



Executive Summary EPIZONE year 5

During recent years the risk of introduction of new infectious agents into the EU or spread within the EU has increased due to the increasing number of people and animal movements across EU member states. In addition global warming is likely to enhance the risk of spreading of arthropod borne diseases such as Bluetongue, African Horse Sickness, Crimean Congo haemorrhagic fever and West Nile Fever. Despite extensive control measures, over the last few years several new epizootics have occurred, including the introduction of BTV into Europe, the threat of Peste de Petit Ruminants from Morocco, and the introduction of New Influenza into Europe from Mexico. Innovative and rapid control strategies will be needed to combat these new epizootic disease outbreaks. EPIZONE aims to apply its integrated research activities to more rapidly develop new cost-effective prevention and control strategies, which will help to effectively combat such epizootic diseases and reduce the social impact and costs implicated.

Mission and objectives

The mission of our Network of Excellence: EPIZONE is to develop a network of excellence to improve research on preparedness, prevention, detection, and control of epizootic diseases within Europe to reduce the economic and social impact of future outbreaks of Foot-and-mouth disease, Classical swine fever, Avian influenza, and other relevant epizootic diseases like Bluetongue and African swine fever, through increased excellence by collaboration.

This mission can be divided into four main objectives:

- To establish joint scientific integration activities encompassing research on four themed areas, Diagnostics, Intervention Strategies, Surveillance and Epidemiology, and Risk Assessment related to preparedness, prevention, detection, and control of epizootic diseases.
- To develop and implement Strategic Integration activities for establishment of international priorities in scientific activities, strategic review and planning in themed areas.
- To establish Spreading of Excellence between partner institutes and beyond in order to ensure optimal use of scientific resources, expertises, skills, and specific knowledge of (improved or new) methods and of (new or re-) emerging diseases.
- To develop and establish a sustainable and democratic management structure based on a "Virtual Institute" with clear rules, written processes and procedures including mechanisms for review and assessment, and appropriate administrative support as defined by a Consortium Agreement.

Global dimension

The activities of EPIZONE are based around a "Virtual Institute" concept. The "Institute" comprises 17 institutes of veterinary science, health and agronomy, the Food and Agriculture Organisation (FAO) and 1 Small and Medium Enterprises (SME) from 12 countries (Fig. 1), including over 300 acknowledged experts in animal diseases. Inclusion of China, Turkey, the Food and Agriculture Organisation (FAO), and several partners with an excellent network outside the European Union (EU) ensure a global dimension. The partnership is supported by a legal Consortium Agreement.

	NETHERLANDS	Central Veterinary Institute of Wageningen UR Lelystad, The Netherlands	(CVI)
	GERMANY	Friedrich-Loeffler-Institute,	(FLI)
	UNITED KINGDOM	Institute for Animal Health,	(IAH)
	UNITED KINGDOM	Veterinary Laboratories Agency,	(VLA)
	FRANCE	Agence Française de Sécurité Sanitaire des Aliments,	(AFSSA)
	DENMARK	National Veterinary Institute, Technical University of Denmark	(DTU VET)
	SWEDEN	Statens Veterinärmedicinska Anstalt,	(SVA)
	FRANCE	Centre de coopération Internationale en Recherche Agronomique pour le Développement,	(CIRAD)
	SPAIN	Center of Animal Health, National Institute for Agriculture and Food Research and Technology,	(CISA-INIA)
	ITALY	Istituto Zooprofilattico Sperimentale delle Venezie,	(IZS-Ve)
	CHINA	Lanzhou Veterinary Research Institute,	(LVRI)
	POLAND	National Veterinary Research Institute,	(NVI)
	TURKEY	FMD Institute Ankara,	(SAP)
	BELGIUM	Veterinary and Agrochemical Research centre, VAR-CODA-CERVA,	(VAR)
	GERMANY	Hannover Veterinary School,	(HVS)
	ITALY	Istituto Zooprofilattico Sperimentale della Lombardia e dell' Emilia Romagna Brescia	(IZSLER)
	CHINA	Harbin Veterinary Research Institute,	(HVRI)
	ITALY	Food and Agriculture Organization,	(FAO)
	NETHERLANDS	Digital Value,	(DiVa)

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Figure 1 Involved contractors and coordinator contact details

Organisational structure

The organisational structure of EPIZONE (Fig. 2) comprises a matrix design of joint activities in non-scientific themes 1, 2, and 3, and in scientific themes 4, 5, 6, and 7. Each theme contains a number of work packages and is led by a theme leader assisted by a deputy theme leader, all members of the Executive Committee. The work packages within each theme are led by a work package leader. Additionally, the internal call projects running one year are placed under a corresponding theme. They are led by an internal call leader.

Governance is placed under a Coordinating Forum comprising representatives of all EPIZONE partners. They are supported by the administration bureau, responsible for both the administrative and financial obligations and the Management Advisory Board, five democratically elected representatives at director level from all partners. Scientific advice to network activities is provided by an External Advisory Panel comprising five international senior external scientists, including a representative of the OIE (World Organisation for Animal Health).

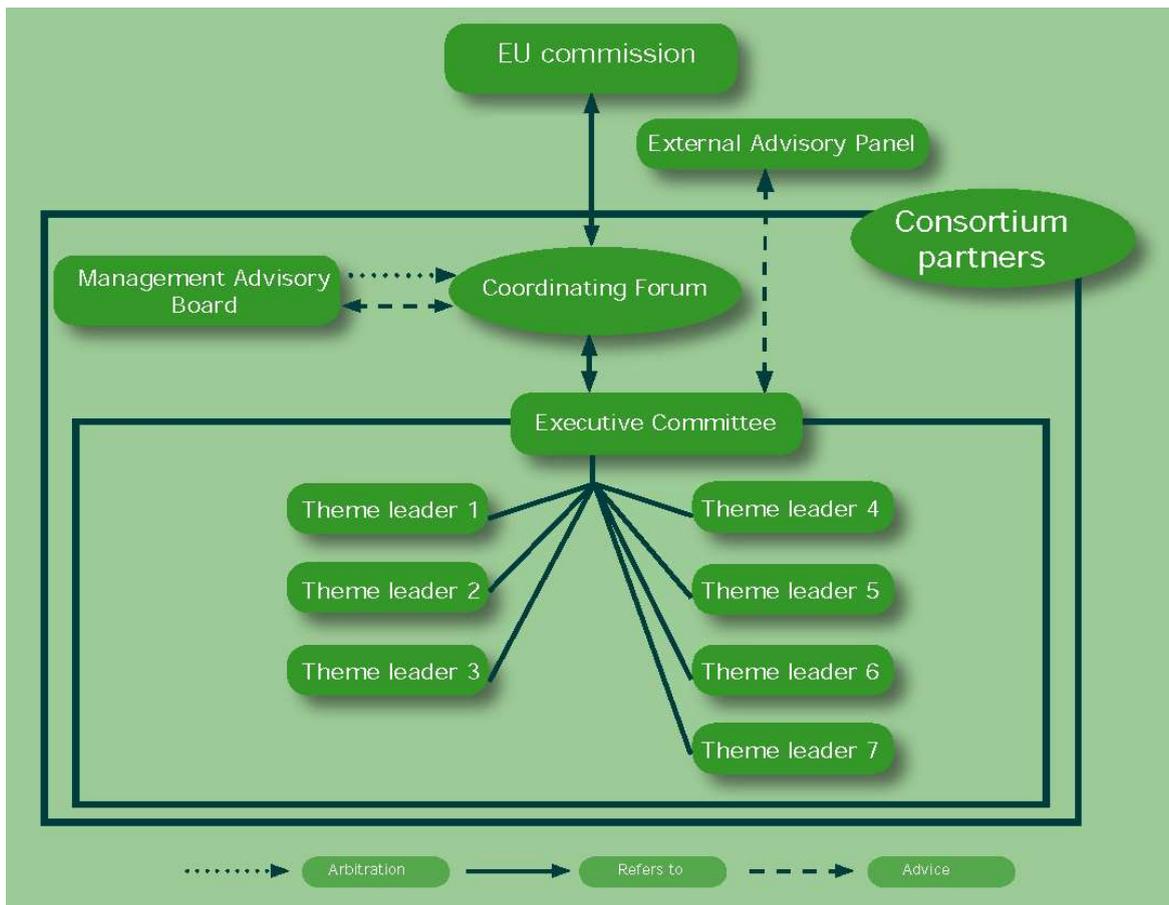


Figure 2 Organisational structure of EPIZONE

Within Theme 1 "Structure and Management", WP1.1, "Virtual Institute", focus has been on the development and implementation of structured administrative and financial management of the network; and WP1.2 included communication. In the final EU funded period of the network, a closure meeting was organised to agree on all arrangements for finalising all tasks in line with full expenditure of the financial budgets. An extension to the project without additional budget had been requested for the latter purpose. In case partners were unable to pay for travel costs of their own budgets this was financed by WP 1.1. The meeting first focussed on the discussion about finalising remaining tasks using unspent budgets in the final 16 months of the network. In addition the new EPIZONE structure after the ending of the EU funded period was discussed. In the extension period EPIZONE joint funds (WP1.1) were used to partly finance a follow up meeting of the formaldehyde workshop, which was held in January 2012. Meetings of EPIZONE WPs, committees and boards have always been very important for EPIZONE and therefore such meetings again were facilitated during the final EPIZONE half yearly meeting in Lelystad (Jan 2011). The final EPIZONE annual meeting (5th) was held in Arnhem, The Netherlands. For the sustainable EPIZONE structure beyond the EU funded period it was agreed to form a European Research Group. For this sustainable structure a legal document (agreement) was drafted. The newsletter "EPIZONE update" was regularly published as planned also within the extension period (June 2011 to March 2012) of the network. All issues of this newsletter "Epizone update" were published on the internal as well as the external website, and clearly contributed to the exposure of EPIZONE for its participants but also for its stakeholders and interested parties outside the network. In addition EPIZONE was presented at several international conferences and meetings.

Theme 2 "Strategic Integration", aimed for effective and strategic integration of the scientific research activities of EPIZONE. This included scientific coordination and strategic planning, and expertise development. In the final EU funded period of the network all information obtained from questionnaires and evaluations performed to improve the integration of EPIZONE research activities were implemented as much as possible. The structure for the organisation

of scientific missions to facilitate internal and external cooperation between scientists was unchanged. Scientific missions were continued in the same way as before and have become a well known instrument among EPIZONE partners. The EPIZONE 5th annual meeting was as successful as the previous ones, with about the same number of attendees, a high standard scientific programme and good networking opportunities. Like in previous meetings the opportunity was given to related (EU) projects to present themselves. Again all presentations during the annual meeting were included in a large abstract book, which has also been made available through the EPIZONE website.

The EPIZONE database coordinator continued the work on the integration of the EPIZONE databases. To improve the accessibility and use of EPIZONE databases two workshops were organised on database use and datasharing in the veterinary field. A superordinate database was built to access all EPIZONE databases through the EPIZONE website. In order to sustain databases also after the EU funded period of EPIZONE, database hosting institutes were assigned for all databases. For all of the databases interfaces or links were built to enable accessibility. It is aimed to continue to have these databases available in future via the website of the EPIZONE European Research Group.

Theme 3 "Spreading Excellence" has been responsible for spreading excellence within and outside the network. It has consisted of two Work Packages, WP3.2 on education and WP3.3 dealing with young EPIZONE. Under WP3.2, training and workshop activities were continued in year 5. A one-week course on classical virology was organised at NVRI for 4 young scientists. It was decided to focus on classical virology since most of new scientists are excellent molecular biologists, but the expertise using the real virus is progressively lost. The WP3.2 has contributed in the support of the organisation of two transversal Theme meetings. The fifth Theme 5 meeting was organised in Copenhagen in November 2011 (3-5/11/2011). This transversal meeting gathered all scientists interested in the four regular work-packages of Theme 5 and those involved in the two internal calls (IC5.5 and IC5.6) within Theme 5. In addition, a Theme 4 meeting was organised on the island of Riems, at the FLI institute, in February 2011 (23-25/02/2011). The success of the short-term training missions was sustained in year 5 (including extended period) with thirty-four applications sponsored for 38 EPIZONE members. The principal achievement of WP3.3 was the reinforcement of young EPIZONE networking and skills through special young EPIZONE newsletters and the organisation of dedicated courses and workshops. Thus, 55 young EPIZONE members attended the projects' annual meeting in Arnhem where specific workshops were organised for them. The Young Epizone participants were also allowed to attend two 'building bridges' workshops, one in Spain (July 2010) and one in China (July 2011). In addition a 3-day course on 'International project management' was organised in Amsterdam in autumn 2011.

In Theme 4 "Diagnostics" the collaboration between all members was intensified within and also between the different working packages. The main task in the last months was to finish the work and fulfil all of the deliverables, which could be achieved due to the very hard and successful collaborative work of all Theme 4 members. It can now be clearly stated that the more than 75 scientists engaged within Theme 4 formed a powerful network and enabled a new level of diagnostic preparedness not only for the participating institutions but also for the whole European Union.

In all working packages of Theme 4, collections of reference materials (e.g. EPIZONE RNA and DNA panels for more than a dozen epizootic diseases like FMDV or ASFV) were completed, which are now available as a unique tool for the validation of molecular assays, also in the future. The real-time PCR assays collection was finalized, the EPIZONE chip was optimized by the network, and ring trials within all of the working packages proved both the power of the different test systems and the ability to work together and exchange data, materials, protocols and also experiences. Furthermore, the working package teams of "DIVA-diagnostics" and "Penside tests" finally tested new methods and improved the overall knowledge about the use of this more and more important tools for the control of epizootic diseases. Beside these core working packages of theme 4, also the internal calls (ICs) were fully integrated and finished their successful work on KHV serology, diagnostics of equine encephalitis and the molecular epidemiology of FMDV. The ICs completed the collection of reference materials and useful assays within Theme 4.

The presentations and working package summaries given by all WP-leaders during the final coordination and progress meeting of Theme 4 at the Friedrich-Loeffler-Institut, Insel Riems, Germany, impressively affirmed the high quality of the work and the close networking of the whole Theme 4 team. For the near future it will be aimed to keep the theme 4 diagnostic network active within the EPIZONE European Research Group.

Theme 5 "Intervention strategies" participants met during the Theme 5 meeting held in Copenhagen (VET-DTU) in November 2010 and the Annual EPIZONE meeting in Arnhem, April 2011. The meeting in Copenhagen was held together with Young EPIZONE and was attended by more than 50 scientists. Presentations and discussion of joint work programmes were held. These topics included; novel platforms for antigen delivery and vaccine development, the ENCRAD network on RVFV and the ASFV vaccine development group. The ASFV vaccine group reported on joint animal experiments and planned a further joint experiment which was completed during the EPIZONE extension period. The results from a joint ring trial of transfection methods involving 14 labs in 7 Institutes were presented. In addition the ENCRAD network held a meeting in Rome which also included invited international experts. The extended work in WP5.1 included RVFV, ASFV and AHSV.

Amongst the publications were joint review articles on non-vectored vaccine strategies for veterinary research (Virus Research), adjuvants and delivery systems in veterinary vaccinology, the immune response to rabies infection and vaccination. In addition there were a number of research articles publications in peer-reviewed Journals. A joint patent application was filed by CIRAD and CISA/INIA. This uses an innovative approach to construct alginate-covered lipoplexes (a lipid and DNA complex used to deliver genes). The team was able to demonstrate proof of concept for delivery of an oral DNA vaccine for trout against the devastating viral haemorrhagic septicaemia virus.

The continuation of existing and development of new collaborations within EPIZONE continued. Many of these will be extended beyond the EU funded period of EPIZONE, within the EPIZONE European Research group. These new collaborations include reproducibility of cytokine and bio-assays, use of avian immunoglobulin (IgY) for haemagglutination assay for antibodies against influenza virus, mapping of antigenic peptides in RVFV.

Research on antivirals progressed and publications included description of the in vitro inhibition of ASFV replication by antioxidants. Further studies on previously described CSFV antivirals was carried out and siRNAs targeted against the fish rhabdovirus VHSV were demonstrated to inhibit virus replication in salmonid cells.

The aim of Theme 6 "Surveillance and epidemiology" was to harmonize, standardize, improve, and develop efficient surveillance programs as well as optimized methods to investigate the epidemiology of epizootic diseases.

The theme included the following WPs: 'Surveillance and epidemiology of emerging viral diseases in aquaculture' (WP6.1); 'Molecular epidemiology and surveillance of Avian influenza and Avian paramyxovirus' (WP6.2); 'Experimental epidemiology' (WP6.3); 'Molecular epidemiology' (WP6.4). Besides the theme also included ICs: 'WILDSURV harmonization' (internal call 6.5); 'Bluetongue epidemiology' (internal call 6.6); 'Blue Tongue (BT) DYNVECT' (internal call 6.7); 'Comparative dynamics of BVDV' (internal call 6.8) and 'Validation of results from BT-DYNVECT' (internal call 6.9). Most of these activities have been finalized. However, this is a summary of the efforts made in the fifth year of the project in the reminding activities: WP 6.1; WP 6.2; WP 6.3; IC 6.8 and IC 6.9.

The WP 6.1 'Surveillance and epidemiology of emerging viral diseases in aquaculture' was extended with a 6 month project on Viral Encephalopathy and Retinopathy (VER) which is a threat for future marine culture in Europe. The objectives of the extension project were: 1) Database development; 2) Diagnostic real-time RT-PCR development; 3) Pathogenesis studies; and 4) Organizing a European workshop on VER and all deliverables and milestones were reached as planned.

In WP 6.1 progress was made in relation to: 1) Sequencing that revealed subdivision of VHSV genotype Ia into two clusters (Kahns et al., manuscript submitted). The origin of VHS outbreaks in Poland have been traced by molecular means (Reichert et al., manuscript submitted) and a large number of VHSV isolates have been sequenced and used in molecular

epidemiological studies.; 2) The development of the database www.fishpathogens.eu. The VHS and IHN databases contain 580 isolates and 446 sequences. A planned database on koi herpes virus is progressing but with some delays. ISA and SVC databases have been created, and a nodavirus database has been created as well and is now currently containing 54 isolates and 94 sequences.; 3) Assessment and partly validation of the best methods to use for KHV diagnosis and surveillance. An inter-laboratory proficiency assay in KHV serology was performed and 3 methods have been created for detection of antibodies in carp against KHV (SNT, ELISA and IFAT). The methods were finally implemented during a 1 week practical workshop organized in October 2011. Three papers with acknowledgement to EPIZONE were published on KHV and several more manuscripts are in preparation.; 4) Validation and final Serology on VHS and IHN.

In the work package 'Molecular epidemiology and surveillance of Avian influenza (AI) and Avian paramyxovirus (APMV) the work on sequencing of AI and APMV genomes continued and the results were submitted to the GISAID and Genbank databases. To date, 1,673 separate AI and APMV gene sequences have been generated and/or submitted to GISAID by the partners. Besides, a manuscript entitled "Genetic data from avian influenza and avian paramyxoviruses generated by the European network of excellence (EPIZONE) between 2006 to 2010 – review and recommendations for surveillance" was submitted to Veterinary Microbiology in March 2011.

In 'Experimental epidemiology' the fifth project year were used to finalize the activities in the WP. However, for Foot-and-mouth disease virus (FMDV) the influence of time after vaccination on the transmission parameters was determined for the IAH data. Combining the data of all partners in the WP, a 3x3 (cattle, pigs, sheep x cattle, pigs, sheep) matrix was constructed with the transmission rate parameters as the matrix elements. In this matrix both within- and between species transmission was quantified in one parameter for each species-species combination. For some combinations several estimates from conducted.

Theme 7 Risk assessment: Assessing the risk of introduction of epizootic disease, and its potential consequences, should be an integral part of any surveillance programme. In the last decade, Risk Analysis has been recognised as a formal tool for doing this, with organisations such as the OIE producing guidelines on best practice. The OIE guidelines describe Risk Analysis as a four-step process consisting of Hazard Identification, Risk Assessment, Risk Communication and Risk Management. Theme 7 has concentrated on the Risk Assessment step.

Despite the availability of the OIE guidelines, there remain differences in the approaches used by different organisations, and in different countries within Europe, when undertaking risk assessments. In addition, criteria for determining whether or not data are appropriate for risk assessments do not exist. In this theme, we have focused on advancing the discipline through the standardisation of methods and the collection of appropriate data. At the start of the network, the number of participants with an interest in Risk Assessment was small in comparison with other themes. However, over the five year period interest and collaboration between scientists from all disciplines has grown and this has been key in generating useful risk assessment data.

Standardisation of methods was the focus of Work Package 7.1 "Standardisation of import risk assessment". In this Work Package, the participants reviewed available risk assessments, considering the needs and quality standards for epidemiological information and the criteria for the inclusion of experimental data within risk assessments. Several published and unpublished assessments were reviewed, leading to a publication on the overall quality that was found. One key finding was that although published guidelines are available they are used relatively infrequently.

Work Package 7.2 "European online database on Epizootic diseases and early warning system" concentrated on standardising the data that are collected for use in risk assessments through the provision of online databases for various pathogens. The database has been successfully developed and implemented through collaboration with several partner countries who have

provided key data. The work package leader has subsequently been commissioned by the DG SANCO to develop an online database for classical swine fever, thus demonstrating the acceptance of this methodology for early warning. After the EPIZONE EU funded period the database will stay accessible for partners of the EPIZONE European research group through the EPIZONE website.

In Work Package 7.3 "Decision support system for CSF" data collection was also critical. Here, a system to aid in assessing the risk of a classical swine fever being present in a herd was developed through extensive collaboration across Partner countries, who provided data.

The potential impact of environmental changes such as global warming is likely to be the focus of many risk assessments over the coming years. Work Package 7.4 "Impact of environment effects on the risk of occurrence of epizootic diseases in Europe: Identification and prioritisation", considered this issue. An expert opinion workshop to collect data on future threats was run, an investigation into the use of genomics data for risk assessment was carried out and initial developments for a risk assessment for CCHFV were made. This work led to 3 papers submitted for publication.

In an attempt to use risk assessment techniques to synthesize the expertises that are available within the EPIZONE Network, an additional Internal Call was run within Theme 7. At the 4th Annual Meeting, an interactive question session was run to gather the opinions of experts on future threats and preventive measures. This session was very successful and demonstrated how risk assessment methodology can be used in practise, with opinions from over 200 individuals being combined to give views on current and emerging threats. A paper detailing the results from this session was submitted for publication by the end of 2011.

Overall, the Risk Assessment theme has developed substantially over the five years of the network and has resulted in a greater appreciation of how the approach can be a useful tool for decision making.