

## FOREWORD

The EC-US Task Force on Biotechnology Research, established in 1990 and renewed in 1996 and 2001, is a unique forum for cross-Atlantic research collaboration with representatives from the US National Science Foundation, the US National Institute of Health, the US Department of Agriculture, the US Department of Energy, the US State Department and the White House Office of Science and Technology and their homologues in the European Commission in the Directorate General for Research.

In the fifteen years of existence, the work of the Task Force has spanned an enormous breadth, from vaccines for childhood diseases to methods for cleaning up polluted environments. The Task force has covered marine biotechnology, the genetic make-up of animals, bioinformatics and mapping of the human brain. Through sponsoring workshops, and other activities, the Task Force also brings together scientific leaders and early career researchers to forecast research challenges and to promote better links between scientific communities.

These proceedings summarize discussions during the EC-US Workshop on “Emerging Infectious Diseases”, which was held in Brussels 21-22 June, 2004.

The workshop focused on the past 30 years experience of successive appearances of new diseases in humans and animals and the reappearance of diseases that had declined dramatically but are again becoming serious problems for a significant part of human and animal populations.

The seriousness of the workshop topic was underscored because the workshop coincided with the SARs epidemic, which was just coming under control, and the emergence of new knowledge about the threat of potential flu pandemic of avian origin.

The workshop participants exchanged views on the global situation and their experiences in studying emerging and re-emerging infectious diseases in humans and animals. This fascinating and complex area of science, as highlighted during the workshop sessions, calls for a strengthening of a multidisciplinary and international collaboration. The workshop participants also identified research gaps, for which increased investment will be of vital importance, for predicting and controlling future disease outbreaks, such as the increased need for study of the role of wildlife as disease reservoirs. It is hoped that the discussion summarized in this document will serve as a catalyst to foster new research efforts including of cooperation and collaboration between the EU and US.

The views expressed in this document are those of the workshop participants, and do not necessarily reflect the views of the sponsors or governments.

Christian Patermann  
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## SUMMARY

Infectious diseases remain the leading cause of death worldwide. Events in the past two decades show that the battle against infectious diseases is not won. The spectrum of infectious diseases is expanding with emergent and re-emergent diseases.

Emerging infectious diseases have been defined as those which have appeared in a population for the first time or those which have existed but are spreading in prevalence or geographical range (HIV, Ebola, West Nile, Dengue, Hendra, Nipah, Hanta, influenza and recently SARS, circoviruses in pigs, iridivirus in fish and amphibians...)

Re-emerging infectious diseases are those that once were major problems globally or in particular country, and then declined dramatically, but are again becoming a problem for a significant part of the population (TB, malaria, cholera, yellow fever, rabies...).

Man and animals are in constant competition and co-evolution with their pathogens and changes of their vectors and reservoirs as well as their ecosystems. Pathogen emergence and host interactions are complex and depend on both the genetics of the host and external conditions.

Factors known to foster the emergence are: ecological changes by human activity (deforestation, reforestation, increased population density, uncontrolled urbanisation, constructions of dams, large scale mining) and natural climate change or meteorological events (El Niño, droughts, increased rainfall). Also important is the movement of pathogens or vectors by human activity (long distance travel, livestock transportation, trade - including illegal trade of wild life). Emergence can also be the consequence of microbial evolution and genetic changes in existing pathogens.

New technologies in the post-genomic era should allow us to answer questions on disease evolution; how do infections become severe or lethal? What diversity exists in pathogens and how do they interact with the host immune system? What mechanisms allow the pathogen to cross the species barrier? All these questions need to be addressed in emerging infections.

However, can we go a step earlier in the evolution chain? Can we predict emergence much earlier? Pathogens causing “new” diseases are already present in the environment and a majority of the emerging diseases are zoonotic. Using the new powerful technologies, can we search for the existing viral families in wildlife? Can we study the ecological factors that govern the ecological niches?

Against this background and within the framework of the EC-US Task Force on Biotechnology Research, a “predictive forward thinking” workshop on emerging diseases was jointly organised by the United States Department of Agriculture (USDA), the National Institute for Allergies and Health (NIAH) and the Directorate E Unit E3 Safety of Food Production Systems on 21-22 June 2004 at the Centre de Conférences Albert Borschette in Brussels, Belgium.

The workshop gathered a total of 17 recognised scientists from different backgrounds and it constituted an opportunity to address the emerging diseases from different perspectives. The scientists exchanged views on their experiences in emerging diseases for humans and animals,

discussed common and divergent opinions/points and identified areas of potential collaboration with the ultimate goal of better anticipated risks and improve efficacy of the response.

The presentations were structured into the following questions:

*What is going on with infectious diseases and what does the future likely to hold?*

*Do we know what really causes disease?*

*What is the basis for host-pathogen specificity and why do some pathogens cross into other species?*

*What would we need to know to predict the emergence and re-emergence of a disease?*

*What do we need to do or know to coordinate efforts on these topics between the EC and US?*

In each session, examples were given and the needs and areas of research were identified

### **Session 1 What is going on with infectious diseases and what does the future likely hold?**

This session allowed the participants to have an overview of all the outbreaks of viral emerging diseases that have hit the globe only in the last decade among which West Nile, Japanese encephalitis, Hanta, Dengue, Lassa Fever, Nipah, Rift Valley fever, Ebola/Marburg, Avian influenza and SARS are only a few examples. Most of them originate from animal reservoirs from which they “jumped” to humans. In animals also some viruses like the morbilliviruses have passed from one species to another or have re-emerged in countries where the disease had been eradicated long ago like foot- and- mouth disease. Many different factors facilitate the emergence or the re-emergence of infectious diseases in humans from animal reservoirs. Most of them have human activities as origin. Some of these directly change the ecosystem altering the existing balance between microbes, hosts and reservoirs: agriculture, deforestation, pollution, global warming, construction of dams. Others derived from changes in the social environment and behaviour of humans: increased population density, urbanisation, increased travel and trade, wars, drug abuse, taboos as well as break down of public health measures. Changes in certain technologies and practices can also facilitate the emergence e.g. medical practices such blood transfusions, vaccination, transplantation or changes in food production.

Several examples illustrated this session. Firstly the outbreak of HPAI H7N7 in The Netherlands in 2003 which devastated the poultry industry and caused disease in humans- mainly conjunctivitis - with one fatal case of respiratory disease. It is believed that the virus was directly transmitted from poultry to humans. The second example was the SARS epidemic. A stepwise fulfilment of Koch’s postulates led to the identification of a new coronavirus as the responsible pathogen in a differential diagnosis with the human metapneumovirus. Well coordinated international cooperation and the scientific advances of recent years were crucial to the relatively rapid identification of the new virus and the suspected animal reservoirs. SARS is an example of how fast a pathogen can be transported from one side of the planet to another in just hours.

Another example was bluetongue virus (BTV) which affects mainly sheep but the virus can be found also in cattle and some wild ruminants. BTV is considered as a model of geographical expansion due to climate change. Eradicated at the end of the 50s in Europe,

BTV was introduced in Greece in 1998 most likely by illegal traffic of sheep from Turkey. Since that date, successive introductions of different BTV serotypes have occurred through the transport of the infected vector *Culicoides* from North Africa by the prevalent winds. Modern molecular techniques have allowed the tracking of these introductions of viruses, through both the hosts and the main insect vectors, *Culicoides sp.* Italy, France and Spain are currently affected and the disease has reached unprecedented latitudes due to the geographical expansion of the vector facilitated by climate change. There are major concerns that new variants emerge due to reassortment of gene segments between viruses of different serotypes. Due to the structural homogeneity of the viruses as a group, a basic recombinant framework such as the virus-like particles can be used as the basis for a wide-ranging vaccine strategy. Thus when a newly emerged variant is encountered, basic studies on its fundamental properties can provide a platform for rapid intervention.

The last example was enteric pathogens and their dispersal in coastal waters. The particular case of cholera and the history of its different outbreaks across the globe since 1961 clearly show the high level of complexity with a multiplicity of variable and interlinked factors involved: the association of *Vibrio cholera* with copepods, the presence of zooplankton and phytoplankton, the sea surface temperature and light. In addition human activities have contributed to the transportation of *Vibrio cholera* and other enteropathogenic pathogens from one side of the planet to the other by the discharging of ballast water from transport vessels. The opportunities for spread are increased by the increase in international maritime trade in recent decades. This example shows that this high level of complexity requires a holistic approach involving multiple disciplines and to face the future an international and cross disciplinary collaboration is required.

## **Session 2 Do we know what really causes disease?**

Two examples responded to this question from different angles.

The first was Ebola and Marburg diseases, caused by viruses belonging to the filovirus family and considered two of the most virulent human pathogens that produce severe hemorrhagic fevers with mortality rates up to 90%. Both are zoonotic diseases where primates are the intermediate hosts, but the natural reservoirs are not yet known. The pathogenic molecular mechanisms and pathways that trigger the spectacular hemorrhagic manifestations and immune suppression are partially known. The endothelium is affected by direct infection and by a mediator-induced inflammatory response and the immune response is impaired by the inhibition of interferon synthesis by a viral protein. Basic research should be pursued to increase our knowledge of the viruses and their interaction with the host in order to develop both prophylactic and therapeutic tools. In addition, efforts to identify the natural reservoirs should continue. Research on these types of diseases requires BSL4 laboratories. Availability of these facilities should benefit from among others, standardisation of safety regulations, provide a combination of diagnostic surveillance and research, training of personnel, facilitating exchange of materials etc.

The second example showed the power of both studying gene expression by microarray techniques and the power of the microarray technology itself. Gene expression is used not only as a means to look at the host-pathogen interactions during infection and to understand the pathogenic process but also as a means for identifying specific pathogen and outcome associated patterns of gene expression for use in microbiological diagnosis and clinical management. Studies require first to identify the primary sources of variation and to establish

the baseline variation in healthy individuals. Variation in gene expression during infection is greater than in healthy donors. Comparative studies in gene expression in leukocytes have been used to achieve microbiological diagnosis in syndromes of suspected infectious etiology. This has been the case of diseases such as Nepal Fever and Kawasaki Disease.

### **Session 3 What is the basis for host-pathogen specificity and why do some pathogens cross into other species?**

Influenza, HIV and Hantavirus illustrated this question.

Influenza A viruses are common pathogens of humans and domestic animals namely horses, pigs, chickens and turkeys. Wild birds are considered to be the natural host. The virus contains eight gene segments of which six are highly conserved and two encode two highly variable surface proteins the hemagglutinin and the neuraminidase.

Host specificity occurs in wild birds and in endemic influenza in domestic animals and humans. However, in some cases influenza viruses cross the species barrier and replicate in other hosts. Efficient replication and transmission is required to allow a virus to become established in the new host. Rapid adaptation, by reassortment and mutation, allows the viruses to acquire the right gene constellation to establish new host ranges. Studies of the cases in which humans have been affected suggest that three models of transmission can be possible: direct transmission from the wild birds, spread through an intermediary host such as poultry and the transmission following the hypothesis of the mixing vessel. In this latter case, an intermediary host susceptible to different influenza viruses would allow for the reassortment of viral genes of the different viruses and the appearance of a new progeny with new virulence characteristics.

In the case of retroviruses, the species-specific limitation of their spread is governed by host cellular proteins that restrict early steps in viral replication as seen with human immunodeficiency viruses (HIV) and various strains of simian immunodeficiency viruses (SIV). Nonetheless multiple transfers of retroviruses across host species can be documented. The HIV are considered new acquisitions. HIV-2 is derived from SIV of sooty mangabeys (SIV<sub>sm</sub>) and may have crossed to humans on numerous occasions –estimated around 1940–without onward transmission. SIV in macaques (SIV<sub>mac</sub>) also originated from SIV<sub>sm</sub>. HIV-1 group M, N and O each appeared to come from a separate cross-over event from chimpanzee to human around 1931. Each group has become locally endemic, only group M has given rise to the global pandemic. The ability to control or stamp out infection depends on the period of infectiousness in relation to the appearance of disease symptoms or diagnosis as well as the replication rate of the virus. In this regard the perspective for the control of HIV, influenza A, SARS and BSE are different. HIV eradication will most likely not happen. In addition, the overall picture is aggravated by the potential effects of HIV/AIDS pandemic on the risks of emergence and on the control of other infectious pathogens.

The chain of events leading to large numbers of new Hantavirus was recently elucidated. El Niño-Southern Oscillations (ENSO) with mild winters with above average precipitations favoured piñon trees and grasses to produce higher levels of seeds which in turn favoured the increase of rodents and hence the risk for humans. Models were designed based on complex sets of variables and driven by environmental change and human modifications of the ecosystems which could predict with a high degree of accuracy as much as a year or more in advance the risk of this zoonotic disease. Other models have been developed for vector-borne diseases such as dengue.

## **Session 4 What would we need to know to predict the emergence and re-emergence of a disease?**

Three presentations illustrated this session.

The first focused on two relevant aspects in the recent emergence of infectious diseases which contrast with the rapid development of new molecular tools.

The first aspect refers to international trade and human habits. It is paradoxically easier to trade wildlife species which are known to be potential carriers of pathogenic organisms than food products produced according to appropriate food legislation. The increased habit in western countries to have “exotic” pets fosters this lucrative international legal and illegal trade. The most recent example was the imports into the USA of rodents from Ghana carrying the monkey poxvirus, which in turned was passed to prairie dogs at the pet retailers and the prairie dogs transmitted the virus to humans. On the other hand prairie dogs are imported without major problems from the USA to the EU though these animals can be affected by tularaemia and plague.

The other aspect calls upon a greater interaction between different fields of knowledge. Particular attention should be given to zoology when searching and identifying an animal reservoir. The literature contains numerous confusions. The most recent case is the identification of the reservoir of the new coronavirus responsible for SARS. Again, in this case there is a contrast between the rapidity by which the virus was identified and confusion in the identification of the animal reservoirs which should, at this point in time, not be acceptable. In addition, the exact phylogenetic identification of the reservoir can provide useful information with regard to shared susceptibility and for the use of laboratory models

A different case is that of the transmissible spongiform encephalopathies (TSEs). Bovine spongiform encephalopathy (BSE), an emerging disease of cattle in the 1980's was found to be zoonotic in 1996 causing a variant form of Creutzfeldt-Jakob Disease in humans. Although the abnormal form of the prion protein is involved in the cause of the disease the exact nature and the mechanism of action have not yet been clearly understood. TSEs constitute, per se, a scientific challenge because of their unique characteristics. However, the most immediate need is the availability of a live animal diagnostic test. Although diagnostic tests have become more and more sensitive, they are all performed postmortem and they all require cumbersome sample preparation.

A review of the epizootics which have re-emerged in Europe in the last decade allowed an opportunity to analyse the factors which contributed to them. Climate change favoured the expansion of the Bluetongue virus (BTV) vector *Culicoides* further north, resulting in an expanded range of the virus. Introduction of BTV from Turkey into Greece was caused by illegal trade of infected animals. Illegal trade of animal products and illegal practices such as the use of untreated swill feeding likely was the source of the FMD outbreak in England. The development of densely populated livestock areas has contributed to the expansion and the magnitude of outbreaks such as FMD, CSF and HPAI as well as increasing the volume of trade. Many of the infectious diseases of domestic animals have a reservoir in wildlife: wild pigs and boars in CSF, wild ruminants in FMD, wild birds in avian influenza, foxes and bats in rabies, badgers and ungulates in tuberculosis, boars, deer, wild rabbits and marine mammals in brucellosis. Humans, domestic animals and wildlife are in constant interaction

and therefore multidisciplinary coordinated actions between the three worlds is imperative. The clear role of wildlife calls urgently for the development of new detection and prevention systems in particular vaccines and vaccination methods for wild life.

### **Session 5 What do we need to do or know to coordinate efforts on these topics between the EC and US?**

With the example of SARS, two issues to be considered for a rapid response in emergence of an infectious agent were addressed. First, the type of vaccine that could be suitable to prevent transmission. Complementary strategies can be envisaged: vaccines based on whole inactivated virus, subunit vaccines, recombinant derived based on attenuated virus and replication-competent, propagation-defective vaccines. The best balance between efficacy, safety and speed would be the development of propagation-defective pseudovirions using previously developed infectious cDNA clones of viruses of the same family engineered to attenuate the virus. Secondly the balance between biosafety, biosecurity and international scientific cooperation. The proposal to classify SARS-CoV as a Select Agent could hamper international cooperation. A series of alternative actions are recommended to ensure biosafety of research with this virus: uniform and improved training in BSL3, develop propagation-defective or attenuated SARS-CoV to minimise hazards in some of the experiments and introduction of the requirement for laboratory licensing by competent authorities and monitoring programmes for the personnel within the laboratories.

The need for the linkage and flow between biotechnology / basic research and applied research aiming at the prevention and control of animal diseases was exemplified in three main topics: the national and international health programmes, risk analysis and diagnostic assays. Biotechnology research has allowed major advances in disease detection and preventive measures. Basic research outcomes need to be implemented and applied. The survival of one is essential to the other, and basic and applied scientists need to work together in an integrated approach.

Epidemiological models which are robust at international level can provide comprehensive scientific answers while reducing the bias of improper risk communication and perception. Interdisciplinary basic and applied research targeting in-depth analysis of specific infectious diseases can increase the capacity to prevent and respond to new emerging diseases. The development of these models requires very detailed data of multiple disciplines. In this regard, the establishment of permanent, computerised longitudinal registers could be the solution. Relational databases may include detailed follow up of multiple characteristics of human subjects that can be structurally linked to contextual data. By concentrating on specific problems and or selected strata of the population at risk, the ability to analyse new phenomena at international level will be enhanced. While the technology to operate these registers is available, the main obstacle that remains is the absence of an agreement for on ongoing data and information exchange.

A review of the different possible scenarios for the generation of pandemic influenza strains was presented. A successful pandemic strain needs an antigenically novel HA and the ability to spread from human to human. The known mechanism for the formation of pandemic strains is by reassortment, placing novel surface proteins on previously circulating human strain. This was the case with the generation of the 1957 H2N2 and 1968 H3N2 pandemic strains occurred by reassortment of a wild bird strain with a circulating human strain. However, in Hong Kong 1997 and South East Asia 2003-4 a wild bird virus infected and became adapted

to poultry as an intermediate host, and the avian virus transmitted directly to humans with reassortments. Another mechanism could combine adaptation and reassortment. Comprehensive phylogenetic studies of each gene segment of the influenza strain responsible for the 1918 pandemic have been carried out to understand its origin. The HA and NA genes may have been accumulating changes in an intermediate host before 1918. The matrix (MA) and non-structural (NS) gene segments are much conserved. The MA segment may have been retained from the previously circulating human strain. The analysis of nucleoprotein gene segment showed 170 synonymous nucleotide differences, but with only 6 amino acid differences. One hypothesis that may explain these results is that the NP was acquired from a currently unknown host whose NP is similar to currently known sequences at protein level but has separated long enough from the evolution point of view to accumulate many synonymous changes.

Global infectious disease surveillance networks and the use of newly developed assays validated to strict international criteria are crucial for disease surveillance and response. In this context, the importance of both basic and translational research in emerging diseases was again highlighted. Microarrays which were derived from fundamental research- using a variety of techniques- are a good of example of the result of translating fundamental research into applications. Their potential to detect multiple agents in a limited number of reactions makes them an invaluable tool. However, major efforts are still needed with regard to gene databases as shown in an example of their application in fish pathogens in which both bench validation and field validation were carried out. Field validation recalled the immensity of the microbial world and the limitation of existing gene databases. The use of biotechnological tools such as microarrays and comparative genomics can help early detection and help us to understand why pathogens emerge to cause disease in what may just be a bystander effect.

An overview of the emerging viral diseases that have occurred in the last three decades shows that most of them are zoonotic and have a wildlife reservoir. Wildlife, with its diversity, is an immense potential reservoir of a vast number of undiscovered viruses. Variability is an intrinsic nature of viruses, in particular in RNA viruses be it by mutations, recombination, reassortment, adaptation or acquisition of host DNA sequences. As shown with lyssaviruses and pestiviruses, viruses often share highly conserved genetics elements, regions or phenotypic characteristics within the same genus. Therefore with the use of new and very powerful tools such as microarrays together with more classic techniques, potentially emerging viruses can be quickly identified and characterized. Viral phylogenetic studies comparing the old and new strains can provide insight into the evolutionary trends and therefore some prediction about potential future virus features.

### **Main conclusions and recommendations**

Infectious diseases remain a constant and changing threat for human and animal health. With the emergence of new diseases or the reoccurrence of diseases that were previously under control, the area of infectious disease research has become only more complicated over time. Two primary themes emerged from the workshop. The first was the growing understanding of the complex interactions of disease agents with wildlife and the environment. The second major theme was the need for interdisciplinary research, specifically human and veterinary medicine, but also including other disciplines like ecology, zoology, engineering, meteorology, etc. Finally, the participants highlighted the need for improved infrastructure, improved communication between scientists, and the need for increased international collaboration.

Areas identified by the participants as priorities for research and collaboration:

- Understanding of the ecology of infectious diseases

This includes areas of ongoing priority research, including understanding the pathogenesis of infectious diseases and the identification and characterization of virulence determinants of pathogens. Three areas of research where more emphasis is needed are the better understanding of the host/pathogen relationship, including the better understanding of why some pathogens will cause disease in some species but not in other closely related species or why disease will occur in some individuals of the same species but not in others. Second, the factors related to the transmission of pathogens, the mechanisms of transmission and the role of biological and mechanical vectors. Third, the need to understand the complete ecology of the disease, including how the pathogens interact with wildlife and/or the environment, what are the requirements for adaptation of a pathogen to a new host, how they co-evolve with their hosts reservoirs. These factors need to be understood before an accurate and predictive response can occur.

- Development of vaccines

The development of biotechnology has greatly expanded the field and have provided new opportunities (rationally engineered attenuated vaccines, subunit, VLP, DNA, vectored vaccines etc.). The goal of safe and efficacious vaccines is required for both humans and animals. Particularly for domestic animals and wildlife, there is a need for marker vaccines that can differentiate infected from vaccinated animals. These DIVA vaccines are important both for disease control in domestic animals and wildlife as well as to facilitate the safe trade of animals and animal products. The need for new methods to vaccinate wildlife was also highlighted as an area of emphasis.

Given the structural homogeneity of a virus, as a group, a basic recombinant framework can be used as the basis for a wide-ranging vaccine strategy. Therefore, basic research on the fundamental properties of an emerging virus can provide a platform for a rapid intervention response when a newly emerged variant is encountered.

- Development of improved and validated diagnostic tests.

The diagnostic field is benefiting greatly from many new techniques and technologies, such as microarrays, that offer huge advances for the diagnosis of disease. Some of these techniques have the potential to identify new disease syndromes before a pathogen has been identified.

- Validated procedures dealing with biosafety.

The standards and procedures for laboratory biosafety can vary between institutions. Research goals identified were to compare biosafety systems reliability at different laboratories, assessing the impact of alternative training strategies and identifying ways to increase compliance within the laboratory. Other priority research areas include improved methods for the safe disposal and decontamination of biological material, and the use of less pathogenic microorganisms to decrease the risk of working with highly pathogenic agents.

Two major tasks have been identified to undertake the construction of a rapid information superhighway for the surveillance of infectious diseases in order to know what is out there, to be there at the right time and for the right reason. Information systems should be strategically linked to a powerful toolbox of data mining engines, which needs to be constructed and maintained collaboratively, to ensure accuracy, user operability, and availability in real time:

- Surveillance

Surveillance across the whole spectrum of human and animal diseases (risk analysis, integrated information systems, shared data bases, data and sample archives) should be supported by enhancing capacity and improved techniques. Acceptable guidelines for national and international real-time data communication and exchange should be developed. Minimum agreed information/characteristics should be collected such as human, animal, vectors and other factors, specific (sub) populations (e.g. immuno-compromised hosts) and eventually other new characteristics. Surveillance systems should be established for unidentified diseases. Densities and infection rates of reservoirs and vectors need to be estimated in view of disease prediction.

- Modelling

Interdisciplinary approaches involving biologists, modellers, and other scientists should be supported and include elements such as data mining and visualisation techniques, advanced mathematical/statistical analysis, predictive model building, classification of algorithms, interactive platforms for model application and simulation techniques. Models should be validated through extensive field testing. Data collection should be model-oriented and information subject to quality control.

### General criteria

Two general criteria have been identified transversal to all tasks, to ensure that maximum support is provided for research that is truly innovative, underpinned by genuinely collaborative and interdisciplinary spirit, and capable of producing durable and reusable outputs. Existing gaps between basic and applied sciences need to be filled so that most effective solutions for the environment and the public can be implemented. The identified criteria directly link to specific requirements that investigators need to meet in order to be granted funding.

#### 1- Interdisciplinary research networks

Inter and multidisciplinary research networks should be established and international cooperation encouraged. Emphasis should be given to comprehensive hypothesis-driven basic and applied research, to population-oriented research and the provision of input for policy.

#### 2- Infrastructure

Increased efforts should be targeted to infrastructures such as funding for permanent communication, secure data flow and prompt dissemination of new evidence. Also important is to increase capacity building for rapid and integrated response to emerging infectious

diseases, including actions for professional development and improved organization for BSL3-BLS4 facilities

Overall it is necessary to expand activities and increase collaboration for the prevention and control of emerging diseases (human and animal) through the development of a ***Global Infectious Disease Research Network***

## ABSTRACTS

### *Emerging virus infections in a changing world*

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In the past century, pandemic outbreaks of influenza and AIDS have cost the lives of tens of millions of people. These events were all caused by multiple introductions of animal viruses – influenza A viruses and SIV of birds and non-human primates respectively – into the human population. Besides these introductions causing major pandemics in humans, a large number of other virus infections have spilled over from animal reservoirs to humans or other susceptible species, resulting in considerable morbidity and mortality as “virgin soil” epidemics. The most recent examples in humans are the introduction of SARS coronavirus and influenza A viruses (H5N1 and H7N7) from the animal world, which caused global concern about their potential to be at the origin of new pandemics. Over the last decades there seems to be a dramatic increase in the emergence or re-emergence of virus threats in humans and animals worldwide. A long list of exotic names like Ebola, Lassa, Rift-Valley, Crimea-Congo, Hendra, Nipah and West-Nile is the illustration of names of just some of the places associated with the origin of viruses that crossed the species boundary to humans, with dramatic consequences in the last ten years alone. Similarly, recent mass mortalities among wild aquatic and terrestrial mammals caused by previously known and newly discovered morbilliviruses, as well as outbreaks of hog cholera, foot-and-mouth disease and fowl plague among domestic animals, highlight this trend.

Although improved detection and surveillance techniques, as well as increased media attention may have contributed to our perception of an increase in the incidence of outbreaks of virus infections, it is becoming more and more clear that major changes in our modern society increasingly create new opportunities for virus infections to emerge: a complex mix of changes in social environments, medical and agricultural technologies and ecosystems continues to create new niches for viruses to cross species boundaries and to rapidly adapt to new species. In combating this global threat, we should make optimal use of the new tools provided by the unprecedented advances made in the research areas of molecular biology, epidemiology, genomics and bioinformatics. Serious investment in these areas in the future will not only be highly cost-effective but will also save many lives of humans and animals.

### *Recent Spread of a Vector-borne Disease*

**Prof Polly Roy, London School of Hygiene & Tropical Medicine, United Kingdom**

Bluetongue Virus (BTV) is the type member of the Orbiviruses and is the most thoroughly genetically and structurally characterised of the family. BTV is vector borne by *Culicoides* sp. and its pattern of infection changes as distribution of the vector responds to global climate change. BTV is closely related to African horse sickness virus (AHSV) of horses and Epizootic hemorrhagic disease of deer (EHDV) and, *in vitro*, is able to productively infect many cell types, both insect and mammalian. Factors affecting pathogenicity of the virus however are complex with the same isolate exhibiting extensive cytopathic effect and pathogenicity in mammalian host but little if any effect in insects. The catholic tropisms, range of hosts, changing geographic distribution and large number of serotypes suggest BTV is a good model of an emerging virus. In this talk I will focus on our historical studies on the molecular phylogeny of BTV and its relationship with AHSV and EHDV. I will show that sequence variation among many isolates is restricted to one gene that encodes the serodominant

structural viral protein. In other structural proteins the conservation at sequence level is also apparent when 3D structures are solved allowing functional swaps between analogous AHSV and BTV domains. An important finding from the structural homogeneity of the viruses as a group is that a basic recombinant framework can be used as the basis for a wide-ranging vaccine strategy. Virus-like-particles that mimic the authentic virion structures provide a very efficient and safe vaccine and provide a framework for the presentation of other epitopes in addition to those encoded by BTV. Thus, basic studies on the fundamental properties of an emerging virus can provide a platform for a rapid intervention response when a newly emerged variant is encountered.

***The Global Infectious Disease Network: A Model for International Cooperation***

**Ivor T. Knight and Rita R. Colwell, Canon U.S. Life Sciences, Inc., Arlington, VA; James Madison University, Harrisonburg, VA; and the University of Maryland, College Park, MD, USA**

The connections between waterborne infectious disease and the environment illustrate the richness and reach of the scientific activity necessary to comprehend and control these diseases. Full understanding of an infectious disease extends from countries to continents and beyond, and connects medicine to many disciplines across science and engineering. The scope of research spans our entire planet, connecting flora, fauna, earth, water, and sky. With this broader perspective comes a responsibility to society to examine the full range of inputs and outcomes.

Cholera is an excellent example. It is an ancient, yet re-emerging disease, caused by an organism that depends on interactions with humans and a complex aquatic ecosystem. The current characterization of the ecology of cholera includes global weather patterns, aquatic reservoirs, phages, zooplankton, collective behaviour of surface -attached cells, and an adaptable genome, together with the bacteria and host.

Connecting cholera to climate exemplifies the complexity of today's science, requiring insights from international teams of physicians, microbiologists, epidemiologists, statisticians, ecologists, remote sensing scientists, and sociologists. Most recently, new insights into the complex biology of *Vibrio cholerae* have come from the exciting new field of genomics. Completing the full genome sequence yielded surprises and confirmed previous results, further demonstrating the complexity of the organism and giving us more tools to better predict outbreaks and epidemics.

Working closely with local authorities, scientists, and industry in both developing and industrialized areas, worldwide, it is imperative that a network be implemented for the prevention and/or mitigation of emerging and re-emerging infectious waterborne disease. This requires a multi-dimensional understanding of the complex interactions (bio complexity) between biological systems, including humans, and the global physical and chemical environment. Such diseases are driven by outside forces, in addition to classical epidemiology, that include climate, worldwide movement of people and goods, sanitation, personal hygiene, and malnutrition. Understanding the role of these forcing functions as an holistic system can lead to the development of models and practical applications for the prediction, prevention, treatment, and/or elimination of these diseases and, in tandem with vaccination programs, could improve the effectiveness of vaccines.

*An International Network for Research and Education in Infectious Diseases, Water, and Health* would address practical and appropriate aspects of eliminating, mitigating, or adapting to emerging and re-emerging infectious diseases globally, with emphasis on waterborne pathogens and their effect on human health, as well as availability of safe water.

***Hemorrhagic fevers caused by Marburg and Ebola viruses***

**Hans-Dieter Klenk, Institute of Virology, Philipps-University, Marburg, Germany**

Marburg (MBGV) and Ebola (EBOV) viruses belong to the most dangerous human pathogens causing severe hemorrhagic fevers with mortality rates up to 90%. They form the filovirus family, a group of enveloped, non-segmented, negative-strand RNA viruses. Their genome is about 19,000 nucleotides in length and encodes 8 structural proteins. 4 of these-NP, VP35, VP30, and L- are constituents of the ribonucleoprotein complex and responsible for RNA replication and transcription. VP40 and VP24 are matrix proteins and play a major role in virus assembly. GP is a membrane glycoprotein that forms the envelope spikes and mediates virus entry into the cell. Expression of EBOV GP which is encoded by 2 overlapping reading frames requires transcriptional editing. Most GP mRNAs are not edited, and they direct synthesis of a non-structural glycoprotein sGP, which is secreted from EBOV-infected cells. sGP is not observed with MBGV, since GP is transcribed here from a single open reading frame. GP as well as sGP undergo a series of co- and post-translational modifications including N-glycosylation, O-glycosylation, and acylation. In addition, both glycoproteins are processed by cellular proteases. GP is cleaved in the TGN by the pro-proteinconvertase furin into the disulfide-linked fragments GP<sub>1</sub> and GP<sub>2</sub>. sGP is also cleaved by furin. The entire ectodomain of GP<sub>1,2</sub> is released in soluble form at the cell surface by the metalloprotease TACE.

The pathogenesis of filovirus infections is only partly understood. The disease is caused by marked replication of virus together with immune and vascular dysregulation. In this way, it is as much an immune syndrome as a virus-induced vascular disease. One of the mechanisms underlying impaired immune response is the interferon antagonism of VP35 which has been shown to inhibit IFN synthesis. Soluble viral glycoproteins, in particular the released ectodomain of GP and perhaps sGP, may also have immune-modulatory functions, since they have been shown to effectively bind antibodies that might otherwise be protective. The disturbance of the blood-tissue barrier, which is controlled mainly by endothelial cells, is another important factor in pathogenesis. The endothelium appears to be affected in two ways: directly by infection with filoviruses, leading to activation and eventual cytopathogenic replication, and indirectly by a mediator-induced inflammatory response. Such mediators seem to originate from filovirus activated cells of the mononuclear phagocytic system which are the main target cells of these viruses. Several groups have shown that the cytotoxicity of EBOV for endothelial cells depends on the level of GP expression. Studies with a recombinant EBOV displaying a modified editing site in the GP gene showed that by down-regulation GP expression, editing is an important control mechanism for cytotoxicity. The establishment of infectious EBOV cDNA clones, which was based on preceding work with artificial minigenome systems, will be instrumental for future studies on replication and pathogenesis of these viruses and on the development of therapeutic and prophylactic interventions.

***Surveying Gene Expression in Leukocytes: Host Response and Classification of Infection***  
**Stephen Popper, ScD, Stanford University School of Medicine, CA, USA**

Sequencing of the human genome, development of cDNA microarrays, and advances in computational analysis, present the possibility to gather data about complex systems and interpret these findings in meaningful ways. Microarrays have been successfully used for in vivo studies of human cancer, including ones that focus on cells of immune origin; these studies identified gene expression patterns that define biological processes and distinguish pathological and clinical outcomes indistinguishable by traditional methods. We propose that the use of cDNA microarrays can be extended to identify host gene expression “signatures” in the context of clinically-based studies of infectious diseases and will allow us to identify pathogens or classes of pathogens, segregated by phylogeny or biological processes, as well as targets from which to develop reagents for diagnosis and treatment of infectious diseases.

In a study examining the transcription profiles of circulating leukocytes in healthy volunteers, we demonstrated that the overall variation in gene expression in the blood of healthy donors is lower than in infected febrile donors, as well as in leukocytes isolated from patients with lymphoma. Only a few of the genes measured in this study exhibited significantly more variation between individuals than within individuals (“intrinsic” genes), indicating that person-to-person differences are unlikely to affect our ability to identify gene expression “signatures” common to classes of infection. We also identified clusters of genes with coherent biological themes that appear to be characteristic of cell subsets, gender, and time of day – demonstrating the potential for uncovering fundamental biological processes among the gene expression patterns found in blood samples, despite the inherent complexity.

In a second study set in Kathmandu, Nepal, we compared gene expression patterns in whole blood samples obtained from individuals who appeared in the local emergency room with fever, and subsequently had a positive microbiological diagnosis. Examination of the data indicated that the species of the infecting organism constituted an important, though not universal, component of the variation in gene expression. Most noticeably, 6 of the 7 bacterial infections caused by the etiologic agent of scrub typhus, *Orientia tsutsugamushi*, had a distinct gene expression profile marked by particularly strong expression of genes related to aspects of the cellular immune response. In addition, using statistical methods developed for analysis of microarray data, we were also able to identify a set of genes which led us to correctly predict infection with *Salmonella typhi* 83% of the time.

A study of Kawasaki Disease is also enabling us to test the utility of profiling host gene expression patterns in a setting where an etiologic agent has not yet been identified. Kawasaki Disease (KD) is a leading cause of pediatric acquired heart disease, and is characterized by an acute, self-contained vasculitis, sometimes leading to formation of coronary artery aneurysms. The epidemiology is strongly suggestive of an infectious process, but the lack of a known pathogen and similarities in clinical presentation to other diseases leads to delays in diagnosis and treatment. Early results from profiling gene expression patterns in whole blood have allowed us to identify sets of genes whose expression in acute KD differs when compared to several “look-alike” infections, including adenoviral and streptococcal infections.

In summary, we have conducted a series of studies that have demonstrated several necessary conditions for the application of host gene expression profiling during infection: variation in

gene expression among healthy donors is low, and person-person differences do not dominate the profiles, obviating the need for each individual to serve as his or her own control; we can identify biologically coherent patterns of gene expression in multiple studies, and microbiological diagnosis is a significant factor determining the degree of variation in gene expression. Continued development of technologies leading to higher throughput and lower costs, and new analytical approaches, promise to promote the feasibility of profiling of host gene expression as a method of identifying potential diagnostic and prognostic markers in infectious diseases.

### ***The Origins and Host Specificity of Type A Influenza Virus***

**David L. Suarez, U.S.D.A., A.R.S., Southeast Poultry Research Laboratory, Athens Georgia, USA**

Type A influenza viruses are common pathogens of humans, pigs, horses, chickens, and turkeys. Although the virus is endemic in a number of different species, all type A influenza viruses originate in wild birds, primarily ducks, gulls and shorebirds. Influenza viruses have eight gene segments, with six segments coding for conserved internal proteins and two coding for extremely diverse surface proteins, the hemagglutinin (HA) and neuraminidase (NA) proteins. Influenza viruses are generally promiscuous and many replicate in both birds and mammals. Introductions of influenza viruses from the reservoir host probably occurs frequently, but rarely do these viruses replicate or transmit well enough in the new host to cause either disease or become endemic. On rare occasions an influenza virus may contain the right constellation of genes to allow sufficient replication and transmission for the virus to become established in a new species. These viruses may cause disease and are characterized by a high evolutionary rate as the virus becomes adapted to the new host species. If a virus continues to replicate in the new host species, enough genetic changes accumulate so that it will no longer replicate well in the original host species. For zoonotic spread to humans, 3 models of spread have been proposed. The first is direct spread of virus from wild birds to humans. Only a few possible examples of this model have been documented including a case of conjunctivitis with an H7N7 AI virus. However, humans have been experimentally infected with duck influenza viruses, but few showed clinical symptoms of disease. The second model is spread through an intermediary host. Several examples of avian influenza viruses infecting poultry that have then spread to humans have been documented, including recent outbreaks of H5N1 in Hong Kong, Viet Nam and Thailand, H7N7 in the Netherlands, and H7N3 in Canada. A wide range of symptoms were observed including conjunctivitis, influenza-like illness, and death. Considering all three outbreaks together, over 100 humans were documented to have been infected. Although the virus replicated well enough in humans to cause disease, human to human transmission was uncommon. The intermediary model can be important by either allowing mutations of the virus that increases the risk of human infection or it can just increase the number of humans that come in contact with the virus. The third model of spread is the mixing vessel hypothesis where an intermediary host susceptible to two different influenza viruses can allow the reassortment of viral genes with the creation of progeny virus with new virulence characteristics. For example, the human H3N2 influenza virus, first observed in 1968, was a reassortant virus with both avian-like viral genes including the hemagglutinin gene, and human H2N2 influenza viral genes. This reassortant virus could replicate and transmit well in humans, and because immunity to influenza is primarily by antibodies to the hemagglutinin protein, the entire human population was susceptible to this new H3 virus. This “antigenic shift” led to a human pandemic. The most commonly suggested “mixing vessel” is in swine, since they have both avian-like (2,3) and human-like (2,6) influenza receptors, and can be infected with both avian and

human influenza viruses. However, the mixing vessel hypothesis remains unproven. Regardless of the mechanism, experts predict that the human population is overdue for another antigenic shift.

### ***HIV and AIDS in Relation to Other Pandemics***

**Robin A. Weiss, University College London, United Kingdom**

Most epidemic viral diseases of humans have an origin in animal reservoirs and have switched host species in recent times, that is, during the last 15,000 years. Other endemic viral diseases and persistent viral infections may have co-evolved with the host, eg, human herpesviruses 1-8. It may even be to the host's selective advantage to maintain some persistent infections. Ecological, environmental and behavioral parameters will influence both the risk of the initial cross-species infection event and also the chance of the virus taking off and spreading among individuals in the new host population. The ability to control or stamp out infection in the human host depends on the period of infectiousness in relation to the appearance of disease symptoms or diagnosis as well as the replication rate of the virus. The success of the HIV pandemic will be compared to the limited spread of Ebola, BSE/vCJD and SARS and the genetic diversity of HIV to that of influenza A virus. Species-specific limitation of the spread of retroviruses is exemplified by HIV and various strains of simian immunodeficiency virus (SIV) which is governed by host cellular proteins that restrict early steps in virus replication. Nonetheless multiple transfers of retroviruses across host species can be documented including the origins of HIV and human T-cell leukemia virus type 1; that is why there is concern over the potential spread of animal retroviruses to humans via contaminated vaccines and by xenotransplantation. It is difficult to predict whether a virus is likely to increase or decrease its virulence upon cross-species infection because we only notice those infections that are pathogenic. Finally, the potential effects of the HIV pandemic on the risks of emergence and control of other infectious pathogens will be discussed. For example, in immunocompromized hosts, the persistence of otherwise acute viral infections (eg measles) is greatly extended, live 'attenuated' vaccines (eg vaccinia) can cause severe disease, and pathogens from zoonotic or environmental sources (eg *Mycobacteria*) may more rapidly evolve to become endemic in the human population.

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### ***Predictive Understanding of Human Risk to Emerging Viruses***

**Dr. Terry Yates, University of New Mexico, Albuquerque, NM, USA**

The epidemiologies of many zoonotic or vector-borne diseases occurring in humans, such as Hantavirus Pulmonary Syndrome, Dengue, Hemorrhagic Fevers, Schistosomiasis, and Malaria are determined in large part by the ecology of the carrier or vectors. Alterations of the

environment and climate change are thought to have led to the recent emergence or increased incidence of many of these diseases throughout the world. The recent recognition of large numbers of new Hantavirus in the United States and South America are thought to be examples of global climatic effects that may have led to ecological conditions favourable to a reservoir species. The epidemiology of hantaviral disease is a direct reflection of the ecology of the small mammal carriers and yet the contributing factors that lead to major population changes in these vectors have only recently been elucidated. Unusual climatic conditions due to the El Niño-Southern Oscillations (ENSO) phenomenon are thought to have led to explosions of wild rodents in semi-arid regions affected by ENSO; for example, prior to the 1993 and 1997 outbreak of Hantavirus in the South-western US. The preceding winters were mild with above average precipitation in the Southwest. Piñon Pine trees and annual grasses produced much higher than normal levels of seed production resulting in rodent population increases and increased risks to humans. Additionally, a growing body of evidence suggests that this phenomenon (ENSO), may also drive the outbreaks of rodent populations in other parts of the world. Similar models based on climate fluctuations have been proposed for increases in human cases of Dengue fever and many other vector-borne diseases. The association between climate change, human induced landscape changes, and ecology is complex and important at many spatial and temporal scales. Modelling and understanding these associations will have implications not only for human health but economics and security as well. The current paper will explore the potential of developing predictive models of human risk to zoonotic diseases based on complex sets of variables. Specifically, models driven by environmental change and human modifications of the ecosystem will be explored. Examples based on Human Pulmonary Syndrome and Bolivian Hemorrhagic Fever will be explored in both North and South America. It will be shown that risk to humans can be predicted with a high degree of accuracy as much as one year or more in advance. The potential of these methods for predicting risk from other naturally occurring or introduced diseases will be discussed.

***Biotechnology research and emergence of new diseases: Perceived versus known risks***  
**Dr François Moutou, Agence Française de Sécurité Sanitaire des Aliments, France**

Whatever the tools used for the epidemiological surveillance of potentially new diseases emergence, the way they will be used depends really of the way the risks linked to these diseases are foreseen, i.e. following more the perceived risks than the known factual risks, which may prove to be different.

Two sets of examples may illustrate this situation.

Cross Atlantic trade is interesting, as it is quite well known. In the way from East to West (Europe and Africa to America), it is possible to notice that it seems much more difficult to trade cheeses from Europe than alive wild caught rodents for exotic pet trade from Western Africa to America. The epidemics of human monkey pox that happened during spring 2003 in USA shows, however, that some of these African giant pouched rats (*Cricetomys spp.*) or dormice (*Graphiurus spp.*) may be more dangerous than “Camembert”, or at least not in the same way.

In the other way, (America to Europe), the ban on hormone bred beef or on GMO food is to compare to the large import of wild caught black-tailed prairie dogs (*Cynomys ludovicianus*), also sold as pet in Europe, even when knowing that their populations were infected by plague or by tularaemia, two diseases associated with bioterrorism. This prairie dog trade was eventually stopped in 2003 because of the monkey pox episode!

The other example is looking at and comparing the balance between bio molecular research on new virus or bacteria and the identification of animal species that could be seen as the reservoir of the virus or bacteria. In 2003, the SARS epidemic was a good support for these comparisons. The rapidity of the isolation, classification, nucleotide analysis, vaccine research linked to SARS CoV strains is to put in front of the confusion associated with the identification of an animal reservoir. In many press releases, but also in more scientific papers, many of the mammals listed were called « exotic species » when they are nearly all native to China. They are just exotic to western scientists. Then the confusions between “civet”, “civet-cat” and “cat”, or between “raccoon”, “raccoon-dog” and “dog”, much more easy to identify than two virus strains, were quite interesting, but not very helpful to trace the reservoir.

As always, whatever the tools, the way they are used is more important than their own qualities. This is more sociology than just medicine or epidemiology.

### ***Techniques and Challenges in the Diagnosis of Prion Diseases***

**Larry Stanker and John Mark Carter, USDA Agricultural Research Service, Western Regional Research Center, Foodborne Contaminants Research Unit, Albany, CA, USA**

Transmissible Spongiform Encephalopathies (TSEs) are fatal transmissible brain diseases that occur in animals and humans. The human diseases include Creutzfeldt - Jakob disease (CJD), Gerstmann-Sträussler Scheinker syndrome, Fatal Familial Insomnia, kuru, iatrogenic CJD, and new variant CJD. Animal TSEs include scrapie in sheep, Chronic Wasting Disease (CWD) in cervids, Transmissible Mink Encephalopathy (TME), and Bovine Spongiform Encephalopathy (BSE), as well as TSEs in cats (Feline Spongiform Encephalopathy) and in exotic ungulates. The causative agents for these diseases are prions. Prions appear to be composed solely of protein. Although the product of a single gene, prion protein (PrP) may exist in at least two forms: a non-infectious conformer referred to as normal PrP (PrP<sup>c</sup>), and an infectious form referred to as PrP<sup>Sc</sup>. The function of normal PrP<sup>c</sup> is unclear. It is a glycoprotein anchored in membranes by a GPI structure. Its tertiary structure contains three alpha-helical regions and a small beta-sheet region. While a crystallographic solution for the infectious form is not available, circular dichroism studies suggest that PrP<sup>Sc</sup> has relatively less alpha-helical structure and more beta-sheet. PrP<sup>Sc</sup> appears to aggregate and to have the ability to convert normal PrP<sup>c</sup> to the infectious PrP<sup>Sc</sup> form. Transmission of BSE disease in bovines occurs via consumption of PrP<sup>Sc</sup> contaminated feed, and transmission to humans (as vCJD) occurs via consumption of contaminated beef. No pre-clinical diagnostic test (excluding a third eyelid test in sheep) is available for TSE diseases. Diagnosis is based on clinical observations and histochemical examination of brain. Typically, spongiform degeneration is observed surrounded by plaque-like aggregates of immunoreactive PrP<sup>Sc</sup> at the rim of the vacuoles. Further complicating the production of effective diagnostics for TSEs has been the difficulty in obtaining antibodies that can distinguish between PrP<sup>c</sup> and PrP<sup>Sc</sup>. In the EU and US, all tests currently approved for BSE screening are post-mortem procedures that measure PrP<sup>Sc</sup> in brain. The first generation of approved tests are based on the observation that PrP<sup>c</sup> is susceptible to digestion with proteases, whereas PrP<sup>Sc</sup> is resistant. In these tests, brain samples are prepared and digested with proteinase K to remove PrP<sup>c</sup>. Then PrP<sup>Sc</sup> that remains is detected using a non-specific anti-PrP antibody. A second-generation test, the Conformation Dependent Immunoassay (CDI), does not rely on proteinase K digestion. Instead it is based on antibodies that bind an epitope exposed in PrP<sup>c</sup> but hidden in PrP<sup>Sc</sup>. Improved diagnostics clearly are needed. To supplement existing clinical diagnostics and post-mortem tests, live animal tests are essential for improved herd management.

Furthermore, tests with greater sensitivity would further strengthen efforts to eliminate prion-contaminated material from feeds and food. Progress in development of sensitive non-immunochemical and immunochemical tests for PrP<sup>Sc</sup> detection and characterization will be discussed.

E.U.-U.S. Task Force on Biotechnology Research "Predictive, Forward Thinking on Emerging Infectious Diseases" June 21-22nd in Brussels

***The role of wild life and other parameters on the emergence and reemergence of animal diseases***

**Prof. JM. Sánchez-Vizcaíno, Facultad de Veterinaria, Universidad Complutense de Madrid, Spain**

In the last few years a succession of serious epizootics of highly contagious animal diseases occurred around the world. These included Foot and Mouth Disease, Avian Influenza, Classical Swine Fever, African swine fever, and Bluetongue. New diseases, like BSE and SARS, have also appeared which affected animals and human health.

These diseases have caused the slaughter of millions of animals at great economic cost and, at the same time, it raised a considerable public and media alarm. Many of the concerns relate to the perception of lack of security on animal health and food products. This situation created a great difficulty to the human and animal health authorities around the world.

A review of the different parameters that probably caused this situation as well as scientific and technical possible solutions will also be reviewed. The economical and technical impact, the climate changes, old vector in new locations and in particular the role of the wild life on the emergence and re-emergence of animal diseases will be specifically discussed. How can we detect in advance these potential danger situations? Are technical methods available today to prevent these situations? How can we monitor such events? How can we know where are the potential sources of disease in wild animals? These are some of the questions we should try to answer.

Such a review would bring together, in a European and American context, the scientific data and individual thinking on these matters to look for possible solutions in the near future.

***Strategies to develop vaccines in emergency scenarios: the SARS example***

**Luis Enjuanes, Department of Molecular and Cell Biology. Centro Nacional de Biotecnología, CSIC. Campus Universidad Autónoma de Madrid, Spain**

During the emergency or re-emergence of an infectious agent a fast response is required for the treatment of the infection and to prevent spreading of the disease. Two issues will be addressed: the type of vaccine that seems more suitable to prevent the transmission of the infectious agent, and the balance required between biosafety, biosecurity and national and international cooperation. Severe Acute Respiratory Syndrome (SARS) was firstly detected in Guangdong province, China. It has been proven that the etiological agent of SARS is a new coronavirus (CoV) with the acronym SARS-CoV that has infected more than 8000 people and caused 10% mortality. SARS-CoV will be used as an example.

We have to be aware that each virus is unique; therefore the correctness of each prediction has to be tested case by case. At least three complementary intervention strategies, vaccination,

immunotherapy, and antivirals are required to protect against emerging virus such as SARS-CoV. In addition, diagnostic kits for the identification of infected individuals at very early steps of the disease are required. Complementary strategies to develop a vaccine could in principle be proposed to guarantee the success: (i) vaccines based on whole inactivated virus, (ii) subunit vaccines, (iii) recombinant derived vaccines based on attenuated viruses, and (iv) replication-competent propagation-defective vaccines. We understand that one of the strategies with best balance of efficacy, safety, and speed of the response is the development of propagation-defective pseudovirions using previously developed infectious cDNA clones of viruses from the same family, in which modifications to attenuate the virus have been engineered.

For achieving the primary objectives of these projects, the availability of an adequate preclinical setting, including animal models, as well as the access to relevant clinical samples are absolute preconditions. In all strategies, several key criteria (efficacy, safety, cost) have to be taken into account.

The development of infectious coronavirus from a cDNA clone has facilitated coronavirus reverse genetics to study gene function and the use of coronavirus genomes replication-competent and propagation-defective as expression vectors. Vector biosafety has been improved by identifying and relocating the genome-packaging signal. This type of vectors could be of high interest for the development of protection against coronavirus induced disease, particularly for SARS.

Emerging viruses represent a risk for the society and a balance between biosafety, biosecurity, and national and international cooperation has to be achieved. In the States, the CDC has recommended (June 2004) that SARS-CoV should be classified as a Selected Agent. Public comment within 30 days has been solicited before the decision to implement this recommendation is finalized. A set of internationally recognized coronavirus experts have presented recommendations to improve the biosafety in the research with SARS-CoV and, at the same time we have strongly suggested that SARS-CoV should not be designated as a Select Agent in order to preserve the national and international collaborations to develop vaccines, immunotherapeutical strategies and antivirals to combat SARS. If SARS-CoV is designated as Select Agent, then research on this virus by most NIH-funded laboratories in the USA and their collaboration with European Commission founded projects would be terminated or seriously delayed. This could result in failure to develop sensitive diagnostic tests, drugs to treat SARS, or vaccines to prevent SARS. In case of another global outbreak of SARS, all these tools will be needed to protect the population.

The recommendation to designate SARS-CoV as a Select Agent was made to protect public health. In considering whether an infectious agent should be designated as a Select Agent it is important to distinguish between Biosafety, which can be controlled by operation of laboratories under clearly defined, improved operating procedures for working safely with SARS-CoV, and Biosecurity, which is directed toward limiting the possible exposure of the population to the infectious agent and preventing the intentional spread of infectious agent from laboratories. A variety of wild animal species in Asia provide a reservoir for SARS-CoV, and the virus continues to be sporadically transmitted from animals to humans, so a new epidemic with human-to-human spread of infection could occur at any time. The designation of SARS-CoV as a Select Agent cannot prevent the virus from spreading from animals to humans.

Several ways to assure the safety of research on SARS-CoV at the BSL3 level without designating the virus as a Select Agent are recommended, such as: (i) to provide uniform training in safe Biosafety Laboratory, (ii) improving BSL3 training for SARS-CoV research, (iii) development of propagation-defective or attenuated SARS-CoV to minimize hazards of many types of experiments, (iv) introduction of the requirement for laboratory licensing by competent authorities (WHO, CDC, NIH, etc.), (v) monitoring programs for all workers in SARS-CoV laboratories, (vi) Medical emergency plans and inspections.

The experience gained with SARS-CoV could be applied to other emerging viruses to improve the efficacy and effectiveness of the response through the European Centre for Disease Prevention and Control, CDC, and other international institutions. We should encourage many talented researchers worldwide to contribute their expertise to conquering the disease.

***Applied Research and Epidemiology – Are They Related to Biotechnology Research of Preparedness for Emerging Animal Diseases?***

**Dr. Mo Salman, College of Veterinary Medicine and Biomedical Science, Colorado State University, Fort Collins, CO, USA**

The term “Applied or Translational Research” has different meanings to various scientists and decision makers. This term is one of the two pillars of sound biotechnological research. Basic research, as one of these pillars, requires application of findings. Applied research by definition requires hypothesis testing as well as an objective assessment of the underlying problem. Applied research for animal diseases is closely related to the discipline of epidemiology. Epidemiology by definition is applied research with the aim to prevent and reduce the impact of the disease on animal and human populations.

This presentation addresses the link of biotechnology research for animal diseases to applied research using three main topics: National and International Animal Health Programs, Risk Analysis Process, and Diagnostic Assays. Each of these topics demands the use of biotechnological advancement that we have gained in recent decades. Unfortunately, applied research scientists who are engaged in these topics have not optimized such uses.

For each of these topics, existing problems and challenges are presented with demonstrations of the value of the link between biotechnology and applied research.

Biotechnology has advanced the methods for the detection of animal diseases and preventive measures. There are however limited applications of these techniques in real-life situations.

The presentation’s conclusion is that both pillars are required for successful and useful research findings that can advance our knowledge in battling diseases and emerging diseases in animal populations. There is a need for integrated disciplinary approaches to deal with animal diseases. These approaches should involve both basic and applied research scientists in order to optimize the available resources and for better outcomes. Both basic and applied research disciplines require consistent challenges for improvement and refinement. Cross-culture of basic and applied scientists is needed to maintain interest and funding opportunities.

***From research to implementation: the challenge of international disease registers and data exchange***

**Dr Fabrizio Carinci, Directorate of Health Planning, Ministry of Health, Italy**

Emerging diseases represent an emerging problem in modern world. SARS made history as the first epidemics of the globalisation era; few years ago AIDS introduced a series of health threats whose real long-term implications are still to be ascertained.

Under these conditions, the scientific community has demonstrated an increased capacity to respond to new emergencies through the rapid organization of research networks and cooperative studies. Such a positive trend has been enhanced by more effective support for research provided by governments and international institutions under the pressure of health emergencies. As a result, we have probably known the biologic mechanisms of AIDS and SARS more rapidly than ever before.

However, this is only part of our work. We too often tend to forget that a crucial role in the equation of emerging diseases is played by cultural, social, and economic factors. Such components do not only affect the immediate spread of the disease - a critical point during emergencies - but they will continue to exert a strong influence in the long-term, determining geographical and temporal patterns that can become quite unpredictable.

At the same time, we need to be aware that health threats are and will continue to be amplified by the constant presence and competing interests of commercial media.

To avoid that substantial biases are introduced in the identification of health priorities and in the consequent allocation of the (already scarce) resources, we need to establish new procedures to ensure a straight, direct interaction between health policy, applied research, and basic science.

This process requires a radical change in intercultural and interdisciplinary collaboration at the international level. We need to move forward to evidence-based health policy setting mechanisms that involve multiple levels to provide more precise, complete and timely information. Most importantly, we need to ensure that this information is promptly translated into guidelines and adequately communicated to the public.

The recent health emergencies have shown that solutions of this kind need to be found beyond the national boundaries. Epidemiologic models that are “internationally robust” may provide immediate, comprehensive scientific answers, while reducing the bias of improper risk communication, risk perception, and the possible discriminations and economical damages. Unfortunately, quality research requires very detailed data, and this is only possible working out ad hoc agreements, a process that usually take a considerable time.

A possible solution is represented by the establishment of permanent, computerized longitudinal registers. Relational databases may include a detailed follow up of multiple characteristics of human subjects, safely de-identified to avoid any possible ethical implication, which can be structurally linked to contextual data, including information on the animal population and other population/geographical aspects. By concentrating our investigations on specific problems, and/or selected strata of the population at risk, we may increase our ability to analyse new phenomena at the international level.

The practical advantages of disease registers are clear. However, it is important to consider the magnitude of the cultural challenge. While the technology available would easily allow spectacular solutions, a possible implementation is still far to come in the absence of any agreement on ongoing data and information exchange, even only for research purposes.

***Evidence of an Absence: Analysis of 1918 Sequences Suggest Origin in a Currently Unknown Source***

**Dr. Ann Reid, Armed Forces Institute of Pathology, Rockville, MD, USA**

The anatomy of the influenza virus, with its eight separate RNA segments, and its ecology, with multiple wild and domestic animal hosts and imperfect host specificity, combine to allow many different scenarios for the generation of pandemic influenza strains. A successful pandemic strain needs an antigenically novel HA and the ability to spread from human to human. In both 1957 and 1968, these preconditions were met by reassortment of a wild bird strain with the previously circulating human strain, resulting in strains with one or two avian-like surface proteins on already human-adapted cores. The infection of humans in both 1997 and 2003/4 by poultry-adapted strains has raised concerns that an avian strain could emerge without reassortment.

As the sequence of each gene segment of the 1918 influenza pandemic strain has been determined, an attempt has been made to understand its origin. In the case of both hemagglutinin (HA) and neuraminidase (NA), the genes were more closely related to their mammalian descendants than to avian strains. A very large number of synonymous nucleotide differences separated the 1918 genes from avian sequences. However, both HA and NA had features suggesting they had not been in mammals for long before emerging on the 1918 strain; antigenic sites matched the avian consensus and, in the case of HA, the receptor binding site had only one amino acid difference from the avian configuration. We concluded that these genes may have spent some time accumulating changes in an intermediate host before 1918. The matrix (MA) and non-structural (NS) gene segments, each encoding two proteins, are very conserved. Without any samples of the strain that circulated before 1918, determining whether the 1918 MA and NS were retained or newly acquired was difficult. In the case of MA, the 1918 sequence has four amino acid differences from the avian consensus in a part of M2 under severe evolutionary constraint, suggesting that the MA segment might have been retained from the previously circulating human strain.

We have recently completed the sequence of the 1918 nucleoprotein gene segment (NP). Analyses of the gene sequence led us to an unexpected conclusion. The 1918 NP sequence has over 170 synonymous nucleotide differences and only 6 amino acid differences from the average avian sequence. It is no more closely related to any individual bird sequence than to the average and is equidistant, phylogenetically, from the Eurasian and North American avian clades. Since 1918, the NP protein has accumulated more than 30 amino acid changes, suggesting that severe functional constraint on the NP protein does not explain the close match between the 1918 and the average avian protein sequence. The large number of nucleotide differences makes it unlikely the 1918 NP came directly from an avian strain similar to those currently characterized. The small number of amino acid differences makes it unlikely NP was retained from the previously circulating human strain. A period of adaptation in an intermediate host would be unlikely to generate such a very large number of synonymous changes with so few amino acid changes. The hypothesis that best explains all of the results is that the NP came from a currently unknown influenza host whose NP is similar to currently known avian sequences at the protein level, but has been evolutionarily separated long enough to accumulate many synonymous changes.

***The Importance of both Basic and Translational Research for Prevention, Detection and Response to Emergent Animal and Zoonotic Diseases***

**Dr. Terry McElwain, Washington State Diagnostic Laboratory, College of Veterinary Medicine, Washington State University, Pullman, WA, USA**

In the relatively short time span of a little more than a quarter century, four scientific breakthroughs have had a profound effect on the way we investigate infectious diseases, whether in the research laboratory or in diagnostics. These breakthroughs include the development of monoclonal antibody technology, recombinant DNA techniques, the polymerase chain reaction, and DNA sequencing methods, particularly in a high throughput manner. The development and application of microarray assays, a direct descendant of fundamental research leading to all four of the above scientific breakthroughs, is a more recent example of combined translational and basic research that can contribute to our understanding of emerging diseases and their early detection.

For a diagnostician, the ability to specifically and sensitively detect multiple agents in a single or limited number of reactions, including potential exotic diseases that may emerge in a non-endemic area, is an exciting development. For our animal and public health stakeholders, an inexpensive and rapid microarray assay can be a valuable asset both for the health of a population and for economic gain. But further research is necessary to implement a microarray approach in emerging disease surveillance and detection. As we continue to develop global infectious disease surveillance networks for animal and human health, it is essential that newly developed assays are validated to strict international criteria, and that to the extent possible, all laboratorians use these validated techniques. Bench and field validation are both critical. One example in our research unit is a recently developed microarray to simultaneously detect 15 different fish pathogens, including a probe for an exotic disease. Bench validation provided very promising results using probes selected through extensive *in silico* analysis. However, a field validation study quickly indicated that, despite careful selection of gene targets, universal primers targeting bacterial 16S rRNA genes were not the best solution, at least in this application. “Polymorphism paradox”, apparent after analysis of false negative results, and discovery of previously unrecognized organisms, emphasize that existing gene databases represent only a very, very small fraction of the microbial world, particularly when we start sampling water and other environmental matrices. Without translational research, these discoveries would have been missed.

More basic comparative genomic studies can be used to address fundamental questions of pathogen emergence. For example, is there a selective advantage to pathogen virulence in humans or animals? Using a microarray in a mixed genome approach, multiple candidate virulence genes for invasion of humans have been identified in *Listeria monocytogenes*. However, for bacteria, it is becoming increasingly clear that the “virulence” of many “pathogens” may be an adaptation to their ecological niche, and *Listeria* may be no different. Evidence in the Chlamydiales, *Legionella*, *Salmonella*, *Burkholderia*, *Francisella*, *Wolbachia*, *Brucella*, and now *Listeria*, suggests that these bacteria either are, or likely recently evolved from, endosymbionts, and may have selected mechanisms for entry into and co-existence with protozoa or filarid worms that can affect their ability to invade mammalian hosts.

Understanding this process from a less “mammalocentric” view, using biotechnological tools such as microarrays and comparative genomics, can help us understand why pathogens emerge to cause disease in what may just be a bystander effect

The fundamental research that enabled development of each of the breakthroughs above was translated into everyday use through the application of science. In my view, it is critical that we recognize the importance of, and fund appropriately, both basic science, and its translation. Each is vital for the prediction, early detection and characterization of emerging diseases, for the response to these diseases, and for recovery from them; and each can lead to important discoveries.

*Strategies for new viruses discovery*

**D. Cavanagh, Institute for Animal Health; J.F. Valarcher, Compton Laboratory, P. Pastoret, Pirbright Laboratory, United Kingdom**

Within the last decades, the number of outbreaks of emerging or re-emerging zoonotic and non-zoonotic infections has steadily increased, some of which previously unknown.

This is thought to be due to several factors including globalisation of human activities (Trade, Tourism, Travel ...), global warming, unfastening of ecosystems, and increased contact with wildlife.

Among wildlife, bats, which represent approximately 24% of all known mammalian species, are often the source of potentially zoonotic infections.

In particular, insectivorous bats play an important role in the epidemiology of rabies and some rabies-like viruses, while the haematophagous vampire bats, such as *Desmodus rotundus* are the major wildlife vector for rabies in Latin America.

In contrast, the role of fruit bats (flying foxes) in the epidemiology of the recently discovered Australian bat lyssavirus, as well as hendraviruses, is only just emerging.

Bat lyssaviruses are most probably the ancestors of all known lyssaviruses infecting bats or terrestrial species as evidenced by phylogenetic studies.

This exemplifies that wildlife with its biodiversity is the potential source of a vast number of undiscovered viruses. If one takes also into account the mutation rate of viruses (especially RNA viruses) and their ability to reassort or recombine, variability is the intrinsic nature of viruses. Fortunately within the same genus, viruses often share genetic (highly conserved regions) or phenotypic characteristics.

Using new available technologies such as polymerase chain reaction or micro arrays, coupled together with more classic techniques like virus isolation, will help us to discover new potentially emerging viruses. Viral phylogenetic studies comparing old and new strains of already known virus species allow insight into virus evolutionary trends and therefore some prediction about potential future virus features.

# AGENDA

Monday June 21, 2004

## Morning session

9:00 Welcome

EU: Dr Christian Patermann, European Commission, co-chair of the Task Force  
USA: Dr Mary Clutter, National Science Foundation, co-chair of the Task Force

### 1. What is going on with infectious diseases and what does the future likely to hold?

9:20 *"Emerging virus infections in a changing world"*

Prof. Albert Osterhaus, Erasmus University, Rotterdam, The Netherlands

9:40 *"Recent Spread of a Vector-borne Disease"*

Prof Polly Roy, London School of Hygiene & Tropical Medicine, United Kingdom

10:00 *"The Global Infectious Disease Network: A Model for International Cooperation"*

Dr. Ivor Knight, Canon U.S. Life Science, Arlington, VA, USA

10:20 Questions/Discussion

### 2. Do we know what really causes the disease?

10:40 *"Hemorrhagic fevers caused by Marburg and Ebola viruses"*

Prof Klenk, Philipps University Marburg, Germany

11:00 *"Surveying Gene Expression in Leukocytes: Host Responses and Classification of Infection"*

Dr. Stephen Popper, Department of Microbiology and Immunology  
Stanford University School of Medicine, Stanford, CA, USA

11:20 Questions/Discussion

## Afternoon session

### 3. What is the basis for host-pathogen specificity and why do some cross into other species?

13:20 *"The Origins and Host Specificity of Type A influenza Virus"*

Dr. David Suarez, Southeast Poultry Research Laboratory, Agricultural Research Service, Athens, GA, USA

13:40 *"HIV and AIDS in Relation to Other Pandemics"*  
Prof Robin Weiss, Department of Immunology and Molecular Pathology, University  
College London

14:00 *"Predictive Understanding of Human Risk to Emerging Viruses"*  
Dr. Terry Yates, University of New Mexico, Albuquerque, NM, USA

14:20 Questions/Discussion

**4. What would we need to know to predict the emergence or re-emergence of a disease?**

15:00 *"Biotechnology research and emergence of new diseases: Perceived versus known risks"*  
Dr François Moutou, Agence Française de Sécurité Sanitaire des Aliments, France

15:20 *"Techniques and Challenges the Diagnosis of Prion Diseases"*  
Dr. Larry Stanker, Food-borne Contaminants Research, Agricultural Research Service,  
Albany, CA, USA

15:40 *"The role of wild life and other parameters on the emergence and re-emergence of animal diseases"*  
Prof. José-Manuel Sánchez-Vizcaíno, Universidad Complutense de Madrid, Spain

16:00 Questions/Discussion

20:00 **Dinner** Charlemagne building

**Tuesday, June 22, 2004**

**5. What do we need to do or know to coordinate efforts on these topics between the EC and US?**

9:00 *"Strategies to develop vaccines in emergency scenarios: the SARS example"*  
Prof Luis Enjuanes, Centro Nacional de Biotecnología, Spain

9:20 *"Applied Research and Epidemiology – Are They Related to Biotechnology Research of Preparedness for Emerging Animal Diseases?"*  
Dr. Mo Salman, College of Veterinary Medicine and Biomedical Sciences  
Colorado State University, Fort Collins, CO, USA

9:40 *"From research to implementation: the challenge of international disease registers and data exchange".*  
Dr Fabrizio Carinci, Directorate of Health Planning, Ministry of Health, Italy

10:00 *Evidence of an Absence: Analysis of 1918 Sequences Suggest Origin in a Currently Unknown Source"*  
Dr. Ann Reid, Armed Forces Institute of Pathology, Rockville, MD, USA.

10:20 Break

11:00 *“The Importance of both Basic and Translational Research for Prevention, Detection and Response to Emergent Animal and Zoonotic Diseases”*

Dr. Terry McElwain, Washington State Diagnostic Laboratory, College of Veterinary Medicine, Washington State University, Pulman, WA, USA

11:20 *“Strategies to new virus discovery”*

Prof. Pierre-Paul Pastoret, Institute for Animal Health, United Kingdom

11:40 Questions/Discussion

12:30 Lunch – Buffet

## **6. Findings and Recommendations**

14:00 Development of Findings and Recommendations

16:00 Report Drafting (Co-Chairs)

# LIST OF PARTICIPANTS

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*"Hemorrhagic fevers caused by Marburg and Ebola viruses"*

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*“Strategies to new virus discovery”*

# PRESENTATIONS