites and laboratory contamination. Several different species of mosquito are able to act as vectors for transmission of the RVF virus. To date, no human-to-human transmission has been documented.

From the end of 2006 to date, major RVF outbreaks have started in Eastern Africa and are still on-going in Southern Africa. According to WHO, in Kenya, Somalia and Tanzania alone, a total of 100,000 human infections can be estimated. During this wave, RVF transmission has been reported in contrasted eco-epidemiological patterns.

Joint WHO/FAO field investigations in most of the affected countries provided an opportunity to review the ecology of RVF major outbreaks and to distinguish two ecologically distinct situations: primary and secondary emergence sites. At primary foci sites, RVF virus spreads through transmission between vectors and hosts and is maintained between outbreaks through vertical transmission in *Aedes* mosquitoes. During major outbreaks in primary foci, the disease can spread to secondary foci through livestock movement or passive wind-borne dispersal of mosquitoes. At secondary foci sites RVF virus spreads between naïve ruminants via local competent mosquitoes like *Culex* and *Anopheles* that act as mechanical vectors. Irrigation schemes, where populations of mosquitoes are abundant during long periods of the year, are highly favourable places for secondary disease transmission.

An innovative RVF primary versus secondary area map is proposed, based on expert opinions and review of historical and recent outbreaks. A joint FAO/WHO database including approximately 2000 records from official and unpublished data has been developed. These data are now used to improve the models for the determination of RVF suitable areas and real-time monitoring developed by collaborative centres, with the final objective of improving RVF outbreak forecasting and early warning.

OIE Laboratory Twinning Programme

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The OIE network of expertise includes OIE Reference Laboratories, which provide expertise for a named OIE listed disease, and OIE Collaborating Centres which provide expertise for a designed sphere of competence. The network provides global support for surveillance, diagnostic testing and control of important animal diseases including zoonoses.

Today, the distribution of this network tends to favour developed countries and the northern hemisphere. Through the OIE Laboratory Twinning programme, OIE aims to extend the network to provide a more even geographical distribution, so that more countries will have access to highly quality diagnostic testing and expertise essential for early detection and rapid control. Expertise is essential to ensure proper application of OIE standards and equal representation of developing/in transition countries in international scientific debate.

Each twinning projects links existing OIE Reference Laboratory or Collaborating Centre with a “candidate” Laboratory. Through this link, knowledge and skills are exchanged allowing the candidate laboratory to develop capacity and expertise for a disease or a topic that is priority in its region in order to better comply with OIE International Standards.

The OIE World Animal Health and Welfare Fund provides financial support to the link between the two institutes for the duration of the project; however funds are not available for purchase of laboratory equipment or for upgrading of laboratory infrastructure. There is scope within a twinning project to support surveys, conducted by experts, that can then be used to attract further support from other donors for infrastructure or equipment.

OIE Laboratory Twinning is therefore a tool to both strengthen sustainable links within the animal health laboratory network and to extend the network to provide better global coverage, particularly in developing and in transition countries. The eventual aim is to create a network of diagnostic capacity and expertise that it is well distributed globally and that provides support in areas where it is needed (e.g. North Africa). This will have long term benefits for animal and human health.

LINKING TO OTHER EU-FUNDED PROJECTS

The EpiSouth Plus Project

Increasing health security in the Mediterranean area and South-East Europe by enhancing and strengthening the preparedness to common health threats and bio-security risks at national and regional levels in the countries of the EpiSouth Network

Ait-Belghiti F¹, Barboza P¹, Giese C¹, Leventhal F², Dente MG³, Bejaoui M⁴, Fabiani M², Alfonsi V², Lausevic D⁵, Salamina G⁶, Victoir K⁷, Kalaydioglu H³, Simon Soria F⁹, Martin de Pando C⁹, Hannoun D¹⁰, Riccardo F³, Nabeth P¹¹, and Declich S³ on behalf of the EpiSouth Network

1 Institute for Public Health Surveillance-InVS, Saint Maurice France; 7 Institute Pasteur, Paris, France;
2 Middle East Consortium on Infectious Disease Surveillance-MECIDS; 8 Refik Saydam National Hygiene Center, Ankara, Turkey;
3 Italian National Institute of Health-ISS, Rome, Italy; 9 Carlos III Health Institute-ISCIII, Madrid, Spain;
4 Ministry of Health, Tunis, Tunisia; 10 National Institute of Public Health, Alger, Algeria;
5 Institute of Public Health, Podgorica, Montenegro; 11 WHO-LYO
6 Local Health Unit, Turin, Italy;

<http://www.episouthnetwork.org/>

At the occasion of the Year of the Mediterranean (2005), a number of countries that share the same Mediterranean ecosystem and therefore have common public health problems, agreed to develop the project called “EpiSouth”: its aim was to create a collaboration framework on epidemiological issues in order to improve communicable disease surveillance, communication and training in the Mediterranean region and South-East Europe.

“EpiSouth” started in October 2006 with the financial support of the European Commission (EU),

the Italian Ministry of Health and the participating countries. The first EpiSouth phase ended in June 2010. As of June 2010, 27 countries (17 non-EU countries plus 1 candidate to enlargement country) were part of EpiSouth which is therefore the biggest inter-country collaborative effort in the Mediterranean region.

The second phase called EpiSouth-Plus officially started on 15th October 2010 and is expected to last until 15 April 2013. EpiSouth Plus aims at contributing to the control of public health threats and other bio-security risks in the Mediterranean region and South-East Europe. Based on the achievements and lessons learned during firsts years, this new phase will yield a shift of activities with a wider approach to address regional gaps and needs identified in the fields of Epidemic Intelligence, Vaccine Preventable Diseases and Migrants, Cross Border Emerging Zoonoses and Training.

EpiSouth Plus is funded by the European Union (DG-SANCO/EAHC and EuropeAid) together with the participating national Institutions. The Project is also supported by the Italian Ministry of Health and ECDC.



EpiSouth participating countries



EpiSouth Meeting, Rome, April 2010

EpiSouth Plus Objectives and Organisation

The EpiSouth Plus project aims at increasing health security in the Mediterranean area and South-East Europe by enhancing and strengthening preparedness for common health threats and bio-security risks at national and regional levels in the EpiSouth countries in the framework of the International Health Regulations. The reinforcement of trust based relations in the region is an objective and an instrument in the scope of the project's implementation.

Ensuring a successful response to this challenge requires a solid framework of collaboration and information exchange among the 27 participating countries. For this purpose, Focal Points from each participating country have been appointed and asked for active involvement and collaboration in the project's activities.

The project is organised in seven Work Packages (WP), jointly co-led by EU and non-EU countries. WP leaders work in close collaboration with the corresponding WP Steering Team, while a Steering Committee, constituted by all WP leaders and the Project General Assembly, constituted by all participants, are responsible for the general strategic decisions. An Advisory Board, constituted by representatives of the collaborating institutions and external experts, provide support for the preparation of relevant documents and recommendations.

Activities

Apart from three transversal WPs (i.e., WP1-Coordination; WP2-Dissemination; WP3- Evaluation) the project's activities are articulated in four WPs:

- 1) Establishment of a Mediterranean Regional Laboratories Network to facilitate common threats detection (WP4).
- 2) Promotion of common procedures in interoperable Generic Preparedness and Risk management among the countries involved in the Network (WP5).
- 3) Enhancement of Mediterranean Early Warning functions allowing alerts and Epidemic intelligence information sharing among EpiSouth countries through the development of interoperability with other Early Warning platforms and especially the European Early Warning and Response System (EWRS) as forecasted by the current EU legislation (WP6).
- 4) Production of a strategic document, with guidelines based on assessments and surveys, aimed at facilitating IHR implementation (WP7).

Nota Bene

The project is led by the Italian National Institute of Health and counselled by an advisory board composed by EC, ECDC, WHO and other international experts. It is co-funded by the European Union DG-SANCO/EAHC and EuropeAid together with the participating national partner Institutions. The financial support of the Italian Ministry of Health and ECDC is also acknowledged.

The contents of this publication are the sole responsibility of the Italian National Institute of Health and can in no way be taken to reflect the views of the European Union.

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BOSNIA & HERZEGOVINA (Ministry of Civil Affairs, Sarajevo; Ministry of Health and Social Welfare, Banja Luka, Republic of Srpska; Public Health Institute, Mostar, Federation of B&H);
BULGARIA, Sofia (National Center of Infectious and Parasitic Diseases);
CROATIA, Zagreb (Croatian National Institute of Public Health);
CYPRUS, Nicosia (Ministry of Health);
EGYPT, Cairo (Ministry Of Health and Population);
FYROM–Former Yugoslav Republic of Macedonia, Skopje (Institute for Health Protection; Clinic of Infectious Diseases);
FRANCE (Institute for Public Health Surveillance, Saint Maurice Cedex; Institute Pasteur, Paris);
GREECE, Athens (Hellenic Center for Diseases Control and Prevention);
ISRAEL (Center for Disease Control, Tel Hashomer; Ministry of Health, Jerusalem);
ITALY (National Institute of Health-ISS, Rome; Teaching Hospital, Padua; National Institute for Infectious Diseases-IRCCS “Lazzaro Spallanzani”, Rome; Intrauniversity Consortium, Casalecchio di Reno; Local Health Unit of Turin, Turin);
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SLOVENIA, Ljubljana (Institute for Public Health);
SPAIN, Madrid (Carlos III Health Institute);
SYRIA, Damascus (Ministry of Health);
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TURKEY, Ankara (Ministry of Health; Refik Saydam National Hygiene Center);
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Collaborating Institutions

ECDC-European Centre for Disease Prevention and Control, Stockholm, Sweden;
EUROPEAN UNION DG SANCO Public Health Directorate, Luxembourg;
14 EUROPEAN UNION DG EuropeAid, Brussels, Belgium;
MOH-Ministry of Health, Rome, Italy;
WHO–EMRO Regional Office for Eastern Mediterranean, Cairo, Egypt;
WHO-EURO Regional Office for Europe, Copenhagen, Denmark.

Fighting Emergence of CCHF in Europe “CCH Fever”

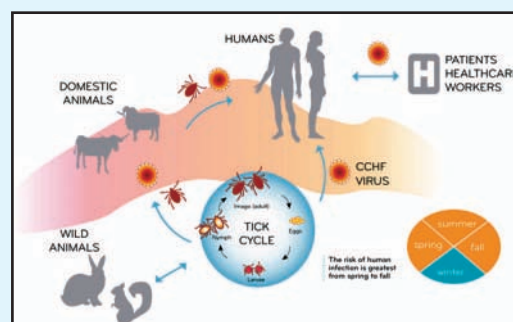
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CCH Fever is a European research network (Collaborative Project) supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme (Grant agreement n° 260427).

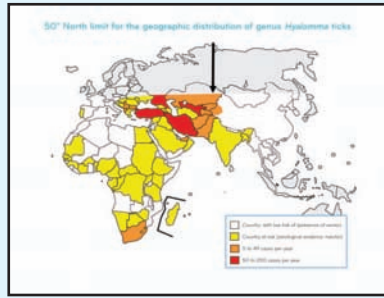
Natural epidemics and outbreaks of emerging infectious diseases are growing problems internationally. Events like SARS, Bird Flu, Swine Flu, Ebola in the Congo, Foot-and-mouth disease in Great Britain, and the recently discovered Crimean Congo Hemorrhagic fever (CCHF) cases in Turkey, Greece and Albania illustrate that the world is facing more and more infectious disease epidemics. Over the last several years, we have experienced an increase of large outbreaks of CCHF, caused by the CCHF virus (CCHFV), in several European countries and neighbouring areas.

CCHF is a human tick-borne disease characterized by high fever, prostration, and hemorrhagic manifestations, with high fatality rates. The disease is enzootic and asymptomatic in domestic animals, such as cattle, sheep, goats, and wild animals. CCHFV belongs to the Nairovirus genus of the Bunyaviridae family.



TRANSMISSION CYCLE of CCH fever virus

This disease poses a great threat to public health due to its high mortality rate in man, its multiple modes of transmission (tick-to-person/animal, animal-to-person, person-to-person) and its geographical distribution. CCHFV is widely distributed throughout large areas of sub-Saharan Africa, South-Eastern Europe, Middle-East, Central Asia down to Pakistan and as far east as the Xinjiang province of Northwest China, (almost 30 countries). In fact, of all medically significant tick-borne diseases, CCHFV is the geographically most widespread pathogen



CCH fever virus is distributed through large areas of Sub-Saharan Africa, South-Eastern Europe, Middle-East, Central Asia and North- West of China.

Context : WHO data

In the 21st century, outbreaks have become more frequent in Europe (cases or outbreaks have been recorded in Kosovo, Albania, Greece and Bulgaria).

To date, the understanding of CCHFV migration, transmission and recombination is extremely limited. Except for ribavirin, there is no effective therapy available. There is no vaccine or vaccine candidate available and a selective antiviral drug for the treatment or prevention of the disease is not expected in the near future.

At the current time, a broad and multidisciplinary research consortium with focus on CCHF disease in Europe has not yet been developed. The research activities concerning this disease have been restricted to very few institutes/laboratories, for several reasons such as i) the handling of the virus requires high containment laboratories (BSL-4), ii) sporadic outbreaks in endemic countries which have no facilities for performing a basic and/or applied research program, iii) lack of clinical specimens from the patients, animals and ticks.

It is obvious that the basic knowledge on CCHFV biology, pathogenesis, vaccine development, therapeutic, and integrated control measures is highly limited for this important bio-threat.

It is, thus, imperative to build a **multidisciplinary research activity with focused goals**. To achieve an effective program, multidisciplinary research activities proceeding from different specialties are required to produce the knowledge that can contribute to develop improved diagnostics and surveillance / control measures, effective prevention, and therapy strategies.

The CCH Fever program has build on existing leading-edge expertise in Europe, Asia, USA and Africa, and brought together new constellations of scientists to work towards solving important public health and medical problems concerning CCHF that are not tractable by individual groups. This program aims to investigate and integrate basic virology, antiviral and vaccine development, epidemiology, genetic analysis, field diagnostics and medical training. The basis for suggesting this multi-disciplinary approach has a strong scientific rationale.

The major objective of this joint initiative is to create a multidisciplinary research activity that spans over the following subjects concerning CCHF:

- Improvement of Field Diagnostics.
- Studies on epidemiology, immune response, phylogeny and evolution of the virus.
- Vaccine candidate development.
- Development of strategies for the discovery of new effective CCHF therapeutics.
- Dissemination of knowledge



MAIN ACTIVITIES within the CCH fever project

Partners

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	FRANCE Inserm-Transfert SA Jerome WEINBACH*
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	USA The National Foundation for the Centers for Disease Control Stuart NICHOL*
	ISRAEL Ben-Gurion University of the Negev Robert S. MARKS*
	GERMANY Philipps Universität Marburg Friedemann WEBER*

European West Nile R&D Collaborative Project “Eurowestnile”

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EuroWestNile

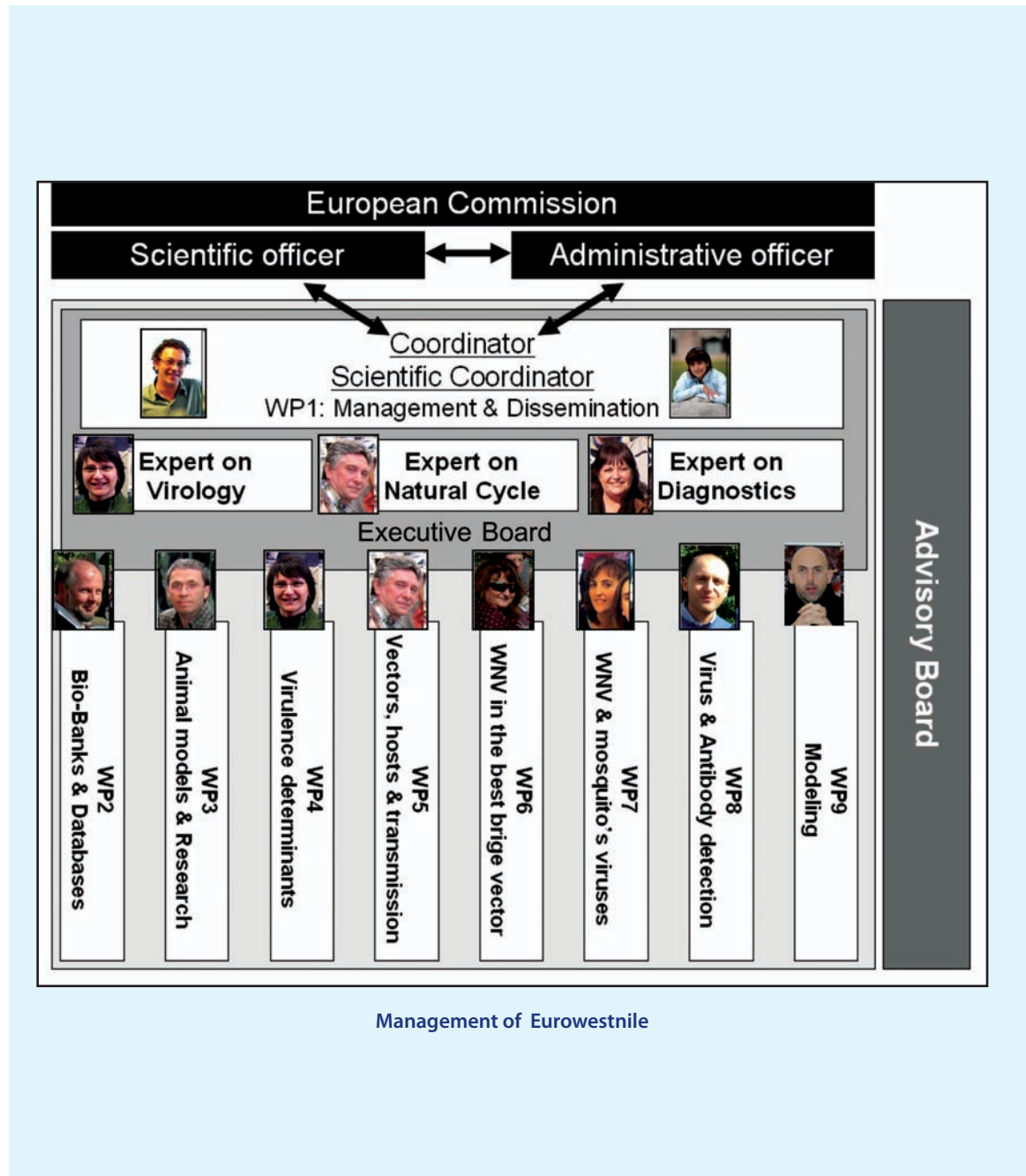
European West Nile R&D collaborative project

The EuroWestNile project is a recently started small collaborative project funded by EC under the theme HEALTH.2010.2.3.3-3: [Integrated disease-specific research on West Nile Virus infections, Chikungunya and/or Crimean Congo Haemorrhagic Fever. FP7-HEALTH-2010-single-stage].

This project is specifically focussed on West Nile Virus, a virus circulating in Europe and the Mediterranean region for decades, but with its recent re-emergence with an unprecedented virulence has increased the level of concern for the European Community. The number of human and veterinary cases, as well as of countries where disease activity is being detected, is increasingly higher. The reasons for this re-emergence are not known, but it coincides with the highest increase in geographic range for this virus, which reached the Americas in 1999, where it has caused the worst West Nile outbreak ever known, with approximately 28,000 human cases and more than 1,100 deaths (<http://www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm>). Since then, West Nile virus (WNV) is considered the most widespread arbovirus in the world (Kramer LD et al, 2008). In Europe and the Mediterranean basin, WNV geographical presence is not continuous, but concentrated in four main areas: Western Mediterranean (including France, Italy, Portugal, Spain, Morocco and Tunisia), Central Europe (or Danube countries: Hungary, Austria, and Romania), Caucasus (Southern Russia), and Middle East (Israel). Though sharing many WNV epidemiological characteristics, these four areas also present significant differences in the observed epidemiology of West Nile disease, with a decreasing gradient from East to West. These differences can be analyzed experimentally at four levels, corresponding to the four biological players interacting in this mosquito-borne disease: **the virus**, **its reservoirs**, **its vectors** and **the hosts**. Comparative analysis of the four geographical areas could help decipher the main factors accounting for the differences in WNV epidemiology. Moreover, and more importantly, comparing the data obtained in the present situation with the data obtained in the past, could greatly help to determine the key factors involved in the current recrudescence of West Nile disease in Europe and the Mediterranean. Concerning **the virus**, in the Western Mediterranean region similar WNV strains have been isolated since 1996 that belong to a single phylogeny clade. This suggests a single introduction like the American scenario. However, this pattern is not prevalent in the other areas, where WN disease is caused by viral strains belonging to different viral variants or clusters. Indeed, in addition to lineages 1 and 2, associated to neurological disease in human and horses, three other WNV lineages have been detected in field research in Europe: lineage 3 (Austria-Czech Republic), lineage 4 (Southern Russia) and lineage 7 (Spain), confirming the ancient presence of the virus in Europe. Furthermore, a putative eighth lineage has been recently detected in Senegal. The pathogenicity and viral ecology of these four West Nile viruses is still unknown, but their study will generate new data for understanding and controlling West Nile disease in Europe, and will lead to new concepts such as the hypothesis of less pathogenic strains protecting WNV **reservoirs** (birds, but perhaps also frogs) from infection by more pathogenic West Nile virus strains in certain European areas by raising cross-protecting antibodies. As to **the vectors**, although *Culex pipiens* is likely an effective bridge vector for transmission from the birds to humans and horses, little is known about the main vectors involved in reservoir to reservoir transmission. Moreover, nothing is known about WNV **ecology** regarding its interactions with other viruses infecting mosquitoes. Closing the circle, **human patients and horses** need more efficient diagnostics (covering the whole diversity of WNV), prevention and treatment strategies.

The project is coordinated by Dr Antonio Tenorio of the The Carlos III Health Institute of Madrid (ES) (www.isciii.es), supported by Dr Annapaola Rizzoli of the Edmund Mach Foundation (Trento, Italy) as scientific coordinator and Dr Carlos Curia as Project Manager.

The executive board is composed of five members: the Coordinator, the Scientific Co-coordinator and three experienced researchers in the areas of Virology (Dr. Pardigon, of the IPP), Transmission (Dr. Soriguer of the Consejo Superior Investigaciones Científicas) and Diagnostics (Dr. Bin of the Medical Research and Development Fund for Health Services, Israel) (Figure 1).



The Advisory Board includes prominent scientists and representatives from the Project's end users of the Project, belonging to the World Health Organization, Directorate General for Health and Consumer Affairs of the European Commission (DG SANCO), European Centre for Disease prevention and Control (ECDC), European Network for Imported Viral Diseases (ENIVD), European Network for Arthropod Vector Surveillance for Human Public Health, other FP7 related projects such as ARBO-ZOONET and others funded under the same theme, diagnostics industry and the European Dialysis and Transplant Association.

18 The EuroWestNile Consortium includes researchers with broad experiences, ranging from basic virology to transmission (entomology, bird ecology), mathematical modelling, epidemiology and diagnostics, both in human and veterinary WNV infections.

It includes 14 partner institution belonging to 7 EU Countries (Table 1):

Participant	Country
Instituto de Salud Carlos III (ISCIII)	Spain
Veterinaermedizinische Universitaet Wien, (Vetmeduni Vienna)	Austria
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES)	France
Institut Pasteur de Paris (IPP)	France
Central Virology Laboratory (CVL)	Israel
Istituto Zooprofilattico Sperimentale della Lombardia ed Emilia Romagna (IZSLER)	Italy
Istituto Superiore di Sanità (ISS)	Italy
Fondazione Edmund Mach (FEM)	Italy
Central Research Institute of Epidemiology, (CRIE)	Russia
Institut Pasteur de Dakar (IPD)	Senegal
Instituto Nacional de Investigación y Tecnología, Agraria y Alimentaria (INIA)	Spain
Agencia Estatal Consejo Superior de Investigaciones Científicas (CSIC)	Spain
VIRCELL (VIRCELL)	Spain
INGENASA (INGENASA)	Spain



General Assembly of Eurowestnile

The strategic aim of this Project is to develop an integrated European research capacity on WNV, specially focused on generating new knowledge and innovative products of specific interest to the European citizens, through the cooperation between experts from different countries and fields of knowledge.

The EuroWestNile Project's specific objectives are:

- To further characterize the **eco-epidemiology** of WNV disease at the virus, host and vector levels in each of the regions within Europe and the Mediterranean basin where WNV is prevalent in order to understand the basis of different epidemiological behaviour as well as the current recrudescence of WNV disease.
- To use the eco-epidemiological data to elaborate **models of WN disease** in different habitats/ regions, thereby helping to make predictions and evaluate risks, in strong collaboration with the HEALTH.2010.2.2.3-1 selected research project.
- To identify and characterize the **pathogenicity** determinants of the different WNV lineages in Europe and the Mediterranean region.
- To develop better **diagnostic tools** suitable for, and adapted to, the evolving WNV situations within Europe and the Mediterranean region.
- To develop suitable **animal models** representing the natural virus life cycle in Europe and the Mediterranean region.

- To evaluate new and effective **treatments** against West Nile virus disease, including antiviral drugs and immunotherapy, as well as **vaccination strategies**.

This proposal exploits the basic research results previously obtained by the Consortium's groups, which are highly experienced in collaborative work between basic virology, entomology, ecology, modelling, and human and veterinary diagnostics and epidemiology.

This large collaborative effort is devoted to:

- Obtain a **biobank** of WNV lineages and strains available for each participant country.
- Develop new **animal models for research** on West Nile infection.
- Identify the best available **antiviral treatments** in animal models.
- Characterize the **genomes, pathogenicity** and **neuroinvasiveness** of the diverse West Nile viruses detected in Europe, and identify those viral sequences involved in pathogenicity and neuroinvasiveness.
- Develop infectious clones with the most and the least pathogenic WNV strain, along with their recombinants, in order to use them for reverse genetic studies and to develop a vaccine strategy in the future.
- Characterize the vectors involved in the natural cycle of WNV and in its transmission to birds, humans and equines in different geographical areas with different epidemiology of West Nile disease.
- Characterize the **viral ecology** interactions between WNV and other viruses commonly detected in its most probable vectors.
- Develop mathematical **models** integrating also data on the virus and its interactions with other viruses and its vectors.
- Develop innovative prototype kits for WNV **diagnostics** and surveillance, able to detect any of the WNV lineages.

Integrated Research on Chikungunya “ICRES”

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Chikungunya virus (CHIKV) was first isolated in 1953 in East Africa and has since been associated with periodic outbreaks of human disease. The recent epidemic rose to prominence in 2005/6 following infection of >250,000 people on the French island of La Réunion. The virus rapidly spread to other islands in the Indian Ocean, India and SE Asia. Since 2006 it has infected millions of people, with estimates as high as five million. Chikungunya cases in returning travellers have been reported in other parts of the world, most notably in the EU and USA. In summer 2007 a traveller from India to Italy introduced the virus into Emilia-Romagna initiating a locally transmitted outbreak which infected over 200 people with one death from encephalitis. This small contained EU outbreak caused considerable problems not only for the local medical care system but also for public health authorities and blood supplies. The animal reservoirs of infection and the mosquito species competent to spread the infection in different parts of the world remain unknown; though the anthropophilic *Aedes albopictus* Asian tiger mosquito is one important vector and played an important role in the outbreak on La Réunion. *Ae. albopictus* has recently established itself around the Mediterranean coast from Spain to Greece. It is predicted that it will continue to expand to include much of Western Europe increasing the likelihood of outbreaks or even epidemics of Chikungunya or other arboviruses. Acute Chikungunya fever is characterised by debilitating and painful high temperature fever, myalgia and arthralgia. The rapid onset, fever profile and severe arthralgia which often persists for weeks or months, provide the clinical differential diagnosis from dengue fever. Fatal neonatal encephalitis also occurred in the La Réunion epidemic. There is presently growing evidence of long-lasting (years) chronic arthralgia / arthritis in a small but significant number of people who have recovered from acute infection.

The pathogenic mechanisms leading to the acute rash, myalgia, arthralgia, rare encephalitis and chronic arthralgia / arthritis are unknown precluding rational therapeutic intervention. There are no antivirals. There is no licensed vaccine.

ICRES integrates the expertise of EU laboratories with a long and strong track record of research on alphaviruses with EU laboratories that started work on CHIKV following the 2005 outbreak in La Réunion and laboratories from SE Asia working on CHIKV in this region. The aim is to coordinate research within and to some extent beyond the EU, to build capacity and generate the outputs required to enhance surveillance, diagnosis and understanding of disease processes and to provide pre-clinically evaluated candidates for treatment and prevention.

The principle objectives of the ICRES programme are to:

- Generate new molecular and cellular tools for research and applied studies
- Standardise, quality assure and distribute key diagnostic tests and develop new ones
- Determine key virus genetic changes across time, geographical regions and species
- Discover interactions between virus and human cells
- Determine pathogenesis of the acute and chronic disease in humans
- Characterise rodent and non-human primate models of acute and chronic infection
- Screen libraries of characterized pharmaceutical and bioactive compounds for antiviral activity
- Develop a vaccine which at the end of this project is ready to enter clinical trials

The partners are:

John Fazakerley, University of Edinburgh, UK (coordinator)

Peter Liljeström, Karolinska Institute, Sweden

Andres Merits, University of Tartu, Estonia

Tero Ahola, University of Helsinki, Finland

Marc Lecuit and Thérèse Couderc, Pasteur Institute, France

Philippe Gasque, University of La Réunion, France

Pierre Roques and Roger Le Grand, Commissariat à l'Energie Atomique, France

Christian Drosten and Beate Kümmerer, University of Bonn, Germany

Thomas Meyer and Peter Braun, Steinbeis Innovation Centre for Systems Biomedicine, Germany

Lisa Ng, Singapore Immunology Network, A*STAR

Sazaly AbuBakar and Jamal I-Ching Sam, University of Malaya, Malaysia

The project is funded for 4 years from 1st December with €3M funding from EU FP7 and additional funds from A*STAR Singapore and University of Malaya.

Further details will be available in due course on the programme website www.icres.eu

Biology and Control of Vector-Borne Infections in Europe “EDENext”

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EDENext, Biology and control of vector-borne infections in Europe, is a research project bringing together 46 international partners dedicated to investigating the biological, ecological and epidemiological components of vector-borne disease introduction, emergence and spread, and the creation of new tools to control them.

EDENext has been structured to ensure it meets the European Commission's expectations: "Knowledge on vectors generated under this project is expected to deliver a better understanding of the biology of vectors relevant to human and veterinary diseases. This new knowledge in turn should help (i) to predict the emergence and spread of new vector-borne diseases (VBD), and (ii) to assess the efficacy of different interventions and develop new interventions to interrupt or limit the spread of VBDs with the goal of protecting European citizens from these threats. A major impact is also expected on strengthening European research capacity in this field."

Specifically, each vector group (ticks, rodents and insectivores, mosquitoes, Culicoides, and sand flies) addresses research questions to improve our understanding of:

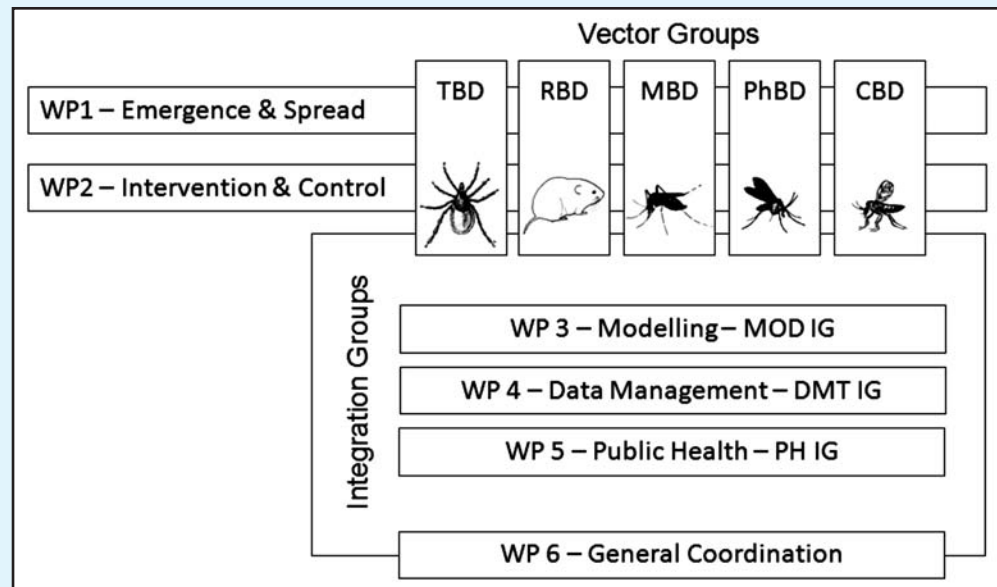
1. Emergence and spread of VBD
2. Intervention and control of VBD

Furthermore, a major effort is being made to better understand VBD risk perception and communication through a specific public health work package prioritising Crimean-Congo haemorrhagic fever and nephropathia epidemica, which are major public health issues in Europe. This work is expected to make a significant contribution in bringing research outputs to public health decision makers and thus benefiting European citizens.

EDENext is building further on the networks, expertise, field work-oriented research and integrative research established by EDEN, and will therefore continue to have a positive impact on the European research capacity in the field of VBD. The assets bequeathed by EDEN include a 60-strong PhD network of researchers working in the field of VBD and more than 220 peer-reviewed scientific papers.

EDENext aims not only to strengthen multidisciplinary research within and between its own vector and integration groups, but also strengthen links with other European and international initiatives, including relevant 6th and 7th Framework Programme projects.

EDENext is structured along the lines used to great success by the EDEN project. Therefore a set of vertical vector groups (ticks, rodents and insectivores, mosquitoes, Culicoides, and sand flies) is complemented by horizontal themes which provide integrated technical input, minimising duplication and ensuring a coordinated approach throughout the project. These 'integration groups' comprise three work packages: modelling, data management and public health.



Structure of EDENext

The vectors which have been selected are not only arthropods, but also rodents and insectivores, which harbour a wide range of pathogens (viruses, bacteria and parasites) some of them infective to humans without the intervention of arthropod vectors, such as hantaviruses and Bunyaviridae.

The main arthropod vector groups of human and animal diseases in Europe are also included: hard ticks (Acari, Ixodidae), mosquitoes (Diptera, Culicidae), sand flies (Diptera, Psychodidae), and biting midges (Diptera, Ceratopogonidae). The vertical structure will allow EDENext to provide expertise and useful information regarding the 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 .

To focus the project's objectivities and produce specific results regarding VBD in Europe, a range of relevant diseases has been selected. These diseases have been selected because they are (i) diseases with insufficient epidemiological knowledge or control measures to produce efficient intervention programmes and (ii) priority diseases for European public health activities.

Mathematical and statistical modelling are important tools for assessing, analysing and predicting the emergence and spread of VBD, and the potential impact of new and existing control and intervention methods. 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, the project is drawing on the datasets, experience and capacity gained in the EDEN project. An important step will be to model vector and disease spread in the context of environments changing in terms of time and space. Mathematical tools have been applied to some VBD EDENext seeks to address, and methods and tools have been developed in EDEN to characterise climatic and environmental changes, including landscapes at various resolution scales. Furthermore, progress has been made to integrate environmental, landscape and mathematical approaches to explain disease spread and this integration will be developed further within EDENext.

Data management has been a key strength of EDEN, providing data and related services to a broad network of partners involved in specific research tasks. This will be improved under EDENext, which will have a wider remit and seek collaborations with other European Union funded projects and networks. There is a particular focus on host distribution mapping and wind spread models.

Finally, the public health integration group aims to assist agencies, stakeholders and decision makers in fulfilling their duties both before and when an epidemic or epizootic begins. The focus is on elucidating the public health aspects of the research results, to find methods and modes to distribute this information to governmental and non-governmental bodies and to provide advice to these groups in setting up the most effective counter measures. The group will concentrate on two model diseases selected for their importance: Crimean-Congo haemorrhagic fever in south-eastern Europe and haemorrhagic fever with renal syndrome in Fennoscandia, Belgium, northern France, Luxembourg and Germany.

CONFERENCE AND MEETING REPORTS

Summary report of the GF-TADS meeting “Rift Valley fever vaccine development, progress and constraints”

Rome, January 19-21, 2011

Communicated by

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The workshop “Rift Valley fever vaccine development, progress and constraints” was organized by the Food and Agricultural Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) under their joint initiative known as “the Global Framework for the Progressive Control of Transboundary Animal Diseases (GF-TADS). The workshop was supported by the government of the Netherlands and the US Centers for Disease Control and Prevention (CDC), with participation of the World Health Organization (WHO), the International Atomic Energy Agency and the Central Veterinary Institute of Wageningen University and Research Centre (CVI-WUR). The workshop was held at FAO headquarters in Rome from January 19-21 and was attended by foremost scientists involved in RVFV vaccine development, policy makers and representatives of international organizations. Stakeholders from the industry were represented by delegates from the International Federation for Animal Health (IFAH). The main objective of the meeting was to establish consensus about the desired characteristics of novel veterinary RVFV vaccines for applications in different areas of the world and to discuss how incentives can be established to ensure that these vaccines come to market. The need for emergency stockpiles was also discussed as well as the need for a human vaccine. This report summarizes the major conclusions of this meeting and brings recommendations to policy makers, industry and the scientific community that should facilitate global control of RVFV in the near future.

Past and present control of RVF

RVFV is a negative-strand RNA virus that belongs to the phlebovirus genus of the Bunyaviridae family. The viral genome is fragmented into a large (L), medium (M) and small (S) segment (1). The L segment is of negative-sense polarity and encodes the viral polymerase. The M segment, also of negative-sense polarity, encodes at least two non-structural proteins collectively referred to as NSm and the structural glycoproteins Gn and Gc. The S segment encodes the nucleocapsid protein in the genomic-sense orientation and a non-structural protein, referred to as NSs, in the antigenomic-sense orientation. The NSs protein functions as an antagonist of host cell innate immune responses and is the main virulence factor of the virus (2-5).

RVFV was isolated for the first time during an epizootic of RVFV that occurred in 1930 on the shores of Lake Naivasha in the Great Rift Valley in Kenya (6). This outbreak was investigated by Daubney and co-workers, who were able to show that the virus was transmitted by mosquitoes and affected sheep, goat, cattle as well as humans. In the 80 years to follow, the virus was identified across most of the African continent, and also spread to the Arabian Peninsula, Madagascar, the Comores and the French island of Mayotte. In most of these areas, RVF is now endemic. Considering that susceptible livestock species as well as potential mosquito vectors are globally prevalent, there is a great concern for future RVFV incursions into previously unaffected areas.

The major species affected by RVFV infection are domesticated ruminants, of which sheep are clearly the most susceptible. Infection of adult sheep can either remain subclinical, or result in overt disease resulting in a mortality rate of up to 20%. In cattle and goats, mortality is estimated at 10%. Unborn and newborn lambs under the age of two weeks are the most susceptible to RVFV infection, resulting almost exclusively in death. Human infections mostly occur via contact with contaminated animal tissues and fluids and sporadically by mosquito bites. In most cases, human infections remain either subclinical or manifest as a temporal febrile illness. In a small percentage of infected individuals RVFV infection results in severe complications such as retinal lesions and blindness (0.5-2% of individuals), meningoencephalitis (<1%) or jaundice and hemorrhagic disease (<1%).

There is no vaccine for the control of RVF in humans. In endemic regions, RVF can be controlled by vaccination of livestock with the live-attenuated Smithburn vaccine. Although the Smithburn vaccine can provide lifelong immunity after a single vaccination, residual virulence of this vaccine virus can induce teratogenic effects in the unborn. As a safe alternative, a vaccine based on inactivated whole virus is available. For optimal efficacy however, this vaccine must be administered twice and yearly vaccination is required to maintain immunity. The shortcomings of the classical RVF vaccines explain the need for novel vaccines of optimal efficacy and safety.

View from international organizations and industry

The GF-TADS meeting was attended by representatives from the OIE, the European Commission (EC), the United States Department of Agriculture (USDA), the Global Alliance for Livestock Veterinary Medicines (GALVmed) and the International Federation for Animal Health (IFAH). The representatives of these organizations acknowledged the disadvantages of the classical RVFV vaccines and support the notion that vaccines of improved efficacy and safety are urgently needed. There was a general consensus that a novel RVFV vaccine should be safe to produce, safe to apply regardless of the physiological state of the animal, and should provide swift and durable immunity after a single vaccination. The representatives also acknowledged the value of a vaccine stockpile that can be deployed for emergency vaccination in any country of the world. The value of a human vaccine was also recognized, particularly to protect farmers, professionals in the livestock value chain, laboratory workers and veterinarians. To facilitate rational selection of novel vaccines, standards should be formulated that need to be met by new vaccines. Finally, incentives for vaccine manufacturers need to be established to ensure that the selected vaccines will come to market in the next decade.

The second generation of RVFV vaccines

Modified-live vaccines

One of the candidate live-attenuated vaccines that was discussed during the meeting is the MP-12 virus. The MP-12 virus was produced by growing a virulent isolate of RVFV in the presence of the mutagen 5-fluorouracil. This process resulted in the accumulation of attenuating mutations on each of the three genome segments. The MP-12 vaccine was shown to be safe in gestating ewes, young lambs and cattle in initial studies (7-9), but suffered from safety concerns after it was demonstrated that the vaccine virus causes foetal malformations when ewes are vaccinated in the first trimester of gestation (10). The safety of the MP-12 vaccine for sheep in the first trimester of gestation was recently re-evaluated by the University of Texas Medical Branch (UTMB, Galveston, Texas, USA) and these experiments suggest that MP-12 can be safely applied in these animals. The safety of the MP-12 vaccine was also evaluated in human volunteers. The combined results suggest that the MP-12 vaccine does not cause serious adverse reactions and that the vaccine is highly immunogenic in both humans and livestock.

With the aim to develop an MP-12-based vaccine that enables the Differentiation between Infected and Vaccinated Animals (DIVA), a recombinant MP-12 virus was produced that carries a large deletion in the pre-Gn region of the M genome segment. The resulting arMP-12 Δ NSm virus was shown to be equally immunogenic as MP-12 in mice and sheep and the immune responses induced by these viruses could be differentiated by Western blots (communicated by Dr. George E. Bettinger, UTMB). Further studies are required to determine if ELISAs based on the NSm protein can be used as DIVA tests.

The Clone-13 vaccine virus is another well-known example of a live-attenuated RVF vaccine. The Clone-13 virus is a natural isolate of RVFV that does not produce the NSs protein (2). The Clone-13 vaccine virus is avirulent in mice and sheep and it was recently reported that a single vaccination of gestating ewes provides full protection against a challenge with the virulent virus (11). The Clone-13 vaccine virus was recently registered in South Africa and is currently used in the field (communicated by Dr. Michèle Bouloy, Institut Pasteur, Paris, France). GALVmed has supported the marketing of this vaccine and will support plans to stockpile the Clone-13 vaccine, initially for emergency vaccinations in West- and South Africa.

In an alternative approach to develop a live-attenuated vaccine, a recombinant RVF virus was produced that does not express the NSs and NSm proteins (12). This vaccine virus, here referred to as Δ NSs/ Δ NSm, is completely avirulent in rats and is able to provide solid protection against the virulent virus. This vaccine virus offers the advantage that it contains attenuating mutations on two genome segments. The safety and efficacy of the Δ NSs/ Δ NSm vaccine was recently evaluated in gestating ewes, of which the results are currently being analysed. Interestingly, a recently developed experimental NSs ELISA can potentially be used as a DIVA ELISA to accompany the Δ NSs/ Δ NSm vaccine (communicated by Dr. Stuart T. Nichol, CDC, N.E., Atlanta, USA).

Vaccines based on viral vectors

The vaccines based on attenuated whole viruses hold great promise for the control of RVF epidemics. It is important to note however that epidemics in regions where RVFV is endemic occur sporadically. Although RVFV outbreaks can eventually be predicted using climate and satellite indicators, it can be difficult to convince poor farmers of preventive vaccination. The use of multivalent vaccines can possibly provide a solution for this problem. Multivalent vaccines that are currently being evaluated make use of Capripoxviruses (CPVs) as vaccine vectors (13-15). The CPV genus of the Poxviridae family comprises sheeppox virus (SPPV), goatpox virus (GTPV) and Lumpy skin disease virus (LSDV) of cattle. CPVs cause serious disease in ruminant species that are also susceptible to RVF infection and the habitat of these viruses largely overlaps.

Vector vaccines based on LSDV were developed that either express the Gn and Gc proteins or the NSm and Gn proteins. Experiments performed thus far demonstrate that these vector vaccines induce neutralizing antibodies against both SPPV and RVFV. Although the challenges in the experiments performed thus far seemed relatively mild, first results suggest that CPV-vectored RVFV vaccines induce protective immunity against both RVFV and SPPV (communicated by Dr. David B. Wallace, Agricultural Research Council-Onderstepoort Veterinary Institute, Onderstepoort, South Africa; Dr. Reuben K. Soi, Kenya Agricultural Research Institute, Nairobi, Kenya and Dr. Catherine Cêtre-Sossah, CIRAD, Montpellier, France). The further development of CPV-vectored RVFV vaccines is supported by GALVmed.

In another approach, the avian paramyxovirus Newcastle Disease virus (NDV) is used as a vector of RVFV antigens (16, 17). An important advantage of using NDV as a vaccine vector is that this virus

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is an exclusive pathogen of birds. Since mammals are not natural reservoirs of NDV, vaccine efficacy in the field is unlikely to be compromised by pre-existing immunity against the vector. By making use of reverse-genetics, recombinant NDVs were produced that either express the Gn protein or both the Gn and Gc proteins. The NDV-Gn virus was shown to induce neutralizing antibodies in cattle and the NDV-GnGc virus was shown to protect mice from a lethal dose of RVFV and to induce neutralizing antibodies in sheep, even after a single vaccination. Experiments are planned to study the protective efficacy of the NDV-GnGc vaccine in sheep (communicated by Dr. J. Kortekaas, CVI-WUR, Lelystad, The Netherlands).

DNA vaccines and their combination with Modified Vaccinia Ankara (MVA) or Alphavirus replicon-based vaccines

DNA vaccines are easy and inexpensive to produce, they do not require a cold chain and can be safely applied in both animals and humans. DNA vaccines based on the RVFV structural glycoproteins Gn and Gc were previously shown to provide complete protection in mice and a DNA vaccine based on the N protein was shown to provide partial protection. Furthermore, it was demonstrated that efficacy can be improved by combining RVFV genes with genes encoding molecular adjuvants, such as C3d (18, 19). DNA vaccines can also be applied in heterologous prime-boost vaccinations. In recent experiments, mice were vaccinated with plasmids expressing either the N protein or the Gn and Gc proteins and subsequently boosted with MVA vectors expressing the corresponding proteins. These experiments suggest that DNA prime-MVA boost vaccination regimens can be more effective than homologous prime-boost DNA vaccination. The efficacies of the MVA vaccines were also evaluated independent of DNA vaccination. Although a single vaccination with an MVA virus expressing the N protein (MVA-N) did not provide protection, vaccination with an MVA virus expressing the Gn and Gc proteins (MVA-M4) protected all mice from a lethal dose of RVFV (communicated by Dr. Alejandro Brun, CISA-INIA, Madrid, Spain and Dr. Sarah Gilbert, University of Oxford, Jenner Institute, Oxford, UK). This work suggests that MVA-M4 is a promising vaccine candidate that should be evaluated in the natural target species of RVFV. Of note, this vaccine candidate could also be evaluated in non-human primates, since MVA is an accepted vaccine vector for human use as well.

An alphavirus replicon vaccine was also evaluated in heterologous prime-boost vaccinations. Three vaccinations with either a DNA vaccine based on the Gn protein coupled to C3d or an alphavirus replicon expressing the Gn protein provided full protection in mice (19). An interesting finding in this study was that the alphavirus replicon elicited a RVFV-specific cellular immune response. The ability of the alphavirus replicon vaccine to induce both humoral and cellular immunity should be studied in more detail and the results obtained in mice with this vaccine warrant further studies in large animals (communicated by Dr. Ted Ross, University of Pittsburgh, Pittsburgh, PA, USA).

Vaccines based on virus-like particles (VLPs)

The development of VLP-based vaccines is aimed to optimally combine efficacy and safety. VLPs closely resemble the authentic virus and are therefore highly immunogenic. Their high safety profile renders VLP-based vaccines suitable for application in both livestock and humans. The major challenge in this approach, however, is to produce a cost-effective vaccine. Cost-effectiveness of VLP-based vaccines can be achieved by improving the efficacy of this type of vaccine, thereby lowering the protective dose, or by improved production methods.

Several studies have demonstrated that VLPs can protect mice from a lethal dose of RVFV, even without adjuvant. It was previously reported that the gag protein of Moloney murine leukemia virus (MoMLV) can increase the uniformity and quantity as well as the stability of VLPs. Adjuvanted RVFV VLPs containing the MoMLV gag protein, referred to as chimeric VLPs (chimVLPs), were shown to protect rats from RVFV, even after a single vaccination (20). This result, together with the recently established improved production methods suggest that VLP-based vaccines can be applied in the near future as safe and cost-effective vaccines (Communicated by Dr. Ramon Flick, BioProtection Systems Corporation, Ames, IA, USA).

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It was previously shown that reporter minigenomes can be packaged into VLPs. These so-called “infectious VLPs (iVLPs)” are capable of infecting cells, followed by primary transcription and low-level reporter protein expression. In recent work, iVLPs were produced that contain the N gene on the packaged minigenome (referred to as “N-VLPs”). A single vaccination of mice with N-VLPs in the absence of adjuvant provided solid protection against a lethal dose of RVFV (21) (communicated by Prof. Dr. Friedemann Weber, Institute for Virology, University Marburg, Marburg, Germany). These remarkable new achievements in VLP-based vaccine development suggest that this approach holds great promise for the future.

Summarizing conclusions

In the past decades, tremendous progress has been made in the development of second-generation RVFV vaccines. Apart from the Clone-13 vaccine which is now commercially available in South Africa, several alternative vaccines could soon become available. Control of RVFV in endemic regions not only reduces the socio-economic impact of RVF in these areas of the world, but will also reduce the chance of incursions into currently unaffected areas. Nevertheless, countries of the EU, the US and Australasia should prepare for a future incursion by training veterinarians to recognize the disease, by implementing diagnostic tools and selecting and stockpiling a vaccine that can be used for emergency vaccination. Vaccines for emergency vaccination in currently free areas should be safe for both livestock and humans, should provide swift immunity after a single vaccination and should preferably fulfil the DIVA criterion. It would be advantageous if novel veterinary vaccines can be administered needle-free, to prevent transmission of the virus via the needle.

To facilitate rational selection of promising vaccine candidates, desired safety and efficacy standards should be predetermined and challenge models with standardized read-out parameters should be established. To facilitate the latter, the European Network for the Coordination of Rift Valley fever Animal Experimentation and Diagnostics (ENCRAD) was recently established. Founding of this network was financed by EPIZONE (Network of Excellence for Epizootic Disease Diagnosis and Control, EU project number: FOOD-CT-2006-016236, www.epizone.net). The institutes that are affiliated with the ENCRAD network now share expertise on RVFV animal experiments and diagnostics.

The only way to make sure emergency vaccines can quickly be deployed upon a RVFV epidemic is to stockpile these vaccines. Importantly, commitment to establish and maintain an international vaccine stockpile is an excellent incentive for vaccine manufacturers to bring novel vaccines to the market.

Apart from the necessity to have safe and effective vaccines available for the control of RVFV in livestock, there is also an urgent need for a human vaccine. Although several of the candidate vaccines described above can potentially be used for this purpose, registration of a human RVFV vaccine is expensive while a dependable market is absent. Also in this field, commitment from public health decision makers to establish an international human vaccine stockpile is needed to provide an incentive for human vaccine manufacturers.

In conclusion, the GF-TADS meeting made clear that international organisations, industry and the scientific community all acknowledge the need for global accessibility of novel veterinary and human RVFV vaccines. Tremendous progress in the development of novel vaccines was made in the past decade and the job is now to bring these control tools to the field.

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A full report of the meeting is available at:

http://www.fao.org/AG/AGAInfo/programmes/en/empres/RVF_2011.html

Special Issue Vector-Borne and Zoonotic Diseases: Arbo-Zoonet Symposium

Vector-Borne and Zoonotic Diseases

Volume 10, Number 7

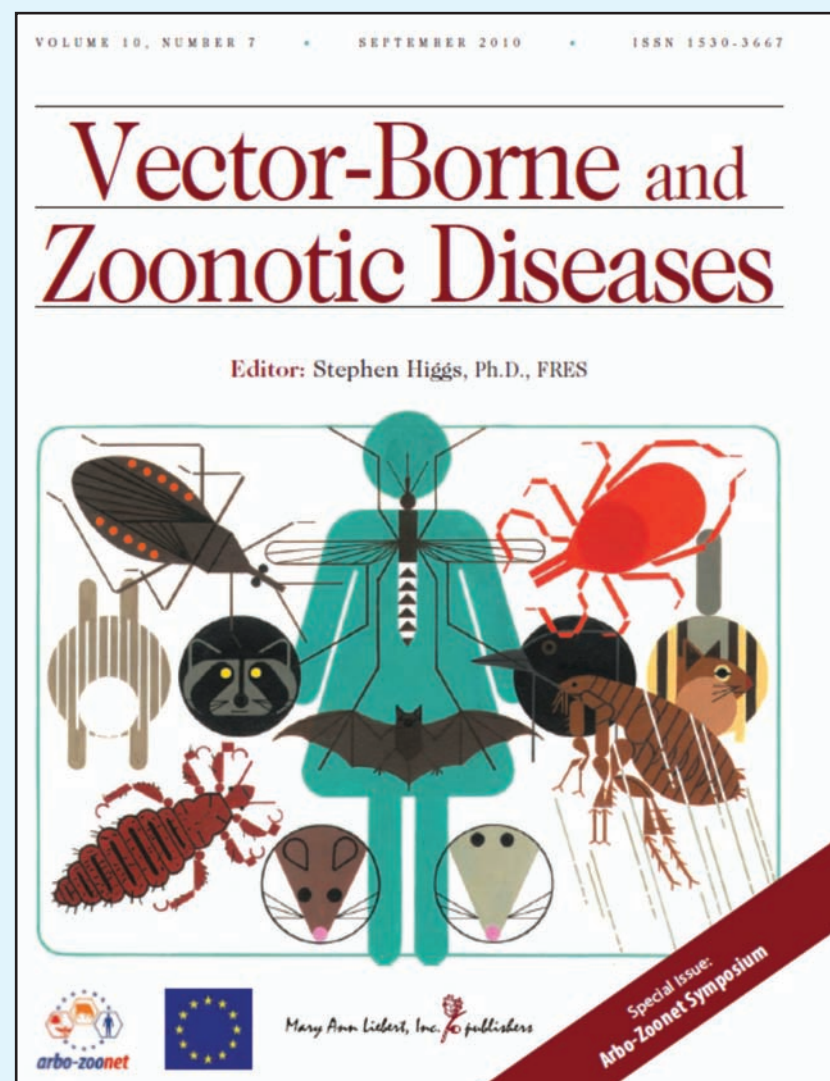
Special Issue: Arbo-Zoonet Symposium

Guest Editors: Anthony R. Fooks, Michèle Bouloy, Jabbar Ahmed, and Ulrike Seitzer

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As a result of the first annual meeting of the Arbo-Zoonet consortium which was held in St. Raphaël on September 30, 2009, selected papers were submitted for peer review and accepted for publication in a special issue of Vector-Borne and Zoonotic Diseases in 2010.

The published articles are listed below and can be accessed at the website indicated above.



Original Articles

West Nile Virus Monitoring of Migratory and Resident Birds in Germany
Diana Seidowski, Ute Ziegler, Jan A.C. von Rönn, Kerstin Müller, Kathrin Hüppop,
Thomas Müller, Conrad Freuling, Ralf-Udo Mühle, Norbert Nowotny, Rainer G.
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ANNOUNCEMENTS

ARBO-ZOONET ANNUAL MEETING 2011

The ArboZoonet Annual Conference 2011 will be held in St-Raphaël, France on October 5, 2011, following the 6th European Meeting on Viral Zoonoses, October 1-4, 2011 (www.euroviralzoon.com).

The meeting will start on Wednesday morning 5th and will end the same day in the evening. The purpose of this meeting will be to review the activities carried out on Rift Valley fever virus, West Nile virus, Crimean-Congo hemorrhagic fever virus and related viruses. The meeting will be devoted to presentations and discussions on presentations by the participants of Arbo-zoonet and to open discussions with other colleagues showing interest to attend the meeting.

A further aspect will be to inaugurate and promote the activities of 'Young Arbo-Zoonet' by offering poster presentation and a 'senior scientist free' cocktail meeting to support networking and discussion among the young scientists in the arboviral research field.

You are kindly invited to send abstracts for oral or poster presentations. For ensuring a successful launch of 'Young Arbo-Zoonet' please encourage your post doc and PhD students to send an abstract. Please consult the website for abstract submission.

YOUNG ARBO-ZOONET

Young Arbo-Zoonet aims to provide a forum for scientists studying for a PhD to share their experiences, information and knowledge of zoonotic arthropod-borne diseases. The rationale of *Young Arbo-Zoonet* is to develop scientists studying for a PhD into the next generation of European scientists with a research focus on arthropod-borne diseases.

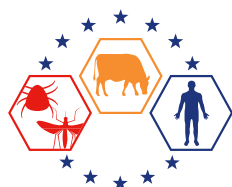
The platform provided by *Young Arbo-Zoonet* will enable students to:

1. Attend meetings where only PhD students are invited. This will promote the ability of all members to discuss PhD studies in an 'open' and constructive forum;
2. Benefit from networking opportunities, where they are able to meet and discuss with senior scientists from all over the world;
3. Apply for *Young Arbo-Zoonet* Travel Awards, where selected students are supported to attend meetings and present their latest data;
4. Apply for short-term missions, where they can spend time working at an Arbo-Zoonet member laboratory.



The inaugural meeting of Young Arbo-Zoonet is scheduled to be held during the next Annual Arbo-Zoonet meeting, on 5th October in St Raphael, France. Students will be asked to bring a poster presentation, which the group will discuss.

If you wish to become a member and are interested in obtaining more information of Young Arbo-Zoonet, please contact Karen Mansfield (AHVLA, UK) at Karen.Mansfield@ahvla.gsi.gov.uk



arbo-zoonet