BUILDING A EUROPEAN COMMUNITY TO COMBAT ZOONOSES

MED•VET•NET

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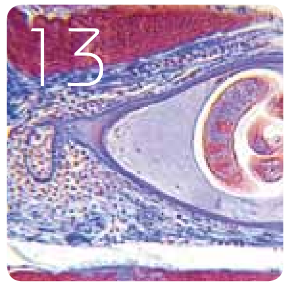

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PREFACE

Prior to 2004, research in food-borne zoonotic diseases in Europe, although of high quality, was fragmented with scientists on the human and veterinary sides often working in isolation.

To combat the increasing threat to both human and animal health posed by microorganisms which know no boundaries — political, social, economic or geographical — a combined approach was urgently needed, bringing together scientists from the human and veterinary disciplines, and others involved in ensuring that our food is safe to eat. This need resulted in the formation, in September 2004, of Med-Vet-Net, a network of multi-disciplinary scientists.

So what has Med-Vet-Net achieved? Over the five years of its life, the Network developed a series of interactive groups of like-minded scientists involved in research in zoonotic diseases throughout the European scientific community, including laboratory-based researchers, epidemiologists and risk assessors, all working towards a common objective of combating diseases in humans and animals. There is now an unprecedented level of collaboration across the spectrum between such scientists in different European countries, who know each other personally and respect and trust each other's work and values.

A primary objective of Med-Vet-Net was to develop a 'virtual institute', using newly available methods of communication, primarily electronic, to assist in spreading ideas and results. This now sounds obvious, but it was not the case in 2004. In its infancy, Med-Vet-Net realized the importance of communication, putting in place a highly sophisticated communications structure, which is now the envy of many other scientific networks world-wide.

Science is always developing, and new methods and techniques are reported almost daily. Scientists have to be aware of these developments so that they can apply them to their own research. Again, this was a need recognized by Med-Vet-Net, which provided training, either individually or in groups, to numerous young scientists from all 15 of the Network's participating institutes. The 300-odd scientists involved in the project were also kept up-to-date with the overall work of Med-Vet-Net by means of a very well-supported scientific conference, held annually at venues throughout Europe.

What of the future? The value of Med-Vet-Net's numerous activities and achievements has been recognized both within and outside the European Union (EU). Funding for continuation of the Network was secured in the short-term through the formation of the 'Med-Vet-Net Association', launched in October 2009. All existing Med-Vet-Net scientific institutes are members of the new Association, and several institutes and research groups outside Med-Vet-Net have expressed interest. This means that, for the immediate future, the aims and objectives of Med-Vet-Net's research network will continue, ensuring ongoing benefits to human and animal health in the EU and world-wide.

As a scientist, I never doubted that research in zoonoses is global and that European scientists wished to work together to ensure the safety of food we eat. Med-Vet-Net has more than filled my expectations — it has been a pleasure to work with such a dynamic group of people and to have contributed, albeit in a small way, to the formation of a truly whole-of-Europe scientific research network.

John Threlfall, Med-Vet-Net Project Manager

MED-VET-NET: WHY & HOW?

Diseases have little care for passport control and with the recent worldwide outbreaks of avian and swine influenza and severe acute respiratory syndrome (SARS), the increased risk of pathogens travelling across borders has never been more evident.

And that's where an organization like Med-Vet-Net offers significant benefits to governments and food industry bodies across Europe.

Med-Vet-Net, funded for five years by the 'Quality and Safety of Food' Priority Area of the European Union 6th Framework Programme, commenced in September 2004.

The Network uniquely brought together medical, veterinary and food science researchers, including many of Europe's foremost research groups, all working on the detection and control of zoonotic diseases.

Zoonoses, which are diseases that can be transmitted from animals to people, are responsible for some of our most serious public health problems. According to the World Health Organization, this group of diseases strikes down 14 million people around the world every year.

Zoonoses have always represented a risk to humans. In fact, zoonotic diseases account for over 75% of new and emerging infections. But recent events, such as avian and swine flu, have shown us that the danger from zoonoses is increasing and has serious worldwide consequences.

While diseases like swine flu dominate the media headlines, it is the zoonoses such as *Salmonella*, *E. coli* and other food-borne diseases that receive less media attention that currently cause much greater economic impact. Food scares like BSE, or 'mad cow disease', also showed the importance of science in uncovering the links between animals and human zoonotic illnesses as well as highlighting the importance of food security and the role of regulators in safeguarding the entire food chain from the 'farm-to-fork'.

Across the European Union (EU), zoonoses of this kind cost the community well in excess of €6 billion a year. In addition, the EU found that the epidemiological information that member states were collecting on trends and sources of zoonotic agents was incomplete and not fully comparable. Thus, the Zoonosis Directive was enforced by the European Commission in 2003, requiring each Member State to monitor 23 identified zoonoses and zoonotic agents in both human and animal populations. This has stimulated the collection and reporting of surveillance data on food-borne illness and, additionally, several countries have implemented special epidemiological studies that provide a more detailed picture of food-borne illness in Europe.

In further recognition of the enormity of the economic impact of zoonotic diseases, and the need for better international cooperation on animal and human health issues between central governments, devolved administrations, and local enforcement and health organizations, Med-Vet-Net was born.

As a new Network of Excellence, Med-Vet-Net became the perfect vehicle for the first ever pooling of scientific expertise from medical and veterinary institutes across Europe.

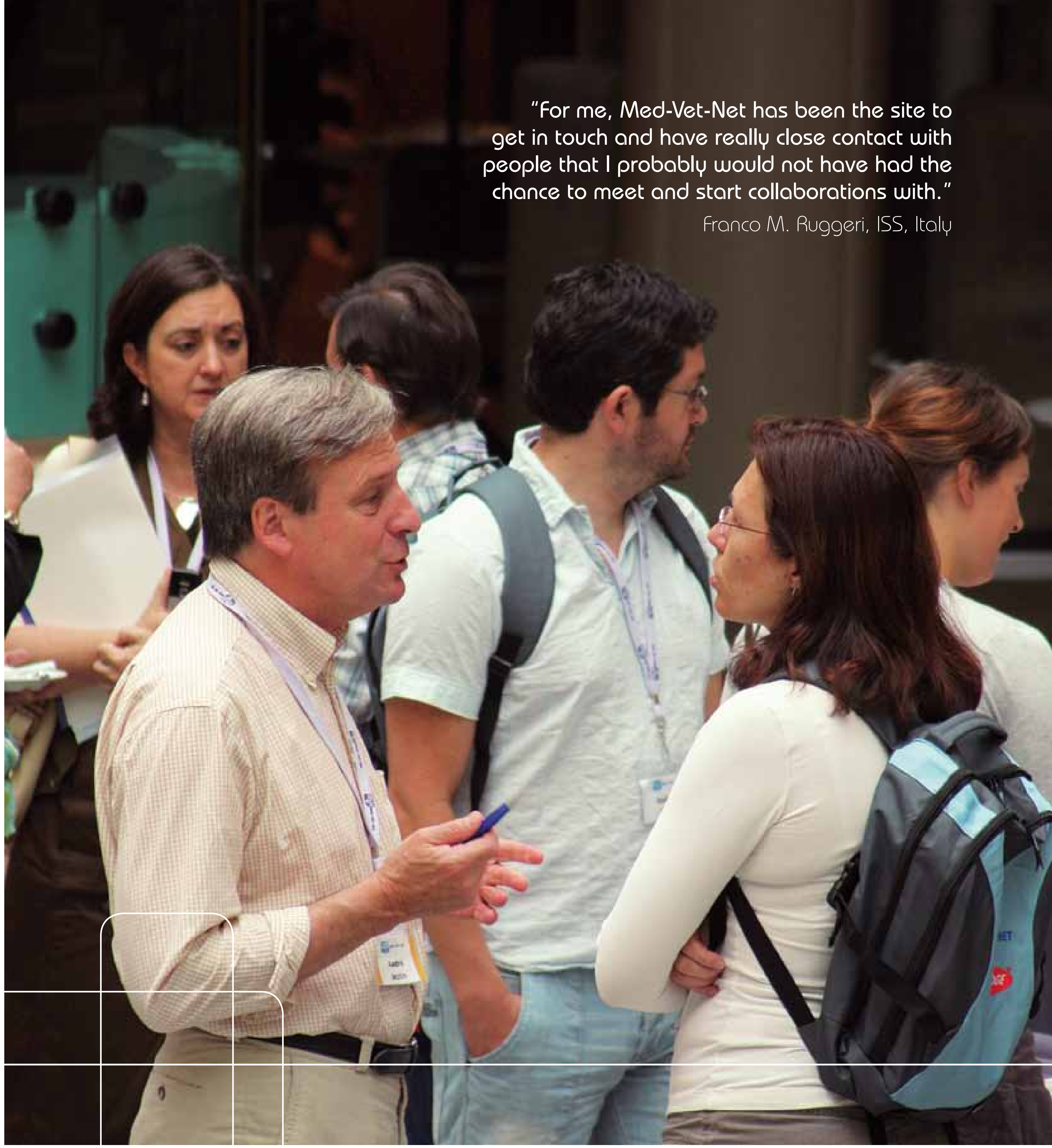
The Med-Vet Network comprised 15 partners and over 300 scientists from 10 countries, including doctors to identify the human diseases, epidemiologists and risk analysts to establish links with animals, microbiologists to confirm those links, and veterinary scientists to control and prevent the risks.

All worked to create a critical mass of knowledge and experience that will significantly improve our understanding of zoonotic illnesses and enhance our ability to respond to emergency disease situations anywhere in the world.

Europe is generally not considered to be a breeding ground for new zoonoses, but the animals we take for granted and come into contact with almost daily can all carry disease that can potentially cause food poisoning, paralysis or even death.

"For me, Med-Vet-Net has been the site to get in touch and have really close contact with people that I probably would not have had the chance to meet and start collaborations with."

Franco M. Ruggeri, ISS, Italy



As existing disease agents change and new disease agents emerge, there is a need for continuous research to ensure we recognize the risks and communicate them to decision-makers to enable the introduction of effective and economical interventions. Integrating economics into food safety decision-making gives greater insight into the cost-effectiveness and benefits of intervention measures and different levels of food safety.

As Europe's leading zoonotic disease research network, Med-Vet-Net has enabled scientists, previously working in isolation, to undertake integrated research to develop the necessary control strategies, identify new risks and provide the expertise to rapidly detect and respond to new and existing disease threats at the whole-of-Europe level.

BACTERIA

Bacteria are a large, diverse group of single cell microorganisms, ubiquitous in every habitat on Earth. Many bacteria live within our gastrointestinal tract, on our bodies or in the environment with which we come into daily contact, without there being any resulting disease. There are typically 40 million bacterial cells in a gram of soil and a million in a millilitre of fresh water. Some species are pathogenic and can cause infectious diseases.

Although diseases like swine flu dominate the media headlines, every year millions of people get sick because of food-borne bacteria such as *Salmonella* and *Campylobacter*, costing the community well in excess of €6 billion a year. The Community Zoonoses Report for 2007, published by the European Food Safety Authority and the European Centre for Disease Prevention and Control shows that in the 27 EU Member States in 2007, infections from *Campylobacter* reached 200,507 cases (an increase), *Salmonella* showed 151,995 people affected (a decline), and Listeria infections remained constant at 1,554 confirmed cases, but showed the highest mortality rate.

The growing prevalence of these food-borne diseases and the economic impact make further research on them essential. Of the bacterial zoonoses listed in the EC Directive to be monitored by Member States, Med-Vet-Net chose five of the eight listed as its highest research priorities.

Listeria

Listeria are the bacteria responsible for listeriosis, a rare but potentially lethal food-borne infection. The case fatality rate for those with a severe form of infection may approach 25%, where *Salmonella*, in comparison, has a mortality rate estimated at less than 1%. The infection is able to spread to the nervous system and cause meningitis, and is also very dangerous to pregnant women as it can cause foetal infections, miscarriages and stillbirths.

Listeria are incredibly hardy and able to grow in temperatures ranging from 4°C (the temperature of a refrigerator), to 37°C (the body's internal temperature). They have been found in uncooked meats, uncooked vegetables, unpasteurized milk, foods made from unpasteurized milk, and processed foods. The bacteria can be killed by pasteurization and cooking.

Q-Fever

Q-fever is a disease caused by the bacterium *Coxiella burnetii*. Cows, sheep and goats are the main carriers of the disease, although they don't usually show any signs, and ticks, fleas, and lice can transfer the pathogenic agent to other animals. The bacteria may be excreted in milk, urine, faeces and blood, and there are also particularly high levels in the placenta of infected animals. The bacteria are very resistant and can survive for long periods outside the animal. Human infections are usually caused by inhaling farmyard dust containing the bacteria. Very few organisms (as low as a single organism) are needed to cause disease in susceptible people; thus it is highly infectious.

Symptoms, which usually begin 2–3 weeks after exposure and can last 1–2 weeks, are only seen in around half of all infected people and include high fever, headache, muscle pain, sore throat and coughing. Some people may develop pneumonia, hepatitis, or chronic fatigue syndrome and long-term chronic Q-fever can be fatal.

Salmonella

***Salmonella* bacteria can cause salmonellosis, a major cause of food-borne illness throughout the world, as well as typhoid fever and paratyphoid fever. Today, there are over 2,500 known types, or serotypes, of *Salmonella*.**

While the majority of serotypes can cause disease in humans, they are often classified according to their adaptation to animal hosts. Most serotypes have a broad host-spectrum and typically such strains cause gastroenteritis (diarrhoea and vomiting), which is often uncomplicated and does not need antibiotic treatment. This group features *Salmonella* Enteriditis and *Salmonella* Typhimurium, the two most important serotypes for salmonellosis transmitted from animals to humans. A few serotypes have a limited host-spectrum (affect only one or a few animal species), for example *Salmonella* Typhi in primates; *Salmonella* Dublin in cattle; and *Salmonella* Choleraesuis in pigs. When these strains cause disease in humans, it is often invasive and can be life-threatening.

The bacteria are generally transmitted to humans through consumption of poultry, pork and beef if the meat has not been cooked sufficiently, as well as eggs and raw milk that have not been prepared or refrigerated properly. Many other foods, including chocolate and contaminated fruit and vegetables, have also been implicated in transmission. They may also be transmitted from reptiles, such as turtles, lizards and snakes, as they carry the bacteria on their skin and in their intestines, and pet rodents. *Salmonella* bacteria can survive several weeks in a dry environment and several months in water; thus, they are frequently found in polluted water, contamination from the excrement of carrier animals being particularly important.

The symptoms of *Salmonella* infection usually appear 12–72 hours after infection, and include fever, abdominal pain, diarrhoea, nausea and sometimes vomiting. The illness usually lasts 4–7 days, and most people recover without treatment. The disease can be severe in the young, the elderly and patients with weakened immunity, and in cases when the bacteria enter the bloodstream.

In recent years, problems related to *Salmonella* have increased significantly, both in terms of incidence and severity of cases of human salmonellosis. Since the beginning of the 1990s, strains of *Salmonella* that are resistant to a range of antimicrobials from the use of antimicrobials both in humans and animal husbandry, have become a serious public health problem.

"Reported cases of *Campylobacter* are estimated to be only one sixth of those that are actually occurring in the community. So while it is never reported, people may have a couple of days off work so there is a high economic impact."

Bob Owen, HPA, United Kingdom

WORKPACKAGES: *LISTERIA*: 04 / Q-FEVER: 25 / *SALMONELLA*: 04, 06, 21, 26, 33

Escherichia coli

***Escherichia coli* (*E. coli*) is a bacterium that is commonly found in the gut of humans and warm-blooded animals. Most strains of *E. coli* are harmless but some strains can cause severe food-borne disease and can produce potentially-lethal toxins (e.g. verocytotoxin) and cause intestinal bleeding.**

Food poisoning caused by *E. coli* is usually a result of eating unwashed vegetables, undercooked meat or swimming in, or drinking, contaminated water. *E. coli* are not always confined to the intestine, and their ability to survive for brief periods outside the body makes them an ideal indicator organism to test environmental samples for faecal contamination. The incidence of *E. coli* is relatively low and most people recover without antibiotics or other specific treatment in 5–10 days, however, the severe and sometimes fatal health consequences, particularly among infants, children and the elderly, make *E. coli* among the most serious food-borne infections.

E. coli O157:H7, an enterohaemorrhagic *E. coli* serotype (EHEC), is particularly important in relation to public health. As well as being transmitted by food, it can also be transmitted by direct contact with infected animals who do not display any symptoms of infection. As such, it is a particular hazard to young children, who may be exposed to the bacteria by handling such animals in, for example, petting farms. Additionally, other EHEC serotypes have frequently been involved in sporadic cases and outbreaks, particularly in countries in mainland Europe.

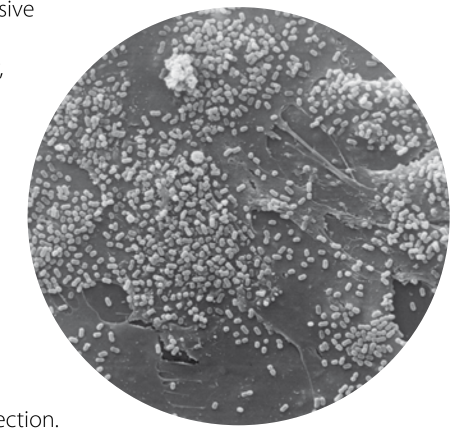
Campylobacter

Campylobacteriosis is a widespread infection caused by certain species of *Campylobacter* bacteria, particularly *C. jejuni,* transmitted mainly by consumption of foods such as raw or undercooked poultry, raw milk, and drinking water. There are 16 different species of *Campylobacter* and it is now the major reported cause of human bacterial food-poisoning in Europe.

Symptoms usually start 2–5 days after infection, and last for 3–6 days and include diarrhoea, abdominal pain, fever, headache, nausea and vomiting. Specific treatment is not usually necessary except to replace electrolytes and water lost through diarrhoea. In 2–10% cases the infection may lead to chronic health problems, including joint inflammation (5–10% cases) and, on rare occasions, bacteraemia or Guillain-Barré syndrome, causing paralysis.

Campylobacters are widely distributed in animals and the environment, and can colonize the intestinal tracts of all food-producing animals (poultry, cattle, sheep and pigs) and domestic pets (dogs and cats) without causing any symptoms. Most human cases are reported sporadically, with no obvious source of infection. Thus, the accurate identification of infectious sources and routes of transmission of *Campylobacter* is often difficult. Any raw meat, especially offal, may be contaminated with campylobacters, but poultry is thought to be a major source.

Camplyobacters are delicate and die if exposed to air for any length of time. They are destroyed by cooking, but, unlike the salmonellas, they do not multiply in food so they seldom cause explosive outbreaks of food poisoning. However, it seems the number of bacteria consumed to cause illness is very small, and therefore it only needs a few organisms cross-contaminating other food (e.g. salad) in the kitchen to cause infection.



"Med-Vet-Net has given us a great opportunity to have a wider coverage of Europe as a whole, particularly for some countries where the data were really limited at the start."

Simone Cacciò, ISS, Italy

Bringing it all together

A significant number of the Med-Vet-Net research projects focused on the key bacterial zoonoses, particularly *Campylobacter*, *Salmonella* and *Escherichia coli* (*E. coli*). As members of the *Enterobacteriaceae* family, *Salmonella* and *E. coli* are both genetically and physically similar to each other, thus making joint research on virulence and genomes sensible.

Med-Vet-Net scientists looked at what makes Verotoxigenic *E. coli* (VTEC) so infectious and able to cause disease. The knowledge they gained will help to see how it is spread, and to find possible treatments.

The distribution of VTEC cases were analysed in a country-specific manner using geographic information systems (GIS), and their correlation to the distribution of cattle farms assessed.

An online catalogue of skills, expertise and resources related to VTEC within Med-Vet-Net was produced and recommendations for future research were made.

The PulseNet Europe project established a real-time web-based database that allows disease detection and rapid communication between food, public health and veterinary laboratories in Europe for *Salmonella*, VTEC and *Listeria moncytogenes*.

Another group studied the distribution and characteristics of Salmonella Genomic Island 1, a cluster of genes which are present in many antibiotic resistant strains of *Salmonella,* and can transfer to some other species.

A database collecting genetic data relating to specific virulence information on *Salmonella* and VTEC was also established. This will allow for the development of appropriate platforms for rapid analysis in future routine diagnosis.

A web-based 'Atlas' of the incidence of salmonellosis in Europe has been constructed using GIS.

Using novel technologies, the host's response to infection by *Salmonella* and *Campylobacter* were further investigated, the results of which will be valuable for vaccine development.

Researchers also developed a new approach to estimating the incidence of *Campylobacter* and *Salmonella* infections by measuring antibodies in serum as an indicator of past infection.

Significant research was also undertaken to investigate different aspects of *Campylobacter* — its detection, control and epidemiology. Current typing tools are limited and the mechanisms by which *Campylobacter* causes disease in humans remains unclear, creating a knowledge gap that hinders accurate risk assessment for campylobacters in the food chain.

Previously characterized strains of *Campylobacter* were used to standardize and apply virulotyping techniques to *C. jejuni* to investigate the physical characteristics that are thought to cause disease. Work then continued to further match epidemiological requirements with microbiological and molecular tools for investigating host-microbe interactions in *Campylobacter*.

A new software programme (CRAF) was also created to store information from each country describing the existing models for microbial risk assessment of *Campylobacter,* and to identify what data are needed to use each model.

The sources, control and prevention of *Campylobacter* in poultry was investigated and an archive was collated based on the relevant European information. Further knowledge on the epidemiology of poultry colonization, and of the survival of *Campylobacter* in the poultry environment was also gained.

Finally, Med-Vet-Net researchers also worked on the development and application of new methods of diagnosing Q-fever in both humans and animals.

Together the results from all of Med-Vet-Net's collaborative research on these key bacterial zoonoses has ensured Europe is in a better position to continue the fight against infectious diseases.

VIRUSES

Until recently, viruses have not been considered an important cause of food-borne zoonoses, but the changing epidemiology of several viruses, the increased circulation of viral pathogens due to global trading and travelling, together with new concepts in animal health and farming have made it necessary to investigate the possible risks associated with virus-infected animals.

There is now also broad evidence confirming that animal viruses, particularly those containing highly mutating RNA genomes, are capable of transmitting to humans, and some of these pose the major future threats to human health.

European Bat Lyssavirus

European Bat Lyssavirus (EBLV) is a rabies-like virus that infects insect-eating bats in Europe. It comes from the same family of viruses as 'classical' rabies but EBLV is a different strain and very rarely infects animals other than bats.

Like rabies, EBLV infection in humans is very serious and once symptoms manifest there is no specific treatment, and all four past human cases in Europe have been fatal.

Fortunately, the risk of EBLV infection to humans is thought to be low, but over the past 30 years more than 720 cases have been reported in bats, predominantly in the Netherlands, Spain, Denmark and Germany. It is possible however, that EBLV is under-reported and that the recorded cases of EBLV in bats represent only a small proportion of the actual number of infected bats.

Moreover, due to the protected status of bats in Europe, our knowledge of EBLV prevalence and epidemiology is limited. Thus, to assess the threat posed by bat viruses, and to ensure we have effective surveillance programmes and rapid response systems, there is a need for accurate collated information on the risk of bat-associated rabies to public health.

Over the past five years, Med-Vet-Net, through a dedicated scientific workpackage and special interest group, worked to provide the European community with that bank of knowledge.

Led by the Veterinary Laboratories Agency in the UK, Med-Vet-Net established the first international network of scientists involved in European bat lyssavirus research and surveillance.

The Network also created the first integrated EBLV database, incorporating clinical details, laboratory investigations and virus sequences of EBLV cases in Europe. Available to external experts, the database is now the single source of data for bat lyssavirus in the European Union (EU).

An unanticipated benefit of Med-Vet-Net's research has been the development of guidelines, published in the WHO Rabies Bulletin, for standardizing surveillance systems across the EU, including recommendations for establishing national bat rabies surveillance networks in all European countries.

Such was the success of the EBLV projects, the Bat Lyssavirus Special Interest Group was further developed and extended to other wildlife species and diseases to become WiREDZ (Wildlife-Related Emerging Diseases and Zoonoses), a Med-Vet-Net sponsored research group focused on scientists working on emerging and zoonotic diseases of wildlife across Europe.

The knowledge generated through Med-Vet-Net's EBLV research has provided invaluable information to researchers and diagnosticians involved in, or wanting to initiate, lyssavirus surveillance in bats. This knowledge will ultimately lead to improved approaches to bat rabies throughout Europe and a better understanding of the public health risks of emerging zoonotic bat viruses.

WORKPACKAGES: 05 & 31

Pioneers on porcine viruses and Tick-borne Encephalitis

Reflecting the growing acknowledgment of the future disease threat of RNA viruses, Med-Vet-Net began a research project in 2005 called ZOOVIRNET to look more closely at the role of food-producing animals as sources of emerging viral zoonoses, and to generate useful knowledge for the implementation of possible infection control measures.

The project team, spearheaded by Italy's Istituto Superiore di Sanita, have since established themselves as pioneers in Europe with their work on pigs as possible transmitters of three significant emerging viruses — Hepatitis E (HEV), Annellovirus, and Encephalomyocarditis Virus. They also investigated the increasingly important transmission of Tick-borne Encephalitis (TBEV) through unpasteurized goat's milk and cheese.

The team performed diagnostic and epidemiologic studies on the prevalence of the porcine viruses, characterizing and comparing the identified viral strains by sequence analysis. They then chose strains to clone, using recombinant viral antigens for immunological assays and the production of reagents. Significantly, the team generated recombinant protein that represents the genotype of the HEV virus that is circulating in Europe. This, along with the new, more appropriate diagnostic tools they constructed, are critical developments in improving the detection and control of HEV in Europe.

In addition, the results from their integrated virological and epidemiological investigations of people and farm animals in relation to TBEV, have shed new light on the potential impact of transmission through unpasteurized dairy products. Their studies suggested that even a substantial dilution of TBEV can cause a large outbreak of the infection, demonstrating the high risk of pooling milk in areas with a marked presence of ticks and milk animals.

The overall success of the ZOOVIRNET project is further evidenced by how much more we know and understand about the role of these RNA viruses as food-borne diseases.

When the project began, different systems and diagnostic methods were used in different countries and there was a significant lack of communication between laboratories and research groups. Four years on, ZOOVIRNET has confirmed the extensive spread of viral pathogens among farmed and wild animals, and developed state-of-the-art methodologies for the study of selected emerging zoonotic viruses. In particular, there now exists an integrated system with common diagnostic tools, supplemented by a sharing of information, expertise and data throughout the EU.

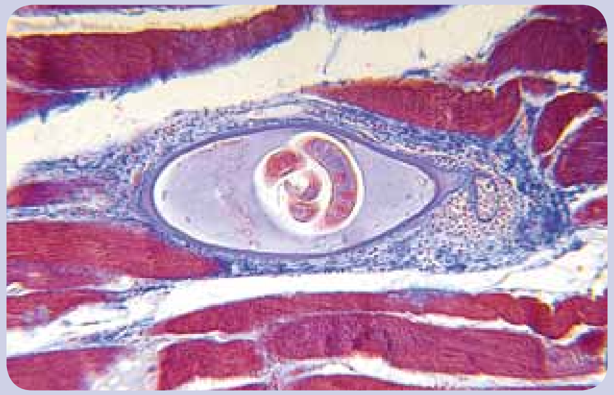
Through ZOOVIRNET, Med-Vet-Net has ensured Europe is in a position to develop better risk assessments and codes of practice to minimise the risks of zoonotic and/or food-borne viruses passing into the community.

PARASITES

Parasites, which range in size from tiny, one-celled organisms called protozoa to worms that can be seen with the naked eye, are commonly misconceived as a Third World problem resulting from malnutrition and poor hygiene practices. Nothing could be further from the truth. Parasites are a serious public health threat the world over and parasitic diseases, such as Trichinellosis, Giardiasis and Cryptosporidiosis, can be deadly.

TrichiNet — making a difference

Trichinella are one of the most widespread and clinically important food-borne parasites in the world, and Trichinellosis, caused by eating raw or undercooked pork and wild game that is infected with the larvae of the _Trichina_ worm, is a re-emerging food-borne parasitic disease responsible for thousands of human infections in Europe every year.



Trichinellosis is listed in the EC Zoonoses Directive requiring the meat of millions of pigs, horses and game to undergo mandatory inspection at an annual cost to the EU of over €500 million.

Several outbreaks during the past 10–15 years, arising mostly from un-inspected and illegally imported meat from new and candidate Member States, have clearly illustrated the need for improved EU guidelines, and new and more cost-effective ways to detect and control Trichinellosis. This is where Med-Vet-Net's work has made a difference.

Identifying a lack of standardized and harmonized surveillance systems for EU Member States, Med-Vet-Net conducted research to improve detection procedures for trichinellosis and investigated how the disease is spread in animals.

The research teams assessed current meat inspection technology, created a European repository for standardization, and developed two new tests for the early diagnosis of pig trichinellosis, with possible extensions to humans.

Epidemiological information collected by Med-Vet-Net on the emergence of *Trichinella* infections in wildlife and free-ranging pigs also showed that emerging and re-emerging cases of trichinellosis are frequent, and the presumed reservoirs of the parasite poorly explain its persistence in host populations throughout Europe.

Of longer-term importance, Med-Vet-Net created an international database and scientific network, called TrichiNet, that extends beyond the Med-Vet-Net partnership and brings together Europe's leading physicians and veterinarians working in the investigation and control of *Trichinella*. Significantly, TrichiNet encourages a far more rigorous collection of epidemiological data, enabling more effective pan-European collaboration, and acting as source of expert advice and information for European policy-makers and authorities, such as the European Food Safety Authority.

> "The Network gave us the tools and support to enlarge the impact of the repository at the whole-of-Europe level."
>
> Pascal Boireau, AFSSA, France

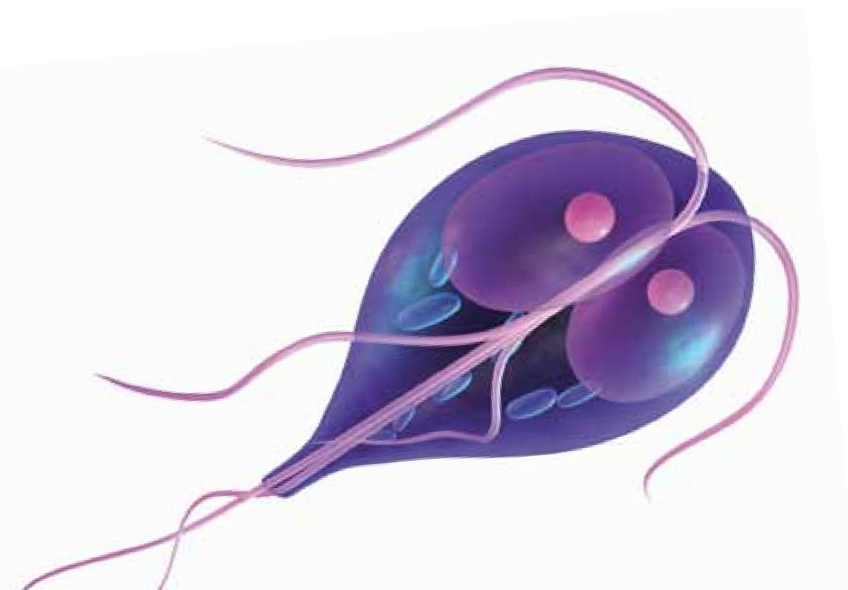
Unravelling the epidemiology of *Cryptosporidium* & *Giardia*

The Med-Vet-Net partnership has also contributed significantly to the detection and control of _Cryptosporidium_ and _Giardia_ — parasites of considerable global interest due to the gastrointestinal problems they can cause in people as well as animals.

Giardiasis is the most common cause of parasitic gastrointestinal disease with up to 20% of the world's population infected. Similarly, cryptosporidiosis has been reported in over 90 countries in six continents. Europe itself has a suggested prevalence of the infection in the general population of close to 15%. Given the growing all year demand, global sourcing, and rapid transport of food, particularly fruit and vegetables, the likelihood of contamination is ever-increasing.

Where these parasites are concerned however, food contamination is just one of several routes of transmission, making the epidemiology of human infection difficult for scientists to unravel. Through the work of two Med-Vet-Net research projects though, the pieces of the *Cryptosporidium* and *Giardia* puzzles are falling into place.

Med-Vet-Net scientists have produced a new, comprehensive and dynamic database called ZoopNet that details the life cycle, biology and treatment options for giardiasis and cryptosporidiosis. The database provides new opportunities to compare data from different countries from both outbreaks and sporadic cases, and has filled the data gaps, particularly for *Giardia*, from specific countries such as France, Poland and Denmark.



In addition, the Med-Vet-Net research team harmonized the detection methods and techniques used in different laboratories across Europe to create a common language and understanding, helping the less experienced institutes by sharing data and expertise.

The research partners also developed new analytical tests that overcome the limitations of previous tests in detecting and identifying *Cryptosporidium* and *Giardia* species. The new assays represent the first step towards establishing a new molecular platform for the rapid detection of multiple pathogens, which could be applied in many areas from water monitoring to clinical investigations.

Above all, the work undertaken by the Med-Vet-Net partnership has enabled European scientists to create a world-class critical mass of knowledge and expertise on these two insidious parasites.

And with that improvement in our ability to detect *Cryptosporidium* and *Giardia* infections, and the subsequent increase in our knowledge, we will find it easier to isolate sources of contamination, identify appropriate control measures and enable more accurate assessments of the risks to public health.

EPIDEMIOLOGY & SURVEILLANCE

In disease research, epidemiology and surveillance are critical to public health preparedness. It is through good epidemiology and surveillance activities that we can identify, track and control diseases and other health threats to the community.

But as well as predicting, observing, and minimizing the harm caused by outbreaks, epidemics and pandemics, disease surveillance also helps us expand our knowledge about the factors that can contribute. Using cutting-edge technology, scientists can identify and map novel or virulent strains of specific organisms that might be causing higher levels of illness.

With that knowledge, health authorities can then decide whether it is necessary to take action against an emergent threat such as an influenza outbreak or infections caused by new strains of *E. coli*, or to monitor new, emerging and imported infections, such as SARS.

Such is the importance of epidemiology and surveillance, it was chosen as one of Med-Vet-Net's four thematic research areas, and the early detection of outbreaks remained a particularly important topic throughout the project.

Over the past five years, several Med-Vet-Net research projects have contributed directly to epidemiology and surveillance activities both within individual countries and across the EU.

Workpackage 4, led by Denmark's Statens Serum Institut, contributed to a significant improvement of surveillance and tracing of food-borne infections at national and European level through the development of PulseNet Europe.

Initially focused on *Salmonella*, verocytotoxin-producing *E. coli* (VTEC) and *Listeria monocytogenes*, the PulseNet surveillance system established by Med-Vet-Net, can be easily modified or expanded to include other infectious disease agents.

With its adoption by the European Centre for Disease Prevention and Control (ECDC), PulseNet Europe will play a vital role in the surveillance and investigation of food-borne illnesses that were previously difficult to detect.

Another integral part of epidemiology is taking into account where diseases occur and here Med-Vet-Net has made another vital contribution — putting GIS (Geographical Information Systems) on the map.

Geographical Information Systems are powerful new tools used to construct maps and analyse spatial data. They can be used to analyse the distribution of zoonotic agents and identify risk factors for zoonotic diseases. They can also be helpful for basic surveillance and outbreak investigations or, for instance, to analyse how contaminated foods are distributed from one country to another.

In spite of its potential, GIS has not been used much for investigating zoonotic diseases, and the skill base among researchers is generally limited. Med-Vet-Net set out to change that.

In addition to capacity building through GIS training courses and workshops throughout Europe, Med-Vet-Net developed an interactive, online 'Salmonella Atlas' comprising a series of maps showing the spread and incidence over time of the 10 most important salmonella serotypes in Europe. The information provided by the Salmonella Atlas assists epidemiologists making trends analyses and investigating outbreaks of one of Europe's most common and problematic gastrointestinal illnesses.

PulseNet Europe

PulseNet Europe is a unique network of 58 public health, veterinary and food laboratories across 30 European countries. It offers real-time surveillance of food-borne infections in Europe enabling scientists across the continent to rapidly compare bacteria from different sources and determine whether an outbreak is occurring, even if the people affected are geographically far apart. With PulseNet, outbreaks can be identified within hours rather than days, as has historically been the case.

"We could not have done this testing without the funding from Med-Vet-Net, and on top of that of course the network through Med-Vet-Net has helped us to identify partners in the different countries that then in turn found serum collections in their countries and provided them for the project."
Gerhard Falkenhorst, SSI, Denmark

After five years of promoting and demonstrating the benefits of GIS, Med-Vet-Net is confident that more research institutes in more countries will start using GIS regularly to produce more maps, and that GIS activities will be an integral part of the work of EU agencies such as the ECDC.

The outputs of Med-Vet-Net's GIS project may not only be taken up by Europe's lead disease control agency, but were also directly and indirectly used by a range of other research projects within Med-Vet-Net including Workpackage 32, which developed an exceptional new approach to estimating the incidence of *Campylobacter* and *Salmonella* infections.

Measuring antibodies in serum as an indicator of past infection, the new serological test developed by Med-Vet-Net epidemiologists has proven to be a much more effective way of comparing data between countries than relying solely on laboratory-based case reporting, which can be misleading due to different reporting systems.

With the new serological approach that uses serum from both healthy people and those with symptoms, the multi-national research team not only found startling differences in the incidence of *Salmonella* infection between the countries tested, but also the countries with the highest reported incidence had the lowest actual incidence.

Med-Vet-Net's serological test results thus offered a much better indication of how well the surveillance and control systems targeting *Salmonella* and *Campylobacter* are working. So effective is the new approach that both the ECDC and the American Centre for Disease Control and Prevention have shown interest in implementing Med-Vet-Net's method for future routine surveillance of gastroenteritis in Europe and the USA.

HOST-MICROBE INTERACTIONS

The interactions between a pathogen and its host are complex and dynamic. The outcome of such interactions is a reflection of the capacity of the microbial agent to infect and the ability of the host to respond to and fight the infection. If the bacteria are able to adhere to or colonize the host, then a disease may occur.

Alternatively, the host may be able to fight and get rid of the pathogen and thus no infection occurs. Or, the bacteria may just be carried with no infection or symptoms. It is essential to have a fundamental understanding of these mechanisms, and why the host response results in either an acute illness such as diarrhoea or a chronic disease like Gullain-Barré Syndrome, in order to develop prevention and control strategies for zoonotic diseases.

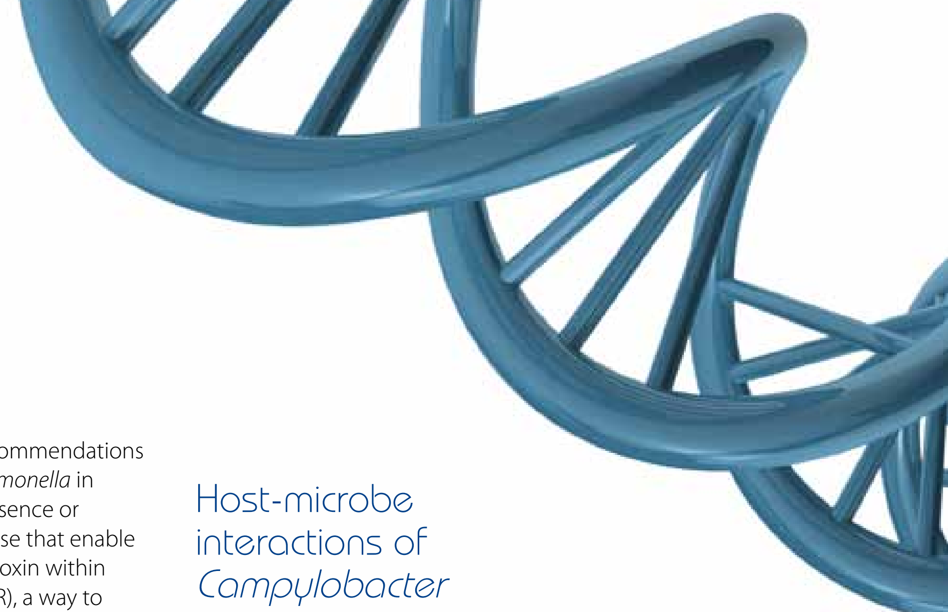
How Verotoxigenic *Escherichia coli* (VTEC) causes disease

When infecting humans, Verotoxigenic *Escherichia coli* adheres to the gut, replicates and produces toxins that enter the blood system where they cause damage and vascular leakage, potentially leading to life threatening disease.

Given its emergence as a major cause of both outbreaks and sporadic cases of human diarrhoeal disease throughout the world, VTEC was selected for one of Med-Vet-Net's first projects — creating an online catalogue of skills, expertise and resources related to VTEC within the partnership. A workshop, involving 27 organizations throughout Europe, reviewed the research and surveillance activities on VTEC and produced a report with recommendations for future research.

It was acknowledged that the true incidence of VTEC is poorly defined within Europe, and priority should therefore be given to improving baseline data on the prevalence of the different types in human infections and animal reservoirs by using harmonized methods, so that the epidemiological trends of VTEC infection can be effectively monitored.

There was also a need to understand the key points of the infection process at the cellular level for the development of effective therapeutic interventions.



Typing methods to detect virulence genes

In 2006, a new project picked up the earlier recommendations to investigate new and emerging VTEC and *Salmonella* in Europe. The research team investigated the presence or absence of a number of virulence genes — those that enable the bacteria to adhere to, invade or produce a toxin within the host. Using Polymerase Chain Reaction (PCR), a way to amplify DNA from bacteria or host cells, the specific product could be visualized. Over 1,000 *E. coli* and *Salmonella* isolates from 11 European countries were collated, analysed by PCR and stored in a repository. A sub-set was then analysed using microarray techniques, whereby thousands of genes are viewed on a glass side enabling scientists to see which genes are turned on or off in response to infection. A further sub-set was subsequently evaluated using comparative genomics, where a specific whole genome of a strain is compared to a database genome.

Both *E. coli* and *Salmonella* can acquire and lose DNA quite easily via plasmids or actual pieces of linear DNA. Plasmids are of particular interest because they frequently carry virulence and multi-drug resistant genes, and they can move from one strain to another and can even transfer from one bacterium to another. It is thought that bacteria lose genes in an aim to become fitter — by losing genes that they are not using they can operate remaining genes at a higher efficiency.

The project identified some interesting differences in serotypes of *Salmonella* and *E. coli* across Europe, which will help with the prediction, diagnosis and control of new and emerging virulotypes. Most importantly, the project facilitated the development of a number of rapid diagnostic platforms for VTEC and *Salmonella* that are now in routine use throughout the EU.

Early host response to *Salmonella* and *Campylobacter*

In response to infection in the host, genes can be switched on (up-regulation) or off (down-regulation). The host may have an immune gene in order to defend itself against infection or a pathogen's gene may be involved in entering cells within the host. To examine the specific regulation of genes, Med-Vet-Net researchers used microarrays.

Although microarray techniques have been around for a number of years, they have been expensive to use and many labs did not have the facilities or opportunity to use them. The ability to study the response to infection within the cell (*in vivo)* is a more recent application, and has proven extremely useful in looking at gene regulation and response to infection in many different cell lines. Most people have looked at exposing cell lines to all types of pathogens and looking at gene regulation but now we are looking at what happens in the intestine at the local site of infection. These findings are of value for vaccine development.

Host-microbe interactions of *Campylobacter*

The main aim of the former EC-funded CampyNet project was to provide standardized molecular methods of typing (classifying the strains according to their molecular properties) for *Campylobacter jejuni* and *C. coli*, which greatly facilitated epidemiological studies of these bacteria. The project resulted in a set of 100 fully characterized *C. jejuni* and *C. coli* strains.

Med-Vet-Net scientists used these strains in CampyNet II to standardize and apply virulotyping techniques to *C. jejuni* to investigate the physical characteristics that are thought to cause disease. Firstly, the CampyNet II team used a subset of strains to find the most suitable and reproducible methods with which to test (assay) invasiveness and toxin activity. The CampyNet strains were tested for virulence potential using these assay systems. In addition, the strains were screened for putative virulence genes (genes which are commonly thought to be associated with the virulence of the organism), to establish the distribution of these potential markers of pathogenicity (ability of the organism to cause damage to the host) in relation to invasion and toxin production. The strain set was also tested for antimicrobial susceptibility using an established panel of antimicrobials. The appropriate technologies were made available to other laboratories and the results were collated and fed into the original CampyNet database.

CampyNet III built on this work to find ways of learning more about how *Campylobacter* causes disease in humans, and why some people get it and others don't. Considerable variation appears to exist among *C. jejuni* isolates in their ability to invade cells or express active toxin. The CampyNet III team included microbiologists, epidemiologists, veterinarians as well as doctors, so that many disciplines were drawn upon to review what is already known and what needs to be done in the future. The group agreed a strategy for microbiological and epidemiological investigation of human illness associated with *C. jejuni*, and outlined a set of recommendations for best practice tools/methods for investigation of host-pathogen interaction.

These methods included the use of multilocus sequence typing (MLST) and pan-genomic analysis using DNA microarrays (genomotyping). A high density *Campylobacter* pan-genome microarray was created based on all genes found present in all available genome sequences. This allowed for the identification of gene networks present in subsets of strains and the prediction of additional virulence properties. A standardized operating procedure for the pan-genome micrarray assay was established to facilitate the transfer of technologies to the participating laboratories.

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance — the ability of a microorganism to resist the action of antibiotics — is not, in itself, a new or even surprising phenomenon. As living organisms, bacteria grow, change and adapt to their environments. The past 50 years that we have been using antimicrobials have changed those environments and consequently bacteria have learned how to flourish in the presence of antimicrobials by sharing genes, by mutating and by adapting.

What is increasingly worrying is how rapidly antimicrobial resistance is accumulating and accelerating in bacteria that cause infections in people and animals, presenting a growing problem to both human and veterinary medicine.

For that reason, research into new and emerging antimicrobial resistance mechanisms is a cornerstone in the battle against infectious diseases. A battle that presented Med-Vet-Net with the unique opportunity to enable results from both human and veterinary antimicrobial resistance research in different countries to be compared in a truly meaningful way.

Med-Vet-Net's first antimicrobial resistance focus was on the human health implications of emerging resistance to beta-lactam antibiotics, the most varied and widely used group of antimicrobials. Because of the popularity of beta-lactam drugs, certain bacteria, including *Salmonella* and *E. coli*, have developed counter-measures to traditional drug therapies, such as penicillin, creating one of the main human clinical problems worldwide.

Despite this, there has been no systematic investigation of the occurrence of different β-lactamases — the enzyme responsible for nullifying the effectiveness of beta-lactam antibiotics — particularly in bacteria from food-producing animals. This is largely a result of the absence of harmonized methods for testing for, and characterizing, the various β-lactamase activities, which precludes comparison between studies, laboratories and countries.

Med-Vet-Net researchers have successfully addressed this through the development of a collection of reference strains covering almost all known published β-lactamases. The collection, along with the common protocols for plasmid isolation, purification and characterization that the team also produced, now provide a unique resource to Europe's scientific community interested in the surveillance and monitoring of β-lactamases in *Enterobactericeae*.

And it is a resource that has already proven itself.

The standardized procedures have enabled the first report of the β-lactamase, OXA-58, in *Acinetobacter baumannii* in Italian hospital patients. *Acinetobacter* enters the body through open wounds, catheters and breathing tubes, and it is thought the bacterium's rapidly spreading resistance throughout Italian hospitals may be due to OXA-58.

Investigating drug-resistant *Salmonella*

In 2006, Med-Vet-Net began two new antimicrobial resistance research projects. One involved investigating the drug resistant strains of *Salmonella* that are causing a rapidly growing number of food-borne disease outbreaks around the world.

Using a large collection of human and animal isolates, the Med-Vet-Net team studied the distribution and characteristics of Salmonella Genomic Island 1 (SGI1), the gene cluster (a set of closely related genes that are grouped together on the same chromosome) thought to be associated with enhanced virulence and multi-drug resistance in *Salmonella* and possibly other enteric bacteria.

"Med-Vet-Net was an incredible opportunity to work together, and it was probably one of the first European projects in which medical and veterinarian doctors worked together in an area where they have been blaming each other about for the past 40 years."

Bruno González-Zorn, UCM, Spain

In addition to developing two new methods for the identification and characterization of SGI1 that are now available for wider epidemiological studies, the research team made a significant contribution to our body of knowledge about the importance and role of SGI1 in antimicrobial resistance. They found that the gene cluster is not only common but has spread to many *Salmonella* serotypes, and they were able to show that a clear relationship does exist between the presence of SGI1 and greater virulence.

The SGI1 project was such a success that it stimulated several applications for further collaborative research, including a direct spin-off in an EU SAFEFOOD-ERA project involving four of the SGI1 partner institutes.

The rise of resistance mechanisms

The second antimicrobial resistance project that started in 2006 looked at the rising resistance to the aminoglycoside family of antibiotics, and other emerging resistance mechanisms in Europe that pose a high risk of spreading between animals and humans.

Under the leadership of Madrid's Universidad Complutense, the project team used the unique and enormous bacterial strain collection available within the Med-Vet-Net partnership to undertake a retrospective genetic analysis of the resistance determinants in strains from both humans and animals across the farm-to-fork chain.

The ensuing results included a number of firsts.

For example, for the first time the resistance determinant gene, *rmtC*, was detected in Europe, and from a food isolate, confirming the spread of this particular determinant and implying a novel route of transmission.

The team also studied the worldwide emerging *armA* gene, which confers high-level resistance to most clinically relevant aminoglycosides. Their results indicated that while *armA* is still rare in Europe, within the EU, Poland is the country in which this mechanism is endemic in Enterobacteria, which cause a number of human illnesses, particularly gastrointestinal diseases.

In a separate study, they also found the *armA* methylase gene in food for the first time — in a multi-drug resistant *Salmonella* sample recovered from chicken meat from a supermarket in La Reunion, a French island in the Indian Ocean.

What they did not find was the *armA* resistance determinant in any animal samples indicating that animals are not involved in spread of the gene. As a result they concluded that surveillance in food-borne bacteria is crucial to determine the role of food in spread of the aminoglycosides resistant genes.

The team's investigations into the genes responsible for resistance to fluoroquinolones also bore maiden fruit with the first identification of a gene conferring resistance to the very important quinolone group of antibiotics, the so-called *qnr* gene, in a *Salmonella* Bredeney sample from an animal, and the first identification of *qnr* in *Salmonella* in Spain. They also showed that poultry could be a reservoir for *qnr*-positive *E. coli*, a particularly pertinent result given the growing concern over the emergence of fluoroquinolone resistance in the bacterium.

Overall Med-Vet-Net's work in the field of antimicrobial resistance has been an outstanding success resulting in major contributions to our knowledge and understanding of the spread and prevalence of antimicrobial resistance mechanisms in Europe.

Above all, however, Med-Vet-Net has shown that medical and veterinary institutions can work together on critical issues like antimicrobial resistance, something that, with a few exceptions, was previously inconceivable.

DETECTION & CONTROL

"If we want to go further to compare epidemiological data, we need to make sure that each country has the same level of sensitivity and uses the same method. Once this is done, we can go further and try to harmonize the reporting system between the EU countries."
Richard Thierry, AFSSA, France

Surveillance of zoonotic agents infecting or colonizing humans and animals is essential for the effective prevention and control of zoonoses. In the past such surveillance in animals has been largely passive, that is, only if a bacteria has actually caused a disease and is reported by a farmer will it be counted.

This practice does not detect the bacteria that exist harmlessly in animals but cause disease in humans. Accurate surveillance requires specific and sensitive detection systems that are effective throughout the food chain and that are rapid and cost-effective. To ensure surveillance activities are comparable throughout Europe, detection methodologies also need to be harmonized and standardized.

Control strategies need to be extremely pathogen-specific, even when the habitat, the host niche and the ecology appear similar, and developing them requires a detailed knowledge of the ecology and epidemiology of the organism and its interaction with its environment.

Med-Vet-Net inner 'networks'

Med-Vet-Net formed a number of inner 'networks' within its lifetime to focus on the detection and control of specific food-borne pathogens.

TrichiNet was established to improve detection procedures for trichinellosis. It assessed current meat inspection technology, created a European repository for standardization, and developed two new tests for the early diagnosis of pig trichinellosis.

CryptNet focused on the zoonotic parasite *Cryptosporidium*, developing a dedicated database and website with technical information on the methodologies of choice for the detection and control of cryptosporidiosis. Repositories were set up to collect, characterize and distribute *Cryptosporidium* reference material, and strategies for the harmonization of methods, particularly molecular-based, for the detection and identification of the pathogen, were developed.

ZOOPNET harmonized the detection methods and techniques used in different labs across Europe for the zoonotic parasites *Giardia* and *Cryptosporidium*, creating a common language and understanding, and helping the less experienced institutes by sharing data and expertise.

ZOOVIRNET developed state-of-the-art methodologies for the study of selected emerging zoonotic viruses: Hepatitis E , Annellovirus, and Encephalomyocarditis Virus, and Tick-borne Encephalitis. An integrated system with common diagnostic tools, sharing of information, expertise and data across Europe now exists.

WORKPACKAGES: 10, 11, 12, 22, 25, 31 & 34

PCR-based methods for detection of food-borne pathogens

An initial Med-Vet-Net project validated and standardized polymerase chain reaction (PCR)-based methods in Europe for both the detection and verification of *Campylobacter* species, *Salmonella enterica*, and food-borne viruses. The work involved establishing European working groups, a PCR database, contribution to the preparation of European draft standards, and standard operating procedures for collaborative trials.

The project team also conducted a collaborative real-time PCR trial on *Campylobacter* in chicken samples, which was awarded NordVal approval. The test is now being used in several Nordic countries for the certified retail production of *Campylobacter*-free chickens.

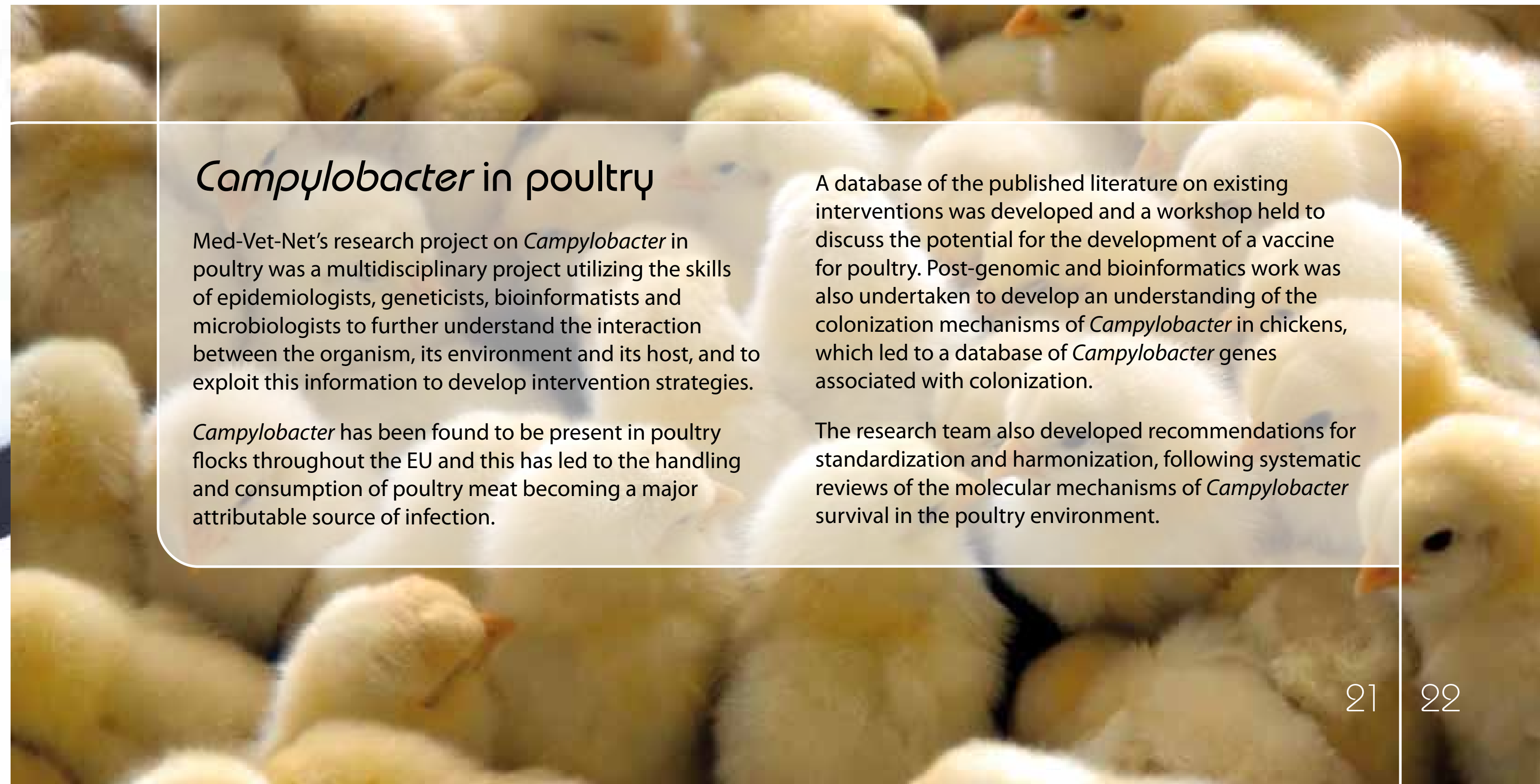
Development and application of improved diagnostics for Q-fever

Until recently Q-fever, caused by the bacteria *Coxiella burnetii*, was relatively unknown in Europe. Ruminants, such as cattle, sheep and goats, are considered the main reservoirs, shedding bacteria through placenta, milk and faeces. Humans can be infected by direct contact or inhalation of aerosols carried in dust. Thus, there is a need for rapid diagnostic methods of the disease in livestock and in the environment to limit human contamination. For many years Q-Fever was not regarded as an important zoonoses in Europe, and was therefore categorized as 'neglected'.

Med-Vet-Net brought together medical and veterinary scientists working on this neglected zoonosis for the first time, enabling them to exchange material, data and protocols. The researchers evaluated all the current tests used (both serological and DNA) in laboratories throughout Europe to detect the bacteria in human and animals, finding considerable variation. In humans, detection of antibodies using complement fixation, immunofluorescent assay (IFA) and Enzyme-Linked Immunosorbant Assay (ELISA) tests were the main methods, whereas, in animals, due to species specificity, a PCR method was generally used.

In order to further compare epidemiological data, it was essential to make sure that each country had the same level of sensitivity of their tests and used the same method. A PCR ring trial was set up to evaluate 17 different methods, resulting in good sensitivity. Several guidelines and recommendations over the use of the methods were established and have been widely distributed.

The group also determined the best typing methods to identify the incidence and prevalence of a given strain within a country, and track its movement between animals and humans, which led to recommendations for best practice in typing of *C. burnetii*.



Campylobacter in poultry

Med-Vet-Net's research project on *Campylobacter* in poultry was a multidisciplinary project utilizing the skills of epidemiologists, geneticists, bioinformatists and microbiologists to further understand the interaction between the organism, its environment and its host, and to exploit this information to develop intervention strategies.

Campylobacter has been found to be present in poultry flocks throughout the EU and this has led to the handling and consumption of poultry meat becoming a major attributable source of infection.

A database of the published literature on existing interventions was developed and a workshop held to discuss the potential for the development of a vaccine for poultry. Post-genomic and bioinformatics work was also undertaken to develop an understanding of the colonization mechanisms of *Campylobacter* in chickens, which led to a database of *Campylobacter* genes associated with colonization.

The research team also developed recommendations for standardization and harmonization, following systematic reviews of the molecular mechanisms of *Campylobacter* survival in the poultry environment.

RISK RESEARCH

Where should our research efforts regarding zoonoses and food-borne illnesses be focused? Should the disease be tackled at its source on the farm level, during the food processing stage, or via the health system once a person has symptoms and is unwell? Is one agent more deadly than another, capable of causing a widespread pandemic or epidemic? Will one be more economically-damaging than another due to health care costs and loss of time at work?

It was these questions that people examining risk research and assessment at Med-Vet-Net set out to answer. While risk analysis is a still a relatively new discipline in the veterinary and medical fields, this approach is being increasingly used within the EU by governmental institutions and industry as a tool to identify, assess and manage risk.

Impact on Public Health

At the commencement of Med-Vet-Net, Workpackage 13 looked at critically evaluating different methods for the assessment of the impact of food-borne illness on public health. They highlighted that scientific advice is relevant in all stages of the policy cycle: to assess the magnitude of the food safety problem, to define the priorities for action, to establish the causes of the problem, to choose between different control options, to define targets along the food chain, and to measure success.

Workpackage 13 concluded that in order to make better food safety decisions, informed by science and analysis, we need an integrated framework to support priority-setting decisions that combines epidemiological information on disease incidence, data on the attribution of these illnesses to foods, knowledge about the symptoms, medical treatments and health outcomes of disease, and the economic and quality-of-life impacts of these health outcomes. This combined approach enabled the concept of 'acceptable risk' to be converted to a monetary value that is easier for policy-makers to interpret and thus make decisions about interventions.

"It is a great opportunity to bring different scientists and data from different countries together to one table and to research such a huge topic all together and do something for the public."

Alexandra Fetsch, BfR, Germany

Primary Production

The complexity of processes and practices that occur in primary production has resulted in a lack of data and sophisticated modelling techniques that include the farm phase in great detail. Workpackage 14 undertook a detailed pre-harvest assessment of multiple pathogens to fill a knowledge gap that is needed to inform the rest of the production chain. A questionnaire was circulated to 18 projects which provided an overview of current pre-harvest Microbial Risk Assessment (MRA). These modelling approaches, mathematical and statistical techniques were then evaluated for their usefulness in pre-harvest modelling.

The group also reviewed model pathways and data requirements for each of the major European production types covering chicken, table-egg, turkey, pig, dairy cattle, sheep and fish production. An increased focus on the pre-harvest phase of production allows the investigation and modelling of multiple pathogens, the properties of their interaction, and the possibilities for synergy and cross-protection of control measures. It was also established that by expressing risk estimates in monetary values (e.g. production costs and reduced expenses on therapeutic drugs), the usefulness of the pre-harvest MRA was improved, especially for risk managers.

Prioritizing Hazards

From the earlier achievements of Workpackage 13, Workpackage 23 set about developing a useful tool for scientists and risk managers to be able to identify and prioritize the data needs for public health, surveillance and targeted projects at the national and European level.

The research team collected and evaluated existing data on the incidence, health outcome and costs of food-borne and zoonotic illness in each participating country, concentrating on eight pathogens involved in food-borne disease that cause gastrointestinal infection. After examining data availability, feasible approaches were chosen to calculate the disease burden and cost of illness based on disability adjusted life years (DALYs), which is a non-monetary method presuming perfect health for the entire lifespan and measures the loss due to illness.

One of the most significant problems encountered was the fact that only a relatively small proportion of people suffering from diarrhoea actually go to a doctor and, of those that visit a doctor, an even smaller proportion provide a stool sample for the pathogen to be identified. Therefore lots of cases are not recorded. In order to close gaps and collect crucial data, telephone surveys in the population were undertaken in five countries. This allowed for gauging the number of 'unreported' cases enabling risk assessors to calculate multipliers to provide a better estimate of disease burden.

Risk Assessment Models for *Campylobacter*

Although it is generally acknowledged that the main route of exposure to *Campylobacter* is chicken meat, scientists are undecided as to the best place to intervene to prevent infection. Should this be in the chicken, during the processing of the meat or with the consumer by teaching thorough cooking of meat and good kitchen hygiene? What is the most effective intervention? And what is the most costly? Risk assessment models can be used to evaluate interventions in terms of the number of people who get ill before and after the intervention.

Workpackage 24 set out initially to develop a consensus model for *Campylobacter* in broiler (chicken) meat by combining the best aspects of individual approaches from different countries in order to improve microbial risk assessment models of *Campylobacter* in Europe. This task proved impractical due to the vast differences existing in models, focus and consumer behaviour between countries. Instead, members combined their experiences to create a software tool — the *Campylobacter* Risk Assessment Framework (CRAF) that stores all the information from each country, describing what models are already in existence and what data is needed to use each model. CRAF allows users to make their own model suited for their situation and to be guided by what has already been developed.

Quantitative Risk Assessment in Pigs

Workpackage 27, 'TrichiMED', examined risk assessment by integrating animal and human case data from those regions where emergence of *Trichinella* in pigs has been followed by human cases. These data have enabled an estimation of the risk of infection to humans in areas where porcine trichinellosis has occurred. This risk assessment model will be used to inform proposed risk-based *Trichinella* regulations to be implemented in the near future.

SPECIAL INTEREST GROUPS

The success of a Network of Excellence such as Med-Vet-Net can be measured by how well it shares its knowledge and expertise, and what it does to assure its relevance and sustainability.

Med-Vet-Net recognized early the need for a strategic approach to conserving its accrued knowledge and making sure it was readily available and exploitable by the European Community beyond the 5-year period of EU-funding.

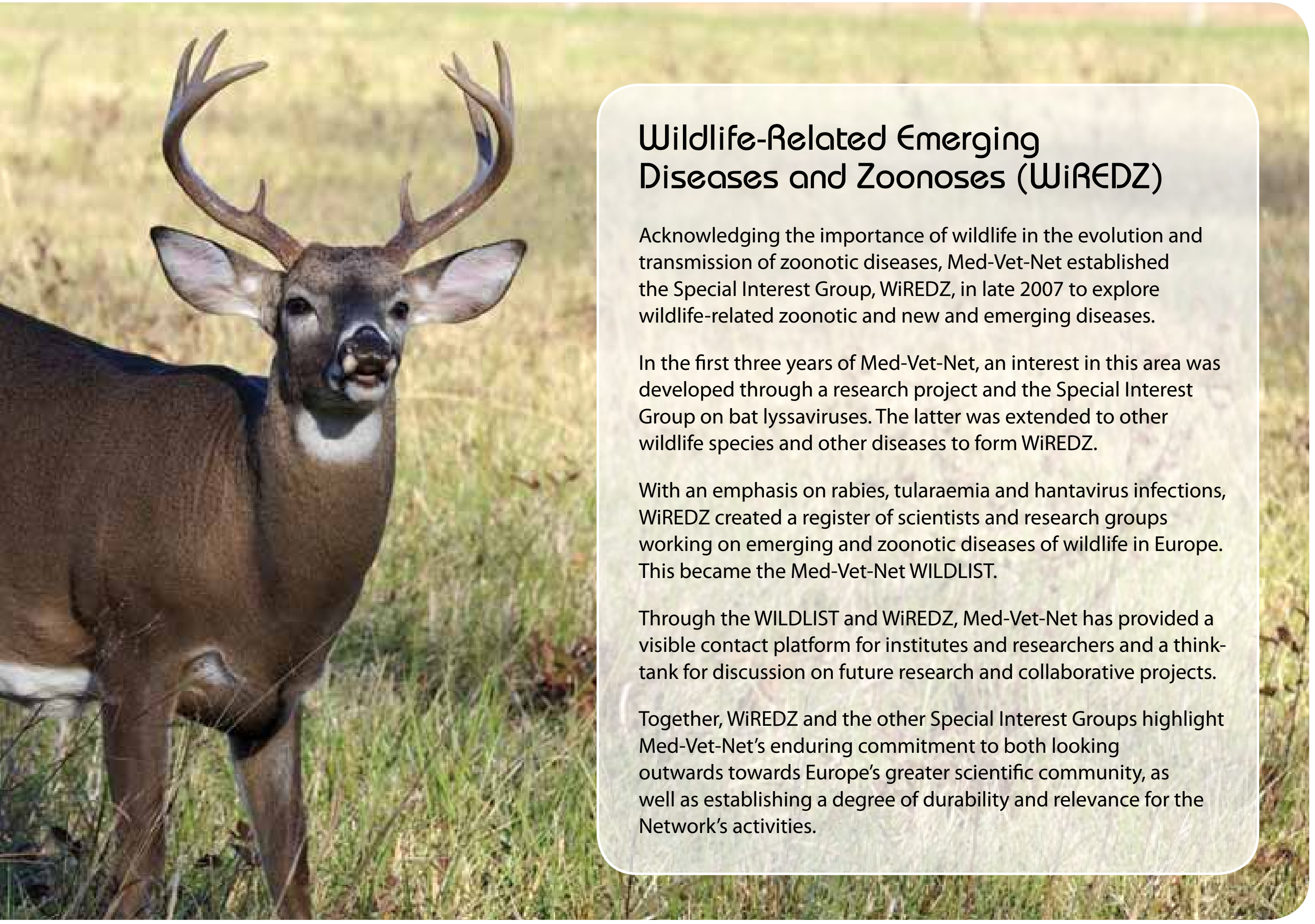
To that end, the Network developed a series of Special Interest Groups (SIGs) to maintain expertise, develop new collaborations and networks, and actively encourage external scientist participation in Med-Vet-Net through SIG activities.

The SIGs used web-based communications to establish a critical mass of expertise from within and outside the Network, retaining and curating specific information in specialized research areas via meetings, databases and knowledge sharing.

Covering a diverse range of subjects from control of bat lyssaviruses to host-pathogen interactions, and emerging wildlife-related zoonoses, the SIGs proved a highly successful mechanism for external collaboration and contributed significantly towards the development and submission of new funding proposals in their respective areas.

Indeed, the 'added value' of the collaboration between institutes and disciplines fostered by the Special Interest Groups cannot be under-estimated.

Med-Vet-Net supported five Special Interest Groups over its lifetime — all direct or related spin-offs of projects within the Network's research programme.



Wildlife-Related Emerging Diseases and Zoonoses (WiREDZ)

Acknowledging the importance of wildlife in the evolution and transmission of zoonotic diseases, Med-Vet-Net established the Special Interest Group, WiREDZ, in late 2007 to explore wildlife-related zoonotic and new and emerging diseases.

In the first three years of Med-Vet-Net, an interest in this area was developed through a research project and the Special Interest Group on bat lyssaviruses. The latter was extended to other wildlife species and other diseases to form WiREDZ.

With an emphasis on rabies, tularaemia and hantavirus infections, WiREDZ created a register of scientists and research groups working on emerging and zoonotic diseases of wildlife in Europe. This became the Med-Vet-Net WILDLIST.

Through the WILDLIST and WiREDZ, Med-Vet-Net has provided a visible contact platform for institutes and researchers and a think-tank for discussion on future research and collaborative projects.

Together, WiREDZ and the other Special Interest Groups highlight Med-Vet-Net's enduring commitment to both looking outwards towards Europe's greater scientific community, as well as establishing a degree of durability and relevance for the Network's activities.

Host-Pathogen Interactions

The Host-Pathogen Special Interest Group, developed to consider the complex and intricate interactions between host and pathogen that contribute to the outcome of disease, was a true success.

The overall goal of the Special Interest Group was to improve comparability and usability of data, thereby providing relevant data for risk assessment in food safety. In addition, the project developed links between groups working in the host-pathogen interaction area in order to harmonize research activities and facilitate the development of new projects. Such harmonization has the potential to assist not only scientists in the area of host-pathogen interactions, but also risk assessors and risk managers in the European Food Safety Authority, the European Commission and individual Member States, which have identified a need for further harmonization of research activities.

The SIG recruited interested scientists and established numerous collaborative links within and outside Med-Vet-Net. Acting as the ideal conduit for collaboration, the group also aided the development of Med-Vet-Net's highly successful research project on early host responses to *Salmonella* and *Campylobacter*, hosting joint scientific meetings that led to wider internal and external participation, significantly enriching the research.

Molecular Epidemiology of European Bat Lyssaviruses

Led by the Veterinary Laboratories Agency, the Special Interest Group on Molecular Epidemiology of European Bat Lyssaviruses grew out of one of Med-Vet-Net's first research projects. The SIG's primary goal was to coordinate and improve the database on DNA sequences from bat lyssaviruses that had been developed in the original research project.

Through additional workshops and meetings the group also strengthened the network of virologists and bat experts established by the previous Med-Vet-Net project, and was integrally involved in a successful Framework Programme (FP7) funding application for a new project to facilitate continued collaboration on wildlife zoonoses.

Emerging and Neglected Zoonoses

The Emerging and Neglected Zoonoses Special Interest Group was set up as an exploratory activity to bring together information, resources and scientists with common interest in the zoonoses that fail to attract much attention or funding, and those that could be considered potential emerging infectious agents. Such zoonoses include viral haemorrhagic fevers, enteric hepatitis viruses, hantavirus, flavivirus, MRSA, rickettsiosis and Q-fever.

The SIG team built a database of experts on different zoonoses and brought together a group of interested scientists to consider the topic of vector science and non-viral vector-borne diseases.

The collaboration also took a leading role in a successful joint proposal to FP7 (International network for capacity building for the control of emerging viral vector borne zoonotic diseases — ARBO-ZOONET).

A further intangible benefit of bringing together people with common interests was providing a voice for zoonoses that may not be currently mainstream but could well be tomorrow's priorities — Q-fever being an excellent example of such a zoonoses.

Epidemiology and Control of *Campylobacter* in Poultry

As the causes of the most commonly reported food-borne disease in Europe, the bacteria *Campylobacter jejuni* and *C. coli* are important research targets. And given the consumption and handling of poultry meat are considered the major sources of infection, it is critical we have a comprehensive understanding of the local factors of importance to colonization, including the epidemiology of campylobacters on farms.

The *Campylobacter* Special Interest Group aimed to catalogue Med-Vet-Net's expertise, skills and knowledge in this area of research, develop an electronic communication system for active debate, and provide a forum for collaboration to respond to future relevant European research calls.

The SIG was subsumed by Med-Vet-Net's final research project on the prevention and control of *Campylobacter jejuni*, which undertook to consolidate the highly fragmented information base on this most common cause of human acute enteritis.

BUILDING A SUCCESSFUL VIRTUAL NETWORK

Bringing together scientists from 15 independent research organizations and multiple disciplines, spread across 10 culturally and geographically-diverse countries, to build a successful, operational and dynamic scientific 'virtual' Network was indeed a challenge.

Med-Vet-Net rose to this challenge by successfully combining the expertise of public health, food safety and veterinary scientists with epidemiologists, statisticians, microbiologists and risk analysts, to collaborate and share their research across international boundaries.

To create the 'virtual institute', the Administration Bureau, led by the French Food Safety Agency, established the necessary management-based mechanisms, procedures and processes to support integrated scientific collaboration. It administered regular meetings of the Governing Board (comprising the CEO/Director representatives of the partners) and the Coordinating Forum (comprising the scientific institute representatives), and provided detailed tracking and reporting of the project's finances.

The Project Management team, coordinated first by the Veterinary Laboratories Agency and then by the Health Protection Agency in the UK, facilitated the scientific programme, setting the research priorities through initial joint 'Thematic Meetings' where four representatives from each partner institute gathered to review state-of-the-art research, identify the knowledge gaps and recommend the future research requirements of the Network. The team has worked tirelessly to gather the project's deliverables, and report the achievements throughout the project.

For the 'virtual institute' to operate effectively, good communication between scientists within and beyond the Network was essential. To coordinate the communication activities, a dedicated unit was set up, led by the UK-based Society for Applied Microbiology. Public and private websites were created early on to provide up-to-date information to Med-Vet-Net scientists and the wide range of network stakeholders. Over 1,500 people subscribed to the regular newsletter that showcased Med-Vet-Net's research, reviewed the outcomes of meetings and provided details of relevant conferences and events. The Communications Unit also implemented an online web meeting facility to enable Med-Vet-Net's people to meet and discuss and share information without timely and costly travel.

Such was the success of the Network's a highly sophisticated communications structure, it became the envy of many other scientific networks worldwide, and in 2008, the dedicated unit evolved into a sustainable small-medium enterprise, Science Communications Ltd.

The virtual community extended to the online sharing of scientific databases that allowed access to various strain sets and molecular data. In addition, the Special Interest Groups built extensive web-based registers of experts in the field of new and emerging zoonoses, host-pathogen interactions and wildlife zoonoses ensuring a critical mass of experts was readily available to advise authorities in times of crisis.

The dissemination of Med-Vet-Net's research achievements has been instrumental to the project's success. Five annual scientific meetings, each attracting more than 180 international delegates, to an enthusiastic exchange of science and ideas on a formal and informal basis set Med-Vet-Net apart. These meetings served to bridge the gap between 'virtual' and 'real', and proved invaluable in fortifying collaborations and friendships. And, through the early adoption of distinctive branding used for all documentation, presentations and output from the Network, Med-Vet-Net's professional and credible reputation was cemented.

The 'virtual institute', as envisaged at the beginning of the project, enabled Med-Vet-Net's 300 members to work together effectively, with a high degree of mutual trust and respect, despite their cultural and geographical separation. It also ensured one of Med-Vet-Net's major goals, to build a durable and sustainable scientific network, came to fruition.

The Med-Vet-Net Association will continue the success of existing collaborations and links and forge new frontiers in the quest against food-borne zoonotic diseases in Europe and beyond.

NURTURING SCIENTIFIC LEARNING

Collaboration and the development of skills and expertise laid the foundations for Med-Vet-Net's outstanding success as a truly European Network of Excellence. The Network decided early on that investing in its scientists and nurturing young talent was critical for enduring achievement.

Med-Vet-Net's 'virtual institute' provided an environment for scientists from a diverse range of specialized areas to share and enhance their knowledge and skills. And this capacity-building was actively facilitated through training courses, workshops, short-term missions, and PhD studentships.

When the Network began, scientists were invited to suggest topics for workshops where knowledge could be shared between partners. As some institutes were more advanced than others in a particular field, such sharing occurred through multi-national workshops, many of which specifically enabled laboratory analysis techniques such as Pulse-Field Gel Electrophoresis (PFGE) image analysis, DNA sequencing and molecular detection to be shared. Others were more general, and gave an overview of topics like bioinformatics, geographic information systems (GIS), disease surveillance and risk assessment. In all, more than 100 Med-Vet-Net and over 200 external scientists were trained during the five years of the project.

The Science Communication Internship programme was also a significant success training a total of 21 scientists from eight partner institutes (and one external), representing 10 countries (Spain, UK, Poland, France, Italy, Denmark, the Netherlands, Norway, Brazil and India).

The internship comprised four modules, each one focusing on a different aspect of science communication and running for two to three weeks. The introductory module covered all essential skills needed for successful communication such as writing, presenting, networking, interviewing, negotiating, and being assertive. The subsequent modules focused on publishing and influencing the media, engaging with stakeholders, and virtual communications. The visits and activities organized over the internship gave the participants an extremely broad insight into the field of science communication, building on their presentation and writing skills, instilling confidence, making them more aware of the needs of non-scientific stakeholders and arming them with basic skills in web design, photography and desktop publishing.

Med-Vet-Net's short-term missions and exchanges to partner institutes offered another rewarding avenue for skill development. In total, 80 scientists participated in the programme by visiting other laboratory groups for periods of two days up to three months. The exchange of knowledge mediated through the scientific missions was of great benefit to the scientific work being undertaken in Med-Vet-Net's research projects, and forged many new scientific collaborations as well as friendships. And, particularly for the younger scientists, the short-term missions enhanced awareness of Med-Vet-Net's international context.

The final building blocks of Med-Vet-Net's knowledge and skills foundations were funded PhD studentships. Support for the training of five PhD students was offered in four Med-Vet-Net's research projects with young scientists from Italy, India, Spain, Denmark and Portugal provided with an invaluable leg-up in their research careers.

Med-Vet-Net PhD

Med-Vet-Net's success was built on collaboration across international boundaries and providing opportunities for scientists across Europe to share their experience, knowledge and skills with their peers.

Dr Sara Monteiro Pires, is the perfect example of how such links between people and organizations benefited Med-Vet-Net and, through it, the European community.

As a PhD candidate, Sara left her home and large family in Portugal to take up a Med-Vet-Net funded place at the Danish Technical University (DTU) alongside researchers working on Med-Vet-Net's 'Attribution of Human *Salmonella* and *Campylobacter* Infections' project.

Although the cooler climes of northern Europe were almost too cool, the warm welcome from colleagues at DTU made for a smooth transition and Sara's Danish experience more than met her expectations.

'Even though I had high expectations, working at DTU, especially on the Med-Vet-Net project, was even more fulfilling than I expected. The working environment, and the colleagues and friends at the department very quickly made me feel at home,' Sara said.

Med-Vet-Net's human attribution project was almost tailor-made for Sara. Her PhD project, "Attributing human zoonotic infection with different animals, food and environmental sources", fit neatly within the project's gambit, and the results from both will help public health officials and governments better identify and deal with human zoonotic infections.

For governments and the food industry to properly manage intervention during a food safety scare Sara says 'it is critical to attribute human zoonotic infections to the responsible sources'. And this is only possible if the relevant data is available and accessible to authorities as they need it.

This is where Sara's and Med-Vet-Net's research comes in. 'I studied, developed and applied [different] attribution approaches to the data available from participating countries, including information on the pathogens, their sources, the routes for human exposure, animal prevalence and the number of cases of the disease in humans. With this collected information, [we developed] quantitative and qualitative models … to estimate the major causes of infection, control the pathogen and define public health intervention strategies.'

This not only makes the jobs of public health officials and the food industry easier, but is good news for the community at large.

'Food safety and measures to reduce the number of cases of zoonotic diseases are of more and more importance, which makes Med-Vet-Net's research important,' Sara said. 'I want to minimize the risk of illness and death to people from food poisoning.'

Such a focus on public health and on the protection of consumers ensures both Med-Vet-Net's and Sara's research will be of great and lasting benefit to the European community.

Ironically, Sara's career could have taken a completely different turn. 'I graduated as a veterinarian, but realized it was not the medical practice I was most interested in.'

Fortunately for Med-Vet-Net and food consumers, Sara attended a lecture on risk assessment during her studies that ignited a passion for research. 'I began to look for ways to work in this area.' But as it was not a well-known field in Portugal, Sara's studies took her out of her home country, first to Switzerland and then to Denmark to become an integral part of the Med-Vet-Net research team.

Sara says the opportunity to work with a pan-European organization like Med-Vet-Net meant she not only broadened her horizons but that she was never alone. Indeed it was the opportunity for international collaboration that first appealed to the young scientist. 'The Med-Vet-Net project allowed me not only to work and learn in the institution where I was based … but also to collaborate with people in other institutions, in different countries all over Europe.'

And that is exactly what Med-Vet-Net strived for.

THE WORKPACKAGES

Over the five years of the Med-Vet-Net project, 25 scientific workpackages were commissioned covering four strategic research areas — epidemiology, host-microbe interactions, detection and control, and risk research. In addition, three overarching workpackages fulfilled the administration, management and communication functions of the Network.

No.	Title	Leader	Location	Theme
01	Virtual Institute	André Jestin	The French Food Safety Agency (AFSSA), France	Overarching
02	Strategic Scientific Integration	John Threlfall	Health Protection Agency (HPA), UK	Overarching
03	Spreading Excellence	Peter Silley	Society for Applied Microbiology (SfAM), UK	Overarching
04	Development of a linked molecular surveillance database system for food-borne infections (PulseNet Europe)	Susanna Lukinmaa	Statens Serum Institut (SSI), Denmark	Epidemiology
05	Molecular Epidemiology of European Bat Lyssaviruses	Anthony Fooks	Veterinary Laboratories Agency (VLA), UK	Epidemiology
06	Development and application of geographical information systems (GIS) and spatio-temporal methods in the epidemiology of food-borne bacterial zoonoses	Steen Ethelberg	Statens Serum Institut (SSI), Denmark	Epidemiology
07	Pathogenesis of verocytotoxin (VT)-producing *Escherichia coli* (VTEC) infection: a new paradigm for VTEC	Alfredo Caprioli	Italian National Institute of Health (ISS), Italy	Host-Microbe Interaction
08	Identification of molecular markers of pathogenicity for *Campylobacter jejuni*	Anne Ridley	Veterinary Laboratories Agency (VLA), UK	Host-Microbe Interaction
09	The human health implication of emerging resistance to beta-lactam antibiotics in *Salmonella* and other *Enterobacteriaceae* from food animals	Frank M. Aarestrup	Danish Institute for Food and Veterinary Research (DFVF), Denmark	Detection and Control
10	Validation and standardization of polymerase chain reaction-based methods for detection and quantitative risk assessment of food-borne pathogens	Jeffrey Hoorfar	Danish Institute for Food and Veterinary Research (DFVF), Denmark	Detection and Control
11	A European network for risk assessment, detection and control of trichinellosis - in old and future member states	Pascal Boireau	The French Food Safety Agency (AFSSA), France	Detection and Control
12	A European network for the detection and control of *Cryptosporidium*	Simone M Cacciò	Italian National Institute of Health (ISS), Italy	Detection and Control
13	Integrating risk assessment, epidemiology and economics to support decision making in food safety	Arie Havelaar	National Institute for Public Health and the Environment (RIVM), The Netherlands	Risk Research
14	Pre-harvest Microbiological Risk Assessment	Danilo Lo Fo Wong	Danish Institute for Food and Veterinary Research (DFVF), Denmark	Risk Research

No.	Title	Leader	Location	Theme
21	Molecular epidemiology of *Salmonella* Genomic Island 1 (SGI1)	Dik J. Mevius	Central Veterinary Institute, The Netherlands	Epidemiology
22	Zoonotic Protozoa network (ZoopNet) — *Cryptosporidium* and *Giardia*	Simone M. Cacciò	Italian National Institute of Health (ISS), Italy	Detection and Control
23	Prioritizing food-borne and zoonotic hazards at the EU level	Arie Havelaar	National Institute for Public Health and the Environment (RIVM), The Netherlands	Risk Research
24	Comparison of *Campylobacter* risk assessment models: Towards a European consensus model?	Maarten Nauta	National Institute for Public Health and the Environment (RIVM), The Netherlands	Risk Research
25	Development and application of improved diagnostics for Q-fever	Richard Thiery	The French Food Safety Agency (AFSSA), France	Detection and Control
26	Virulotyping of new and emerging *Salmonella* and VTEC	Roberto La Ragione	Veterinary Laboratories Agency (VLA), UK	Host-Microbe Interaction
27	Harmonization of *Trichinella* infection control methods, quantitative risk assessment in pigs and an early diagnosis in humans to increase treatment efficacy (TRICHIMED)	Pascal Boireau	The French Food Safety Agency (AFSSA), France	Risk Research
28	Methods of attributing human *Salmonella* and *Campylobacter* infections with different animals, food and environmental sources	Tine Hald	National Food Institute, Danish Techincal University, (DTU), Denmark	Epidemiology
29	Surveillance of emerging antimicrobial resistance critical for humans in food, environment, animals and man	Bruno González-Zorn	Complutense University of Madrid, Spain	Epidemiology
30	Towards a combined microbiological and epidemiological approach for investigating host-microbe interactions of *Campylobacter jejuni* — CampyNet III	Thomas Alter	Federal Institute for Risk Assessment (BfR), Germany	Host-Microbe Interaction
31	Food producing animals as a potential source of emerging viral zoonoses (ZOOVIRNET)	Franco M. Ruggeri	Italian National Institute of Health (ISS), Italy	Dection and Control
32	Public health surveillance for food-borne infections: Design of epidemiological studies and applying seroepidemiology surveillance pyramid to validate the	Kåre Mølbak	Statens Serum Institut (SSI), Denmark	Epidemiology
33	Early host responses to *Salmonella* and *Campylobacter*	Riny Janssen	National Institute for Public Health and the Environment (RIVM), The Netherlands	Epidemiology
34	The prevention and control of *Campylobacter* in broilers	Diane Newell	Veterinary Laboratories Agency (VLA), UK	Detection and Control

PARTNER INSTITUTES, ADMINISTRATION, MANAGEMENT & COMMUNICATIONS

Partner Institutes

01 Technical University of Denmark (DTU), Copenhagen, Denmark
www.dtu.dk

02 Statens Serum Institut (SSI) Copenhagen, Denmark
www.ssi.dk

03 The French Food Safety Agency (AFSSA) Maisons-Alfort, France
www.afssa.fr

04 The Federal Institute for Risk Assessment (BfR) Berlin, Germany
www.bfr.bund.de

05 The Veterinary Medical Research Institute (VMRI) Budapest, Hungary
www.vmri.hu

06 Italian National Institute of Health (ISS) Rome, Italy
www.iss.it

07 National Veterinary Institute (SVA) Uppsala, Sweden
www.sva.se

08 National Institute for Public Health and the Environment (RIVM) Bilthoven, The Netherlands
www.rivm.nl

09 Central Veterinary Institute of Wageningen UR (CVI) Lelystad, The Netherlands
www.cvi.wur.nl

10 National Institute of Hygiene (PZH) Warsaw, Poland
www.pzh.gov.pl

11 Complutense University of Madrid (UCM) Madrid, Spain
www.ucm.es

12 Institute of Public Health Carlos III (ISCIII) Madrid, Spain
www.isciii.es

13 Health Protection Agency (HPA) London, United Kingdom
www.hpa.org.uk

14 Veterinary Laboratories Agency (VLA) Surrey, United Kingdom
www.defra.gov.uk/vla

15 The Society for Applied Microbiology (SfAM) Bedford, United Kingdom
www.sfam.org.uk

Project Management

16 Veterinary Laboratories Agency (VLA) (until 28/02/08) Surrey, United Kingdom
www.defra.gov.uk/vla

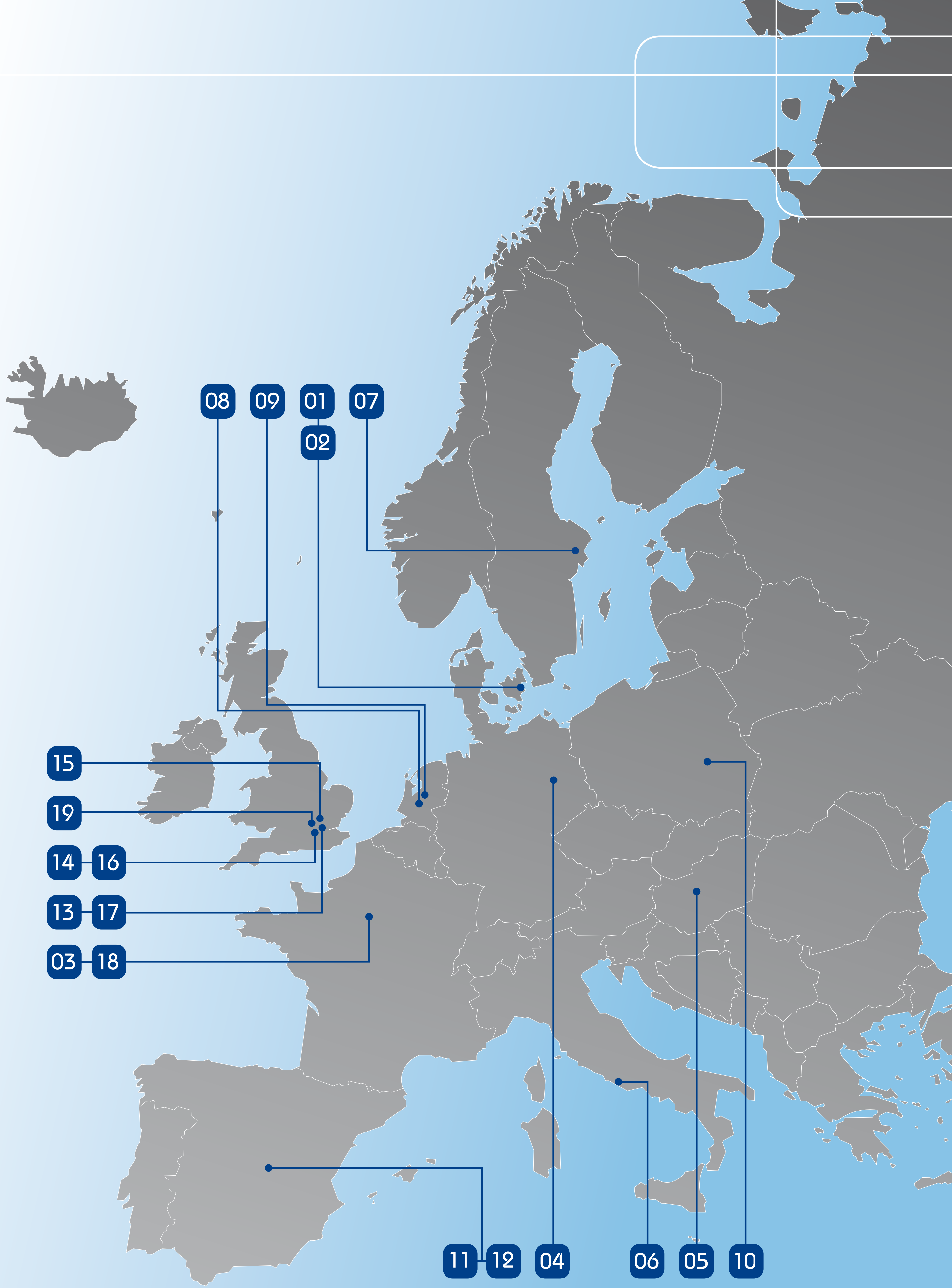
17 Health Protection Agency (HPA) (from 01/03/08) London, United Kingdom
www.hpa.org.uk

Administration Bureau

18 The French Food Safety Agency (AFSSA) Maisons-Alfort, France
www.afssa.fr

Communications Unit

19 Society for Applied Microbiology/ Science Communications Ltd Milton Keynes, United Kingdom
www.sfam.org.uk
www.sciencecommunications.eu



"After Med-Vet-Net most of us will continue working together, which has never happened before."

MED•VET•NET

A EUROPEAN NETWORK OF EXCELLENCE

www.medvetnet.org