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0845 Registration starts

**In the chair:** TIM WREGHITT and WERNER WUNDERLI

0930 *Welcome and announcements*

Exotic viral infections

0940 CATHY E. ROTH (CSR/WHO, Geneva, Switzerland)

*Viral haemorrhagic fevers: global update*

1020 BRIAN MAHY (Centers for Disease Control and Prevention, Atlanta, USA)

*West Nile Fever in New York*

1100 *Refreshment break*

Influenza

1130 JOHN OXFORD (Retroscreen Virology, London)

*The molecular basis for the virulence of influenza virus*

1210 IAN BROWN (Veterinary Laboratories Agency, Weybridge)

*Epizootiology of influenza A viruses in animals and the implications for human health*

1250 *Lunch*

**In the chair:** MARIA ZAMBON and JOE BROWNLIE

Offered papers on influenza and exotic viral infections

1400 *Epidemiology and antigenic drift in swine and human influenza A viruses*

J.C. DE JONG<sup>1</sup>, I. DONATELLI<sup>2</sup>, G. BARIGAZZI<sup>3</sup>, K.-J. YOON<sup>4</sup>, W.L.A. LOEFFEN<sup>5</sup>,  
P. P. HEINEN<sup>6</sup>, R.A.M. FOUCHIER<sup>1</sup>, G.F. RIMMELZWAAN<sup>1</sup>, A.D.M.E. OSTERHAUS<sup>1</sup>

(<sup>1</sup>Erasmus

University Rotterdam, The Netherlands; <sup>2</sup>Istituto Superiore di Sanità, Rome, Italy; <sup>3</sup>Istituto Zooprofilattico Sperimentale, Parma, Italy; <sup>4</sup>Iowa State University, Ames, IA, USA; <sup>5</sup>Animal Health Service, Deventer, The Netherlands; <sup>6</sup>ID-Lelystad, The Netherlands)

1415 *Reduced cold-sensitivity of the polymerase complex derived from the A/Hong Kong/156/97 strain as compared to complexes of Avian influenza viruses*

P. MASSIN, S. VAN DER WERF & N. NAFFAKH (Institut Pasteur, France)

1430 *Mutants of influenza A H5N1 haemagglutinin protein altered in the predicted receptor binding site*

RUTH HARVEY<sup>1</sup>, IAN JONES<sup>1</sup>, MARIA ZAMBON<sup>2</sup> & WENDY BARCLAY<sup>1</sup> (<sup>1</sup>University of Reading; <sup>2</sup>CPHL Colindale London)

1445 *Resurgence of West Nile Fever in Israel 1998-2001*

H. BIN<sup>1</sup>, M. HYNDYIEH<sup>1</sup>, L. SHULMAN<sup>1</sup>, L. WEISS<sup>1</sup>, Z. GROSSMAN<sup>1</sup>, D. GANDACU<sup>2</sup>,  
H. PENNER<sup>3</sup>, S. POKAMUNSKI<sup>4</sup>, S. SCHLEZINGER<sup>1</sup> & E. MENDELSON<sup>1</sup> (<sup>1</sup>Central Virology Laboratory, Israel; <sup>2</sup>Dept of Epidemiology and Infectious Diseases, Israel; <sup>3</sup>Ministry of Health, Israel; <sup>4</sup>Ministry of Agriculture, Israel)

1500 *Description of nosocomial and intrafamilial spread of CCHF in Kosovo in 2001*

M. PETROVEC<sup>1</sup>, D. DUH<sup>1</sup>, S. AHMETI<sup>2</sup>, I. DEDUSHAJ<sup>3</sup> & T. AVSIC-ZUPANC<sup>1</sup> (<sup>1</sup>Institute of Microbiology, Slovenia; <sup>2</sup>Medical Faculty, Kosovo; <sup>3</sup>IPH, Kosovo)

1515 *Issues in managing viral haemorrhagic fevers*

BARBARA BANNISTER<sup>1</sup>, ROBIN GOPAL<sup>2</sup> & KLAUS N.F. FLEISCHER<sup>3</sup> (<sup>1</sup>Royal Free Hospital, London; <sup>2</sup>CPHL, Colindale, London; <sup>3</sup>Medical Mission Hospital, Germany)

1530 *Refreshment break*

Borna virus infection

1600 NORBERT NOWOTNY (University of Vienna, Austria)

*Borna disease virus infection in different animal species and in human beings*

1645 -1815 Business Meetings

ESCV Council / SGM Clinical Virology Group / Expert Surveillance on Equine Influenza



**In the chair:** NICOLA BRINK and DAVID BROWN

Rabies

0900 TONY FOOKS (Veterinary Laboratories Agency, Weybridge)

*Rabies – global situation, disease surveillance and control*

0945 NOEL TORDO (Institut Pasteur, Paris, France)

*Diversity of lyssaviruses and rabies neuropathogenesis*

1030 *Refreshment break*

Offered papers on rabies and general topics

1100 *A lethal bite - a case of rabies in London*

DAN AGRANOFF, NICOLA BRINK, ANTHONY FOOKS & TOM DOHERTY (Hospital of Tropical Diseases and Dept of Virology, University College London Hospitals and Rabies Research and Diagnostic Group, VLA Weybridge, WHO Collaborating Centre for the Characterisation of Rabies and Rabies-related Viruses, Weybridge, Surrey)

1115 *Screening of active Lyssavirus infection in wild bat populations by viral RNA detection on oropharyngeal swabs*

JUAN E. ECHEVARRÍA<sup>1</sup>, ANA AVELLÓN<sup>1</sup>, SONIA VÁZQUEZ<sup>1</sup>, JAVIER JUSTE<sup>2</sup>, MANUEL VERA<sup>1</sup> & CARLOS IBÁÑEZ<sup>2</sup> (<sup>1</sup>Instituto de Salud Carlos III, Spain, <sup>2</sup>Consejo Superior de Investigaciones Científicas, Spain)

1130 *Parapoxviruses: recent developments in diagnosis and treatment*

P.F. NETTLETON, C. LOCKE, J.A. GILRAY & C. McINNES (Moredun Research Institute, Edinburgh)

1145 *Ovine herpesvirus-2 lytic cycle replication and particle production*

J. ROSBOTTOM<sup>1</sup>, M. ACKERMANN<sup>2</sup>, R.G. DALZIEL<sup>1</sup>, H.W. REID<sup>3</sup> & J.P. STEWART<sup>1</sup> (<sup>1</sup>University of Edinburgh, UK; <sup>3</sup>Moredun Research Institute, UK; <sup>2</sup>University Inst. of Virology, Switzerland)

1200 *Sunshine, warts and skin cancer*

T. SURENTERAN<sup>1</sup>, C.M. PROBY<sup>2</sup>, J.M. MCGREGOR<sup>2</sup>, C.A. HARWOOD<sup>2</sup> & J. BREUER<sup>1</sup> (Barts & The London, Queen Mary's School of Medicine & Dentistry, UK)

1215 *An outbreak of Norwalk-like virus at the recent ESCV meeting in Finland*

CARL-HENRIK VON BONSDORF (Haartman Institute, Finland)

1225 Annual General Meeting of the ESCV (all members welcome)

1225 *Lunch and poster viewing*

**In the chair:** SUE SKIDMORE and STEVE EDWARDS

Prions

1400 MARKUS GLATZEL (University Hospital of Zurich, Switzerland)

*Neuroinvasion of prions*

1445 ROBERT WILL (National Creutzfeldt-Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh)

*Clinical and epidemiological features of variant CJD*

1530 *Refreshment break*

Offered papers on Hepatitis E

1600 *Hepatitis E virus in Europe, an emerging zoonosis from a pig reservoir?*

WIM H.M. VAN DER POEL, FROUKJE VERSCHOOR, REINA VAN DER HEIDE & ANA MARIA DE RODA HUSMAN (National Institute of Public Health and the Environment (RIVM), The Netherlands)

1615 *Hepatitis E virus: comparative evaluation of antibody assays in a low-endemicity setting*

M. ASANTE, W. PREISER & H.W. DOERR (J.W. Goethe University, Frankfurt, Germany)

1630 *Are HBV load measurements useful in HIV/HBV coinfecting patients?*

C. AITKEN, K. TEMPLETON, H. WHEELER & C. SKINNER (Barts & the London NHS Trust  
London)





1645 *Study of shingles and its development to postherpetic neuralgia in East London*  
F.T. SCOTT<sup>1</sup>, M.E. LEEDHAM-GREEN<sup>1</sup>, W. BARRETT-MUIR<sup>1</sup>, L. BATTY<sup>1</sup>, K. HAWARAMI<sup>1</sup>, J.  
GALLAGHER<sup>2</sup>, R. JOHNSON<sup>3</sup> & J. BREUER<sup>1</sup> (<sup>1</sup>Barts and The London, Queen Mary's School of  
Medicine and Dentistry; <sup>2</sup>Barts and The London NHS Trust, West Smithfield, <sup>3</sup>Bristol Royal Infirmary)

1700-1800 *Poster viewing (delegates with posters should be available for discussions)*

1930 *Conference dinner at the Royal College of Physicians*



**In the chair:** PETER NETTLETON and AB OSTERHAUS

Emerging viral infections

- 0930 ADRIAN PHILBEY (Moredun Research Institute, Edinburgh)  
*Zoonotic paramyxoviruses of pteropid bats: Nipah, Hendra and Menangle viruses*
- 1010 ADEEBA KAMARULZAMAN (University of Malaya Medical Centre, Kuala Lumpur, Malaysia)  
*The Nipah outbreak in Malaysia – a clinical perspective*

1050 *Refreshment break*

Offered papers on flavivirus infections and general topics

- 1120 *Molecular investigation of a prolonged outbreak of parainfluenza 3 on a haematology unit: implications for infection control*  
H. JALAL, J. BENNETT, D.F. BIBBY & K.N. WARD (Royal Free & University College Medical School, London)
- 1135 *Molecular characterization and severity of symptoms associated with type of respiratory syncytial virus isolates*  
U. ILGERT<sup>1</sup>, U. WEGNER<sup>1</sup>, R. BRUNS<sup>2</sup>, L. GÜRTLER<sup>1</sup> & R. MENTEL<sup>1</sup> (<sup>1</sup>Friedrich Loeffler, Germany and <sup>2</sup>University Hospital, University of Greifswald, Germany)
- 1150 *Yellow fever virus is enzootic in Peru and Bolivia*  
J.E. BRYANT<sup>1</sup>, H. WANG<sup>1</sup>, C. CABEZES<sup>2</sup>, P.C. VASCONCELOS<sup>3</sup>, A. GIANELLA<sup>4</sup>, K. RUSSELL<sup>5</sup>, D.M. WATTS<sup>5</sup> & A.D.T. BARRETT<sup>1</sup> (<sup>1</sup>University of Texas Medical Branch, USA; <sup>2</sup>Instituto Nacional Salud, Peru, <sup>3</sup>Instituto Evandro Chagas, Brazil; <sup>4</sup>CENETROP, Bolivia; <sup>5</sup>U.S. Naval Medical Research Center Detachment, Peru)
- 1205 *Lack of evidence for the cross-species transmission hypothesis for the origin of Hepatitis B virus in humans*  
SOFIE STARKMAN & PETER SIMMONDS (University of Edinburgh)
- 1220 *Diagnosis of flavivirus infections by immunofluorescence and enzyme-linked immunosorbent assay*  
P. KORAKA<sup>1</sup>, H. ZELLER<sup>2</sup>, M. NIEDRIG<sup>3</sup>, A.D.M.E. OSTERHAUS<sup>1</sup> & J. GROEN<sup>1</sup> (<sup>1</sup>Erasmus Medical Centre Rotterdam, The Netherlands; <sup>2</sup>C.N.R des Arbovirus et des Fièvres Hémorragiques Virales, France; <sup>3</sup>Robert Koch-Institut, Germany)
- 1235 *Louping-ill in the UK: A zoonosis with unfulfilled potential*  
H.W. REID & P.F. NETTLETON (Moredun Research Institute, Edinburgh)

1250 *Lunch*

**In the chair:** JURJEN SCHIRM and DAVID PATON

- 1400 AB OSTERHAUS (Erasmus University, Rotterdam, The Netherlands)  
*The ESCV Gardner Lecture “Viruses emerging from animal reservoirs”*

Offered papers on hantaviruses

- 1445 *Genetic diversity of hantaviruses circulating in Slovenia*  
T. AVSIC-ZUPANC<sup>1</sup>, M. PETROVEC<sup>1</sup>, T. TRILAR<sup>2</sup>, K. PROSENC<sup>1</sup> & D. DUH<sup>1</sup> (<sup>1</sup>Institute of Microbiology, Slovenia; <sup>2</sup>Natural History Museum, Slovenia)
- 1500 *Serological evidence of hantavirus in humans and rodents in Barbados*  
J. GROEN<sup>1</sup>, P. KORAKA<sup>1</sup>, C.N. EDWARDS<sup>2</sup>, S.L. BRANCH<sup>2</sup>, K.O. DOUGLAS<sup>2</sup>, A.D.M.E. OSTERHAUS<sup>1</sup> & P.N. LEVETT<sup>2</sup> (<sup>1</sup>Erasmus Medical Centre Rotterdam, The Netherlands, <sup>2</sup>University of the West Indies, Barbados)

1515 *Refreshment break*

Foot and mouth disease

- 1545 *Closing Lecture*  
JIM SCUDAMORE (Chief Veterinary Officer, London)  
*Lessons learnt from the UK FMD experience in 2001*

*The ESCV Gardner Lecture*

**Viruses Emerging from Animal Reservoirs**

**ALBERT OSTERHAUS**

**Institute of Virology, Erasmus Medical Center, P.O.Box 1738, 3000 DR Rotterdam, The Netherlands**

It may seem paradoxical that at a time when we have managed to control, or even eradicate major human virus infections like polio and smallpox, we are increasingly confronted with viruses that cross species barriers, which results in major disease outbreaks and countless deaths in the newly affected species. The most tragical examples are the influenza and AIDS pandemics which have cost the lives of many millions of people worldwide in the last century. Outbreaks like Ebola- and Nipah virus infections, although geographically confined, have also gained a lot of public attention, due to their high case fatality rates.

Foot and mouth disease, hog cholera, phocine distemper and avian influenza are probably the most publicised examples from the animal world, whereas mad cow disease caused by a prion infection of sofar unknown origin, has major consequences for both animal and human health.

A complex mix of social, technological and ecological changes, and the ability of certain viruses to rapidly adapt to a changing environment, seems to be at the basis of this phenomenon. Extensive diagnostic and surveillance networks, as well as novel vaccine- and antiviral development strategies should provide us with the safeguards to limit its impact.

**ORAL PRESENTATIONS****West Nile Virus****BRIAN W.J. MAHY****National Center for Infectious Diseases, CDC, Atlanta, Georgia, USA**

West Nile virus (WNV) was first isolated in 1937 in the West Nile district of Uganda. WNV is classified as a species in the genus *Flavivirus*, belonging to the Japanese encephalitis virus serogroup. It has been associated in Africa, Europe and the Middle East with a silent or short febrile infection in humans, especially children, but a more severe disease which can be fatal may occur in elderly people. The virus was never found in the Western hemisphere until August 1999 when a physician from the Queens district of New York reported two patients with apparent viral encephalitis. Investigation by New York City Department of Health found 8 similar cases in a small 2x2 mile area. Initial diagnosis was difficult, but in September 1999 several exotic birds in the Bronx zoo became ill, and other wild birds, especially crows, were found dead in other parts of New York and in Pennsylvania. The virus causing disease in both humans and birds was identified as WNV, and nucleotide sequencing of the envelope gene established that it was virtually identical to a WNV isolate which caused a serious disease outbreak in geese in Israel in 1998. The virus has continued to circulate in mosquito populations in the Eastern USA, and the genotype has remained stable. It is clear that it can overwinter and is now endemic in several States. In 1999 a total of 56 human cases were identified in New York, 7 of whom (all elderly patients) died. It is not known how the virus moved to the USA, presumably from the Middle East. In addition to humans and birds, horses are susceptible, and in 2000 at least 60 horses were diagnosed with WNV infection. In 2001, 37 human cases of WNV encephalitis had been reported by the end of October, with one death. The prospects for control and treatment of WNV infection, and the possibility of further spread throughout the Western hemisphere will be discussed.

**Epizootiology of Influenza A Viruses in Animals and the Implications for Human Health****I.H. BROWN****Virology Dept, Veterinary Laboratories Agency-Weybridge, New Haw, Addlestone, Surrey KT15 3NB, UK**

Influenza A viruses infect a large variety of animal species, including humans, pigs, horses, sea mammals and birds, occasionally producing devastating pandemics in humans, such as in 1918, when over twenty million deaths occurred world-wide. The two surface glycoproteins of the virus, haemagglutinin (HA) and neuraminidase (NA), are the most important antigens for inducing protective immunity in the host and therefore show the greatest variation with fifteen antigenically distinct HA subtypes and nine NA subtypes presently recognised. Although viruses of relatively few subtype combinations have been isolated from mammalian species, all subtypes, in most combinations, have been isolated from birds. Aquatic birds are likely to be the source of all influenza A viruses in other species. In the 20th Century, the sudden emergence of antigenically different strains in humans, termed antigenic shift, has occurred on four occasions, as follows, in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) and 1977 (H1N1), each resulting in a pandemic. The impact of these events is most effectively measured by monitoring excess mortality due to pneumonia and influenza. Human pandemic strains are thought to have emerged through one of three mechanisms: genetic reassortment of avian and human influenza A viruses infecting the same host, direct transfer of whole virus from another species or re-emergence of a virus which may have caused an epidemic many years earlier. Since 1996, the viruses H7N7, H5N1 and H9N2 have been transmitted from birds to humans but have apparently failed to spread in the human population. Such incidents are rare, but transmission between humans and other animals has also been demonstrated. This has led to the suggestion that the proposed reassortment of human and avian viruses occurs in an intermediate animal such as pigs or chickens with subsequent transference to the human population. To meet the threat of the next human pandemic, which could occur at any time, public health authorities are preparing pandemic plans, one element of which provides greater focus in the animal-human interface.

## **Rabies – Global Situation, Disease Surveillance and Control**

**ANTHONY FOOKS**

**Rabies Research and Diagnostics Group, Department of Virology, Veterinary Laboratories Agency (Weybridge), New Haw, Addlestone, Surrey, KT15 3NB, UK**

Cases of rabies have significantly decreased in Western Europe, largely due to the success of oral wildlife vaccination programmes and the vaccination of domestic animals. In addition, effective surveillance strategies have been instrumental in supporting elimination campaigns to prevent the re-introduction of rabies from endemic countries into areas that have previously been declared rabies-free. Rabies is also under control in some areas of North America although sylvatic rabies still causes problems in specific US states. In contrast however, rabies continues to be a major public healthcare concern in parts of Africa and Asia and in Eastern Europe.

Although rabies may be controlled in many countries, it is unlikely to be globally eradicated. Rabies is continuing to expand worldwide and animal reservoirs that harbour the virus still pose a significant threat. Throughout different parts of the world insectivorous, frugivorous and haematophagous bats continue to be an important reservoir for rabies virus and the rabies-related viruses.

There is little doubt that the legal protection of European bats has direct relevance on our lack of knowledge of the transmission mechanisms and pathogenesis of bat rabies in Europe. Furthermore, there is also little doubt that the lack of effective surveillance systems and diagnostic capabilities in Africa confounds our lack of knowledge of African bat rabies.

Whilst strategies are converging for the control of rabies in domestic animals and other wildlife vectors the threat of a 'spill-over' rabies infection from a bat to domestic and terrestrial animals exists and will be discussed.

## **Diversity of Lyssaviruses and Rabies Neuropathogenesis**

**Y. JACOB<sup>1</sup>, P. PERRIN<sup>1</sup>, P.-E. CECCALDI<sup>2</sup>, H. BADRANE<sup>1</sup>, E. DESMEZIERES<sup>1</sup>, E. REAL<sup>1</sup>, C. TUFFEREAU<sup>3</sup> & N. TORDO<sup>1</sup>**

**<sup>1</sup>Lyssavirus Laboratory; <sup>2</sup>Rabies Unit, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris Cedex 15, France, (33-140613134, ntordo@pasteur.fr); <sup>3</sup>CNRS, Laboratoire de Génétique des Virus, Gif/Yvette, France**

Rabies encephalitis is due to neuron infection by lyssaviruses. After receptor recognition by the surface G protein and cell penetration by endocytosis, lyssaviruses use axonal retrograde transport to reach the perikarion where they replicate, before trans-synaptic spread to other neurons. Because many aspects of rabies pathogenesis remain obscure, we started a descriptive and functional analysis of the lyssavirus diversity.

1. Phylogenetic analysis distinguished 7 genotypes (GT) which segregate into two phylogroups (PG). PG1 comprises the world-wide GT1 (rabies), the European GT5 (EBL1) and GT6 (EBL2), the African GT4 (Duvenhage) and the Australian GT7 (ABL). PG2 comprises the African GT2 (Lagos bat) and GT3 (Mokola).
2. Anti-G virus neutralizing antibodies display cross-neutralisation within PG (>74% aa identity in G protein ectodomain) but not between (<62%). This explains the inefficiency of current rabies vaccines (PG1) to protect against PG2 lyssaviruses and invites to increase their spectrum from anti-rabies to anti-lyssavirus vaccines.
3. PG1 lyssaviruses are pathogenic by i.c. and i.m. routes, PG2 lyssaviruses are only by i.c. Their R<sub>333</sub> (a G protein aa essential for virulence) is replaced by D<sub>333</sub>, possibly explaining attenuated pathogenicity.
4. Three candidate receptors were proposed: the nicotinic acetylcholine receptor (nAChR), NCAM and the low-affinity nerve-growth factor receptor (P75NTR). P75NTR interacts with G proteins of GT1 (rabies) and GT6 (EBL2), not with G proteins from the other GTs (2, 3, 4 and 5). This evokes different lyssavirus receptors.
5. The cytoplasmic dynein light chain (LC8) interacts strongly with P protein which is a constituent of the internal RNP. This P/LC8 interaction is a common property of lyssaviruses. LC8 is a component of cellular motors involved in axonal retrograde microtubule-based transport. This provides support for a model of RNP axonal transport in which RNP (through P) interacts successively with actin filaments in the early step of viral entry, then with the microtubule network for fast axonal transport. As LC8 is also an inhibitor of the neuronal nitric oxide synthase (ncNOS), P/LC8 interaction could also sign a physiopathological aspect of infection.

Studying the diversity of Lyssaviruses not only helps to understand the molecular basis of their immunogenicity and pathogenesis, but also provides a panel of viruses with different neurotropic properties.

## **Neuroinvasion of Prions**

**MARKUS GLATZEL**

**University Hospital of Zurich, Switzerland**

A number of prion diseases are caused by peripheral uptake of prions. How prions actually reach the CNS from peripheral sites is not fully understood. Studies have shown prion replication in lymphoid tissues as early as 7-10 days after prion-administration. Follicular dendritic cells (FDCs) are candidates for prion accumulation of in lymphatic tissues. Inhibition of the lymphotoxin alpha-beta pathway with a lymphotoxin beta-receptor IgG fusion protein leads to the disappearance of functional FDCs. FDC-depleted mice show a reduction of prion infectivity in spleens and a significant delay until the onset of terminal scrapie disease [3].

Transport of prions in peripheral nerves has been indirectly demonstrated in a number of studies. PrPC expression on peripheral nerves seems to modulate neuroinvasion via peripheral nerves [1].

Past studies have proposed a pivotal role of sympathetic nerves in neuroinvasion of prions. Sympathectomized mice show a significant delay until the onset of terminal scrapie disease upon peripheral prion administration. The importance of sympathetic nerves in prion transport is further stressed by the fact that NGF-transgenic mice showing substantial sympathetic hyperinnervation of lymphoid tissues develop terminal scrapie disease earlier and show higher prion titers in spleens than controls [2].

[1] Glatzel, M. and Aguzzi, A., PrP(C) expression in the peripheral nervous system is a determinant of prion neuroinvasion, *J Gen Virol*, 81 (2000) 2813-2821.

[2] Glatzel, M., Heppner, F.L., Albers, K.M. and Aguzzi, A., Sympathetic innervation of lymphoreticular organs is rate limiting for prion neuroinvasion, *Neuron*, 31 (2001) 25-34.

[3] Montrasio, F., Frigg, R., Glatzel, M., Klein, M.A., Mackay, F., Aguzzi, A. and Weissmann, C., Impaired prion replication in spleens of mice lacking functional follicular dendritic cells, *Science*, 288 (2000) 1257-9.

## **Variant Creutzfeldt-Jakob Disease**

**ROBERT WILL**

**National Creutzfeldt -Jakob Disease Surveillance Unit, Western General Hospital, Edinburgh**

There is now compelling evidence that variant Creutzfeldt-Jakob disease (vCJD) is caused by the agent of bovine spongiform encephalopathy (BSE) and it is thought that transmission of this cattle disease to humans was through BSE infection in food. As of November 2001 one hundred and eleven cases of vCJD had been identified in the UK and statistical analysis has shown that the numbers of cases are clearly increasing with time. It is likely that there was extensive exposure to the BSE agent in the human food chain, but there is uncertainty about the total future number of cases of vCJD because of many unknowns, including the mean duration of the incubation period of BSE in humans.

Variant CJD is also a cause for concern in other European countries because of the occurrence of BSE in some countries and the recent identification of affected cattle in countries that were previously thought to be BSE free. A surveillance system for CJD of all types, funded by the European Union, was established in 1993 and now includes all member states together with other countries, including Canada, Australia, Norway, Iceland, Israel and Switzerland. Four cases of vCJD have been identified in France, one in the Republic of Ireland and one in Hong Kong. The Irish and Hong Kong cases had lived in the UK during the 1980s when human exposure to BSE was likely to have been significant, but three of the French cases had never visited the UK, suggesting exposure to indigenous BSE or perhaps to BSE contaminated exports from the UK.

Apart from residence in the UK, the main risk factors for vCJD are a young age (the mean age at death is 29 years) and a particular genetic make-up, methionine homozygous at codon 129 of the prion protein gene. About 40% of the general population and all tested cases of vCJD have this genotype, which may represent a susceptibility factor. However it is possible that genetic variation may influence incubation period and cases with genotypes other than methionine homozygous may yet be identified.

Concern about the risks from vCJD has been increased by the possibility of transmission of infection from person to person through the use of blood or blood products, or from contaminated surgical instruments. Exclusion criteria for blood donors, based on residential history in the UK, have been introduced in some countries such as the USA and Canada. To date there is no evidence of transmission of vCJD through these routes, but with an incubation period potentially of many years, it will be some time before the risks of secondary transmission can be excluded.

Variant CJD represents the first known transmission of an animal prion disease to humans and this has had profound economic and political implications. Human prion diseases continue to be very rare in comparison to many

other neurological disorders, but the full implications of the transmission of BSE to humans will not be known for many years.

## **Nipah in Malaysia**

### **A. KAMARULZAMAN**

#### **Infectious Diseases Unit, Dept of Medicine, University Malaya Medical Centre, Kuala Lumpur, Malaysia**

The Nipah virus outbreak that occurred in Malaysia between September 1998 and May 1999 posed an unprecedented challenge to the medical and public health profession in Malaysia. The disease caused 265 cases of encephalitis resulting in 105 deaths. The clustering of illness amongst employees of the pig farming industry led to the initial assumption that the outbreak was due to Japanese encephalitis (JE), a disease that is endemic in Malaysia. The Nipah virus, a member of the Paramyxoviridae family was first isolated from the cerebrospinal fluid from an encephalitic patient from the outbreak area and was subsequently identified as the causative agent for the disease. In contrast to JE where illness in pigs is not usually described, infected patients reported an increase in sick or dying pigs on the farms.

The disease was characterized by an acute febrile illness following an incubation period of 8-14 days, followed by a rapid deterioration in conscious state. Patients with Nipah encephalitis displayed some distinctive clinical features that included segmental myoclonus and evidence of brainstem dysfunction with hypertension and blood pressure instability, features that were not commonly described with JE. Laboratory examinations in Nipah encephalitis were usually non-specific, thrombocytopenia and elevation in liver transaminases were noted in 30-40 % of patients. Examination of the CSF was in keeping with an encephalitic process. MRI findings of hyperintense lesions in the gray-white matter appeared to be unique to Nipah encephalitis and were useful in the clinical diagnosis of these patients. Treatment consisted of supportive therapy and the antiviral ribavirin. In a historical control study ribavirin was shown to reduce mortality due to Nipah infection by 36% ( $p = 0.011$ ). More recently late onset disease and relapse of Nipah infection have been recognized.

Risk factors associated with acquiring Nipah infection include activities that brought workers into close contact with body fluids or secretions of infected pigs such as feeding, birthing and processing baby pigs. Although Nipah infection in pigs may be associated with an illness with respiratory and neurological symptoms, a significant number of infected pigs did not manifest symptoms. Furthermore other vectors may be associated with disease transmission with the observation that 8% of infected patients reported no direct contact with pigs.

In the initial phase of the outbreak, health-care workers (HCWs) were not using infection-control precautions to protect themselves believing that the encephalitis was due to the mosquito-borne JE. The isolation of Nipah virus from the nasopharynx and urine samples of several patients raised concerns that HCWs may have been exposed to the virus. Despite substantial contact with patients with outbreak-related encephalitis or potentially infectious body fluids from these patients by many HCWs or pathology workers, none had clinical evidence of infection. In a study of 338 health care workers (HCWs) exposed, three tested positive by EIA for IgG antibodies, no IgM response occurred, and the serum samples were negative for anti-Nipah virus neutralizing antibodies. All three had no evidence of clinical disease.

Following recognition of the link between infection in pigs and the outbreak, mass culling exercise was carried out in affected areas, which eventually led to the end of the outbreak. The economic loss to the pig-farming industry from this new disease was estimated to have been approximately RM1.3billion. Ongoing surveillance for infection in pigs continues to be carried out in the country.

Because of the close association between Nipah and the Hendra virus, a search for the natural host focused on pteropid bats, a natural host of Hendra virus in Australia was carried out. Neutralising antibodies to Nipah virus were demonstrated in five species suggesting widespread infection in bat populations in Peninsular Malaysia.

Investigating and managing an outbreak of this nature presents an enormous challenge particularly to countries with limited resources. Some of the lessons that were learnt from this outbreak include the importance of teamwork and cooperation, appropriateness of laboratory approach, careful data gathering and interpretation and rapid response. In a world where microbes are more and more capable of being agents of mass destruction either through a natural process as witnessed in this outbreak, or through deliberate acts, all countries have to be in a state of preparedness for future outbreaks. The importance of having good surveillance programmes, trained personnel, adequate equipment and biosafety laboratories is more crucial than ever.



**Epidemiology and Antigenic Drift of Swine and Human Influenza A Viruses**

**J.C. DE JONG<sup>1</sup>, I. DONATELLI<sup>2</sup>, G. BARIGAZZI<sup>3</sup>, K.-J. YOON<sup>4</sup>, W.L.A. LOEFFEN<sup>5</sup>, P. P. HEINEN<sup>6</sup>, R.A.M. FOUCHIER<sup>1</sup>, G.F. RIMMELZWAAN<sup>1</sup> & A.D.M.E. OSTERHAUS<sup>1</sup>**

<sup>1</sup>National Influenza Centre, Institute of Virology, Erasmus University Rotterdam, Dr Molewaterplein 50, 3015 GE, Rotterdam, The Netherlands; <sup>2</sup>Istituto Superiore di Sanità, Rome, Italy; <sup>3</sup>Istituto Zooprofilattico Sperimentale, Parma, Italy; <sup>4</sup>Iowa State University, Ames, IA, USA; <sup>5</sup>Animal Health Service, Deventer, The Netherlands; <sup>6</sup>ID-Lelystad, The Netherlands

**Background:** Virologically, swine and human influenza viruses are indistinguishable. However, host factors like immune pressure and opportunities for virus transmission differ for the two host species and may cause differences in antigenic drift and epidemiology.

**Methods:** In 1996 and 1997, 6 outbreaks of respiratory disease in finishing pigs in the Netherlands were associated with influenza H1N1 virus and 2 with H3N2 virus. The 26 H1N1 and 13 H3N2 viruses isolated from these outbreaks, 9 swine H3N2 viruses isolated in Italy in 1981-1999, and 4 isolated in the USA in 1999 were characterized by serological and molecular techniques.

**Results:** During the mid 1990s, swine H3N2 viruses in the Netherlands as well as in Italy lost their cross-reactivity with the human A/Port Chalmers/1/73 (H3N2) strain. Four swine H3N2 viruses isolated in the USA in 1999 were found to be antigenically related with the human H3N2 strain A/Wuhan/359/95. No antigenic drift was found with swine H1N1 viruses. Instead, the 26 H1N1 isolates studied showed a considerable heterogeneity. The concerning variants were strictly farm-bound. This contrasts with the epidemiology of human H3N2 viruses, which display a high degree of antigenic drift and a high stability of the resulting variants during geographical spread.

**Conclusion:** Swine influenza A(H3N2) and A(H1N1) viruses and human influenza A(H3N2) viruses show major differences in epidemiology and degree of antigenic drift.

**Reduced Cold-Sensitivity of the Polymerase Complex Derived from the A/Hong Kong/156/97 Strain as Compared to Complexes of Avian Influenza Viruses**

**P. MASSIN, S. VAN DER WERF & N. NAFFAKH**

**Unité de Génétique moléculaire des virus respiratoires, URA CNRS 1966, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France**

The influence of temperature on the functional efficiency of the polymerase complex derived from A/Hong Kong/156/97 (HK156), a strain of avian origin which was isolated from the first human case of influenza H5N1 infection in Hong Kong in 1997, was studied in comparison to complexes derived from human or avian influenza viruses. Making use of a genetic system for the *in vivo* reconstitution of functional ribonucleoproteins, the level of transcription/replication was found to be reduced approximatively two-fold at 33°C as compared to 37°C. This cold-sensitivity was intermediate with respect to complexes of human or avian origin. Cold-sensitivity of the polymerase complex derived from avian viruses was previously shown to be determined mostly by residue 627 of PB2 (a glutamic acid for avian viruses as well as HK156). Analysis of heterospecific complexes suggested that the PA protein could be responsible for the difference in cold-sensitivity between the HK156 strain and the A/FPV/Rostock/34 (FPV) avian strain. We generated cDNAs encoding chimeric HK/FPV- and FPV/HK-PA proteins, which were tested in combination with the HK-PB1, -PB2 and -NP proteins. Our results indicated that the N-terminal domain of the HK-PA protein determined the lower cold-sensitivity of the HK-derived complex as compared to the FPV-derived complex. Based on the alignment of available PA sequences, cDNAs encoding HK-PA proteins mutated at residues 85 (A<sup>↓</sup>T), 101 (D<sup>↓</sup>E), 118 (T<sup>↓</sup>I) or 142 (E<sup>↓</sup>K) were generated. The level of expression of the mutated HK-PA proteins, the efficiency with which they ensure transcription/replication within the HK-derived complex at 37°C and 33°C, and the level of proteolysis they induce were analyzed. The results suggest that the nature of HK-PA amino acid 118 is determinant for cold-sensitivity of the HK-derived complex, and thus may have contributed to the ability of the HK156 strain to replicate efficiently in the upper respiratory tract of humans.

## **Mutants of Influenza A H5N1 Haemagglutinin Protein Altered in the Predicted Receptor Binding Site** **RUTH HARVEY<sup>1</sup>, IAN JONES<sup>1</sup>, MARIA ZAMBON<sup>2</sup> & WENDY BARCLAY<sup>1</sup>**

**<sup>1</sup>School of Animal and Microbial Sciences, University of Reading; <sup>2</sup>CPHL Colindale**

All influenza viruses bind to cellular receptors terminating in sialic acid via their HA protein, but the specificity of HA towards these molecules differs. Avian viruses preferentially bind molecules terminating in Neu5Ac $\alpha$ 2,3 Galactose, whereas human viruses bind receptors terminating in  $\alpha$ 2,6-linked sialic acid. In 1997 there were 18 cases of transmission of H5N1 influenza virus from chickens to humans in Hong Kong, six of which were fatal. Notably, all viruses isolated from humans still bound preferentially to  $\alpha$ 2,3-linked sialic acid, illustrating that avian viruses can initiate infection and indeed cause death in humans without changing the HA protein. However, no human to human transmission was seen, leading to the suggestion that adaptive mutation of HA to change its binding specificity from  $\alpha$ 2,3 to  $\alpha$ 2,6-linked sialic acid is a prerequisite for a virus with true pandemic potential. We are investigating whether single point mutations predicted to increase the affinity of HA for  $\alpha$ 2,6 sialic acid receptors are tolerated by the H5 HA molecule, and whether indeed these mutations alter the protein phenotype as expected. Initially we are using exogenous expression systems to generate mutant H5 HA proteins and assess their intracellular transport and receptor binding properties in eukaryotic cells.

## **Resurgence of West Nile Fever in Israel 1998-2001**

**H. BIN<sup>1</sup>, M. HYNDYIEH<sup>1</sup>, L. SHULMAN<sup>1</sup>, L. WEISS<sup>1</sup>, Z. GROSSMAN<sup>1</sup>, D. GANDACU<sup>2</sup>, H. PENNER<sup>3</sup>, S. POKAMUNSKI<sup>4</sup>, S. SCHLEZINGER<sup>1</sup> & E. MENDELSON<sup>1</sup>**

**<sup>1</sup>Central Virology Laboratory, Tel-Hashomer; <sup>2</sup>Dept of Epidemiology and Infectious Diseases, Jerusalem; <sup>3</sup>Laboratory of Entomology, Jerusalem- Public Health Services, Ministry of Health, Israel; <sup>4</sup>Veterinary Services, Ministry of Agriculture, Beit Dagan, Israel**

West Nile virus is endemic in Israel and outbreaks of West Nile Fever (WNF) were recorded in the 1950's and 1970's. Sporadic human cases were recorded during the early 1980's and none during the late 1980's and early 1990's. In 1997 WNF appeared in domestic geese flocks where it caused fatal outbreaks. To investigate possible human infections the Central Virology Laboratory developed new assays for rapid diagnosis of WNF in humans, including ELISA IgG and IgM, IFA and RT/PCR. A serological survey among geese farmers and veterinarians in 1998/9 confirmed human infections associated with geese infections, and several current human infections were diagnosed in the southern rural region Eilat in 1999 and early 2000. Two fatal cases occurred in Tel-Aviv in the fall of 1999, and an outbreak began in July 2000 and lasted through October. During the 2000 outbreak 439 positive cases were found among app. 1600 patients (27%), 29 of them were fatal (6.6% case-fatality rate). Most cases were in the central region. Seven of 75 (9.3%) mosquito pools collected during the outbreak were positive by Real-Time RT/PCR. In 2001 938 patients were tested from January 1<sup>st</sup> to October 11<sup>th</sup> and 40 were positive (4.3 %) with one fatal case (2.5% case-fatality rate). The vast majority of the patients tested and 38 of the positives were from July on. 16 of 389 (4.1%) of mosquito pools were positive. The difference in the percent of positive cases and case-fatality rate between 2000 and 2001 clearly indicates that an outbreak occurred in 2000, rather than over-diagnosis, but not in 2001. Nucleotide sequence analysis of four human isolates from 2000 revealed two lineages of the virus, one of them closely related to the 1999 New York isolates. Mosquito isolates from 2000 and 2001 are under investigation.

## **Description of Nosocomial and Intrafamilial Spread of CCHF in Kosovo in 2001**

**M. PETROVEC<sup>1</sup>, D. DUH<sup>1</sup>, S. AHMETI<sup>2</sup>, I. DEDUSHAJ<sup>3</sup> & T. AVSIC-ZUPANC<sup>1</sup>**

**<sup>1</sup>Institute of Microbiology, Medical Faculty, Ljubljana, Slovenia; <sup>2</sup>Clinic of Infectious Diseases, Medical Faculty, Pristina, Kosovo; <sup>3</sup>IPH, Pristina, Kosovo**

Crimean-Congo haemorrhagic fever has been known to be endemic in Kosovo since 1954 in the municipality of Suhareke. Furthermore, Kosovo is also an endemic region of Haemorrhagic fever with renal syndrome. Because the clinical picture of CCHF resembling severe form of HFRS laboratory confirmation of the suspected cases is necessary. An outbreak of viral haemorrhagic fever occurred between May until July of 2001 in the Republic of Kosovo. One hundred ninety-two sera from 105 hospitalised suspected cases of viral haemorrhagic fever were available for laboratory testing. Specific anti-CCHF antibodies and/or detection of viral RNA confirmed twenty-nine CCHF cases. Seven patients died. During this epidemic only two patients were found as HFRS infection by demonstration of specific IgM antibodies and viral RNA in serum samples. From the second registered CCHF case during this epidemic three hospital-acquired infections were confirmed and in addition two intrafamilial cases occurred. Viral RNA could be detected in IgM positive samples up to day 16 of illness and in all seronegative patients which later on seroconverted. A portion of the S segment of the viral genome was sequenced from all PCR amplicons obtained. Sequence analysis phylogenetic relationship determined the possible origin of these infections.



## **Issues in Managing Viral Haemorrhagic Fevers**

**BARBARA BANNISTER, ROBIN GOPAL & KLAUS N.F. FLEISCHER**

**Royal Free Hospital, London NW3 2QG, UK; Viral Zoonosis Unit, CPHL, Colindale, London NW19 5HT, UK; Medical Mission Hospital, Salvatorstr. 7,P.B., D-97074 Wurtzburg, Germany**

Aim: to define best practice for delivery of safe and effective management for Viral Haemorrhagic Fevers.

Methods: review of care given, virology and infection control methods in VHF cases in the 1990s.

Results: all patients received appropriate care (antivirals, ventilation, haemodynamic monitoring, and renal support where indicated). No patient with multi-organ failure survived. Lassa virus was present in respiratory secretions.

'Universal precautions' were used before VHF diagnosis; one transmission of Lassa fever occurred, and the case of Ebola resulted from healthcare contact. After confirmation of VHF, methods of infection control included: self-contained respiratory protection, disposable impermeable clothing and patient isolators. Self-contained respirators prevented voice communication, could not be worn for more than 3 hours, and required rigorous decontamination and maintenance. Patient isolators were easy to use and decontaminate, but inhibited haemodialysis (but not peritoneal dialysis or haemodiafiltration). 13 carers commenced (but only 5 could complete) post-exposure ribavirin, which may have prevented one illness. No laboratory accidents or transmissions were recorded.

Conclusions: Critical care for VHF patients is feasible, but has not resulted in survival of severe disease. The patient isolator performed well, despite recent concerns about its usefulness. Universal precautions may not prevent transmissions to healthcare workers. Ribavirin prophylaxis for Lassa fever may be effective.

## **A Lethal Bite - A Case of Rabies in London**

**DAN AGRANOFF, NICOLA BRINK, ANTHONY FOOKS & TOM DOHERTY**

**Hospital of Tropical Diseases and Dept of Virology, University College London Hospitals and Rabies Research and Diagnostic Group (VLA Weybridge), WHO Collaborating Centre for the Characterisation of Rabies and Rabies-related Viruses, Weybridge, Surrey**

Case Report: A 56 year old man presented to hospital having being bitten on the palm of the hand by a dog whilst visiting the Philippines. He had not previously received rabies vaccine and did not seek post-exposure prophylaxis. Forty-three days after the bite he developed paraesthesiae over the palm, and a pain in the arm and neck. This progressed to complete dysphagia. On admission (Day 1) he had a low grade fever, was agitated and apprehensive but fully conscious. He exhibited hydrophobia and aerophobia with hyperventilation and laryngeal spasms which were worse on the sight or mention of water. The diagnosis of rabies was considered and on day 2 blood, saliva and a nuchal skin biopsy were tested using RT-PCR for rabies RNA and the Fluorescent Antibody Test (FAT) for rabies antigen; both were negative. From day 1-3 the patient's symptoms fluctuated with paroxysms of hyperventilation and dysphagia usually provoked by the sight or sound of water. On day 4 he developed confusion, urinary incontinence and atrial fibrillation followed by respiratory spasms, profuse salivation and ultimately a cardiorespiratory arrest. Cerebrospinal fluid, saliva and two skin biopsies (from the nape of the neck and the wound site) were submitted for repeat investigation. No rabies antigen was detected by FAT. However, RT-PCR detected rabies virus RNA in saliva and both skin biopsies, but not in CSF. On day 6 the virus was reported as classical rabies virus (genotype 1). Subsequent analysis showed the patient's virus to have a 99% homology to the Philippine dog strain. The patient was managed supportive in intensive care but died on day 8.

Conclusion: This case has illustrated the value of molecular diagnostic tests for the rapid identification of rabies in ante-mortem samples. However, the initial diagnosis still often rests on clinical and epidemiological features. Negative tests do not exclude a diagnosis of rabies.

## **Screening of Active Lyssavirus Infection in Wild Bat Populations by Viral RNA Detection on Oropharyngeal Swabs**

**JUAN E. ECHEVARRÍA<sup>1</sup>, ANA AVELLÓN<sup>1</sup>, SONIA VÁZQUEZ<sup>1</sup>, JAVIER JUSTE<sup>2</sup>, MANUEL VERA<sup>1</sup> & CARLOS IBÁÑEZ<sup>2</sup>**

<sup>1</sup>Centro Nacional de Microbiología, Instituto de Salud Carlos III, Ctra. Majadahonda -Pozuelo s/n , 28220 Majadahonda, Madrid, Spain, <sup>2</sup>Estación Biológica de Doñana, Consejo Superior de Investigaciones Científicas, 41013 Seville, Spain

Brain analysis cannot be used in Europe for the investigation of active lyssavirus infection on healthy bats because most bat species are protected by conservation directives. Consequently, serology remains as the only tool for performing virological studies on natural bat populations, however, the presence of antibodies merely reflects past exposure to the virus and is not a valid marker of active infection. A new nested RT-PCR technique specifically designed for the detection of the European bat virus 1 (EBV1), but able to amplify all the remaining rabies-related lyssaviruses was successfully used for surveillance of 24 serotine bat (*Eptesicus serotinus*) natural colonies in southern Spain from 1998 to 2001. Lyssavirus RNA was detected on 23 out of 548 samples. In one colony involved in a case of human exposure in a public building, slaughtering of bats was exceptionally authorized for sanitary reasons, so that simultaneous brain and oropharyngeal swab could be taken from 33 animals. Lyssavirus infection was detected on 13 oropharyngeal swabs, but in only 5 brains. The lyssavirus involved could be identified as European bat virus type 1 by automatic sequencing of the RT-PCR products obtained from 5 brains and 3 bat oropharyngeal swabs. In conclusion, RT-PCR on oropharyngeal swab will permit screening of wild bat populations for active lyssavirus infection, for research or epidemiological purposes, in line not only with conservation policies but also in a more efficient manner than classical detection techniques used on the brain.

## **Parapoxviruses: Recent Developments in Diagnosis and Treatment**

**P.F. NETTLETON, C. LOCKE, J.A. GILRAY & C. McINNES**

**Moredun Research Institute, Pentlands Science Park, Bush Loan, Edinburgh EH26 0PZ, UK**

Parapoxviruses cause orf in sheep and goats, papular stomatitis and pseudocowpox in cattle and skin lesions in other animals including red deer, seals, squirrels, reindeer, musk ox and camels. Human infection from contact with domestic animals is a common occupational disease with infection rates up to 34% in at-risk farming communities. As well as acquiring orf from sheep and goats and milker's nodule from cattle people can be unwittingly infected from other species. Human infections have been reported from seals, reindeer, musk ox and free-living deer. Our development of diagnostic PCRs has investigated eight sets of primers. Three sets amplified regions of 2 genes situated in the central conserved region of the genome, while 5 other sets were targeted at 4 genes situated in the terminal variable regions of the orf virus genome. A semi-nested PCR amplifying a 235bp region of a conserved envelope gene reliably amplified all of 10 orf virus isolates tested. Sequencing of products amplified by other primer sets has identified regions of DNA which could be useful for differentiation of parapoxviruses originating from different species. The activity of cidofovir against selected parapoxviruses has recently been evaluated *in vitro*. The growth of all three parapoxviruses was strongly inhibited justifying its evaluation as a candidate drug for the treatment of parapoxvirus infections in humans and animals.

## **Ovine Herpesvirus-2 Lytic Cycle Replication and Particle Production**

**J. ROSBOTTOM<sup>1</sup>, M. ACKERMANN<sup>2</sup>, R.G. DALZIEL<sup>1</sup>, H.W. REID<sup>3</sup> & J.P. STEWART<sup>1</sup>**

<sup>1</sup>Laboratory for Clinical and Molecular Virology, The University of Edinburgh, Summerhall, Edinburgh EH9 1QH, UK; <sup>3</sup>Moredun Research Institute, Pentlands Science Park, Penicuik, EH26 0PZ, UK;

<sup>2</sup>University Inst. of Virology, Winterthurerstr. 266a, 8057 Zurich, Switzerland

Ovine Herpesvirus-2 (OvHV-2) is the cause of sheep associated malignant catarrhal fever (SA-MCF), a lymphoproliferative and inflammatory disease of cattle, deer and other ruminants. The disease is found worldwide and is almost always fatal. Lymphoblastoid cell lines have been propagated from the tissues of cattle, deer, and rabbits affected with MCF. Although these cell lines transmit disease, little evidence of lytic viral replication has been found in these cell lines. This has hampered study of the virus and only limited sequence is available. To generate more sequence data we constructed a cosmid library using DNA extracted from an OvHV-2 infected bovine cell line. This has generated a series of overlapping clones spanning the majority of the virus genome. From sequence data of these cosmids, probes have been generated to show by RT-PCR for the first time evidence of expression of early and late viral genes in these cell lines. In addition, OvHV-2 particles were visualised for the first time in lysates from these lines by electron microscopy.

## **Sunshine, Warts and Skin Cancer**

**T. SURENTERAN<sup>1</sup>, C.M. PROBY<sup>2</sup>, J.M. MCGREGOR<sup>2</sup>, C.A. HARWOOD<sup>2</sup> & J. BREUER<sup>1</sup>**

**<sup>1</sup>Dept of Dermatology, Barts & The London, Queen Mary's School of Medicine & Dentistry, University of London, 2 Newark Street, London E1 2AT; <sup>2</sup>Dept of Virology, Barts & The London, Queen Mary's School of Medicine & Dentistry, University of London, 37 Ashfield Street, London E1 1BB**

It is speculated that HPV infection may be associated with the greatly increased incidence of skin cancer in immunosuppressed renal transplant recipients (RTRs). Unlike cervical cancer where the role of specific oncogenic mucosal HPV types has been established, the diversity of HPV types found in the skin and difficulties with HPV detection, have limited studies attempting to identify specific oncogenic cutaneous viruses. Using a highly sensitive and comprehensive degenerate PCR method we confirm a very high prevalence (>80%) of epidermodysplasia verruciformis-related HPV types (EV-HPVs) in transplant SCC with a lower prevalence (27%) of these EV-HPVs in immunocompetent SCC.

Paired biopsies found no difference in prevalence of HPV DNA from sun exposed and non-exposed normal skin. Prevalence of EV-HPV types was much greater in RTR than immunocompetent normal skin.

In the immunocompetent population, only EV-HPVs are found in skin cancers, whereas common cutaneous HPVs are present in benign viral warts. The picture is more complicated in transplant SCC where there is a high frequency of EV and cutaneous HPV types plus frequent co-detection of multiple HPV types within single tumours. Further analysis of viral localisation, load and replication status together with mechanistic studies are necessary to establish the contribution of HPV to skin carcinogenesis.

## **An outbreak of Norwalk-like virus at a recent ESCV meeting in Finland**

**CARL-HENRIK VON BONSDORFF**

**Haartman Institute, Department of Virology, Helsinki University**

At the 5<sup>th</sup> annual meeting of ESCV in Lahti, Finland in September 2001 food- and waterborne viral outbreaks were for the first time as a topic in the program of these meetings. The session took place on Tuesday the 4<sup>th</sup>. In the evening a banquet dinner was served. Less than 24 hours later, starting in the evening of the 5<sup>th</sup> a number of participants fell ill with vomiting, diarrhea and mild fever as the main symptoms. The onset of the illness for all affected occurred within 24 hrs.

Stool samples from the affected were obtained and studied at three different sites; RIVM Bilthoven, SMI Stockholm and HUCH Laboratory Diagnostics, Helsinki. In all instances a NLV of the type Melksham was recovered as determined by line blotting and amplicon sequencing. Based on these findings and on the clustering of the times of onset of the disease, a common source - preferably food or drink - could be suspected. As one victim ate only of the banquet buffet at the meeting, the suspicion was directed towards its menu.

Since e-mail addresses were available for all the participants, a rapid questioning could be undertaken on the occurrence and onset of disease. Close to 180 participants answered and 40 reported disease at the time in question. Subsequently an epidemiological survey was undertaken over a web-site. The survey was conducted by the Finnish NPHL. About one hundred answers were obtained. The analysis of the results is under way and will hopefully shed some light on the possible source of infection.

Stool samples of 13 persons of the kitchen personnel were studied. One was positive for the same NLV virus. She served at the banquet and fell ill the day after the banquet. This excludes her as causing the outbreak and suggests, that the outbreak did not originate from inadequate handling of the food locally. Interestingly, three other weakly positive samples of other than Melksham NLV strain were found among the personnel.

## **Hepatitis E Virus in Europe, an Emerging Zoonosis from a Pig Reservoir?**

**WIM H.M. VAN DER POEL, FROUKJE VERSCHOOR, REINA VAN DER HEIDE & ANA MARIA DE RODA HUSMAN**

**Microbiological Laboratory for Health Protection (MGB), National Institute of Public Health and the Environment (RIVM) P.O. box 1, Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, The Netherlands. +31 30 2743666; fax: +31 30 2744434; e-mail: Wim.van.der.Poel@rivm.nl**

Hepatitis E virus (HEV), a non-enveloped RNA (7.5 kb) virus, previously classified as a calicivirus but at present provisionally classified into a separate family of HEV-like viruses, is a major cause of viral hepatitis in much of the developing world. Clinical illness resembles other forms of acute viral hepatitis. Although the mortality rate is usually low (0.07-0.6%), the illness may be particularly severe among pregnant women, with mortality rates reaching as high as 25%. In non-endemic regions like Europe, HEV infections present like single cases, primarily reported among travellers to HEV-endemic regions. However, HEV antibodies can be detected in non-travellers and there are several recent reports of HEVs detected in hepatic patients who had not been abroad. In these cases the origin of the infection was unknown. A spill-over from an animal reservoir could be an explanation for this observation.

To investigate if HEVs are commonly present in swine in the Netherlands, pooled stool samples, collected from 115 swine farms, were assayed by a reverse transcription-polymerase chain reaction (RT-PCR) amplification. HEV-RNA was detected in 25 of the specimens (22%). RT-PCR amplification products were sequenced and compared with published sequences. HEVs from swine in the Netherlands were clustered in at least two groups, together with European and American isolates from swine as well as humans. Our data show that HEVs in swine in the Netherlands were genetically closely related with HEVs isolated from humans.

So far viruses identical to the detected swine HEVs have not been found in humans, and zoonotic transmission has not been proven. Nevertheless these findings indicate that swine may be reservoir hosts of HEVs, and it needs to be elucidated if the species can be a risk factor for HEV infection in humans in Europe. Since swine tissues are the primary tissues in studies of xenotransplantation, HEV infection may constitute a public health hazard in xenotransplantation.

## **Hepatitis E Virus: Comparative Evaluation of Antibody Assays in a Low-Endemicity Setting**

**M. ASANTE, W. PREISER & H.W. DOERR**

**Institute for Medical Virology, J. W. Goethe University, Paul Ehrlich -Str. 40, D-60596 Frankfurt a. M., Germany**

Background: Antibody testing remains the most commonly used technique for the diagnosis of hepatitis E virus (HEV) infection. However, the sensitivities and specificities of current HEV antibody tests are still unknown. Studies in non-endemic areas found seroprevalence rates of several percent without matching histories of non-A-D hepatitis. There is also continuing uncertainty about antibody persistence after infection and about the possibility of zoonotic transmission of HEV or a closely related agent.

Objective: To compare the performance of three HEV antibody assays in a low -endemicity setting.

Methods: Sera from long-term expatriates in endemic countries were routinely tested by Abbott EIA. Forty-five were selected on the basis of at least borderline reactivity and eight as negative controls. Assays (recombinant antigens) used were: Abbott EIA (C-terminus of ORF2, full ORF3; Burmese strain); Genelabs ELISA (specific type-common epitopes from ORF2 and ORF3; Mexican and Burmese isolates); Mikrogen recomBlot (N-terminal, C-terminal and middle portion of ORF2, full ORF3; Madras isolate).

Results: Concordance rates between assays were: Abbott - Genelabs 51.3 %, Abbott - Mikrogen 79.4 %, Genelabs - Mikrogen 61.9 %.

Conclusions: Like previous investigators, we found a high rate of divergent results. The interpretation of HEV antibody test results remains problematic. A "grey zone" needs to be defined as low -level reactivity is common and mostly cannot be confirmed by additional tests.

## **Are HBV Load Measurements Useful in HIV/HBV Coinfected Patients?**

**C. AITKEN, K. TEMPLETON, H. WHEELER & C. SKINNER**

**Virology Dept and Infection and Immunity, Barts and the London NHS Trust, St Bartholomew's Hospital, Smithfield, London EC1A 7BE**

Purpose of study: To investigate the changes and clinical significance of HBV DNA load measurements over time in an HIV/HBV co-infected cohort.

Summary of methods and results: 45 HIV/Hepatitis B (30 eAg+ 15 eAb+) coinfecting patients were identified. Mean CD4 count 150 (20-420) and HIV viral load log 5.1 (range 3.0-6.0). 35 were treated with a 3TC containing regimen for their HIV disease. Retrospective HBV DNA testing was performed on stored samples. Mean duration of follow up was 25 months.

Results: 11/46 patients were ARV naive and HBV DNA levels remained constant in 10 (<0.5 log variation). Of the 3TC treated patients (34) 20 showed a partial response (2 log drop in load with return to baseline (15 eAg+ 5 eAb+) and 14 a sustained response (sustained HBV DNA < log 5, 7 eAg+ 7 eAb+). M552V mutation was detected in all partial responders when HBV DNA levels increased, in 17 of these patients biochemical hepatitis was detected and 4 patients required hospitalisation. 3TC withdrawal precipitated hepatitis in a further 7 patients, no 3TC mutations were detected in these patients.

Conclusions: 3TC withdrawal can be associated with severe hepatitis. Routine monitoring of HBV DNA levels may be useful in the management of coinfecting patients.

## **Study of Shingles and its Development to Postherpetic Neuralgia in East London**

**F.T. SCOTT<sup>1</sup>, M.E. LEEDHAM-GREEN<sup>1</sup>, W. BARRETT-MUIR<sup>1</sup>, L. BATTY<sup>1</sup>, K. HAWARAMI<sup>1</sup>, J. GALLAGHER<sup>2</sup>, R. JOHNSON<sup>3</sup> & J. BREUER<sup>1</sup>**

<sup>1</sup>Dept of Virology, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London, 37 Ashfield Street, London E1 1BB; <sup>2</sup>Dept of Anaesthesia, Barts and The London NHS Trust, West Smithfield, London EC1A 7BE, <sup>3</sup>Dept of Anaesthesia, Bristol Royal Infirmary, Maudling Street, Bristol BS2 8HW

Our prospective population study takes referrals from General Practitioners and the Hospital Trust. We aim to identify virological factors influencing the reactivation of Varicella, and develop guidelines to identify those at risk of developing PHN.

We note basic demographics and medical history, and assess prodromal and present pain using a variety of measures. Samples of vesicle fluid and blood are collected. Patients are then seen at 6 weeks, 3 months, 6 months 1 year or discontinued when PHN resolves.

200 referrals (73.8%) have laboratory confirmation of diagnosis; 17.5% have other dermatological conditions including HSV. Gender is evenly distributed. Age shows a bimodal distribution not related to immunosuppression. 77.5% (155) felt pain was affecting their ADL. 136 have now been followed up for 1 year: 18(13.2%) have developed PHN or residual abnormal sensations: 9(6.6%) of these report their ADL and sleep are still affected. 81(40.5%) patients commenced antiviral therapy within 72hrs of rash onset, compared to 8(44%) of patients who developed long-term PHN.

### Conclusions:

- 17.3% of patients were incorrectly diagnosed with Shingles.
- 56% of patients with PHN at 1 year had not received optimum acute antiviral therapy.

PHN may develop despite appropriate treatment.



## **Molecular Investigation of a Prolonged Outbreak of Parainfluenza 3 on a Haematology Unit: Implications for Infection Control**

**H. JALAL, J. BENNETT, D.F. BIBBY & K.N. WARD**

**Dept of Virology, Windeyer Institute of Medical Sciences, Royal Free & University College Medical School, 46 Cleveland Street, London W1T 4JF**

Parainfluenza virus (PIV) is a cause of pneumonia and death following stem cell transplant (SCT). A 5 month outbreak of PIV3 involving three wards on a haematology unit was investigated using RT-PCR and sequencing of part of the PIV3 F gene to assess strain variation. Sequence analysis of nasopharyngeal aspirates taken from 27 patients involved in the outbreak showed that 26 of these patients had identical sequences, confirming transmission within the unit. Analysis of the same region of the PIV3 genome of 5 community isolates circulating at the same time as the outbreak yielded different strains. Infection control was difficult as lengthy shedding of virus occurred in several SCT patients; measures included closing the unit and cohort nursing of patients but the outbreak was not controlled until it became possible to transfer the remaining infected patients to the hospital's infectious diseases unit. Studies of nasopharyngeal aspirates from 5 haematology patients who became infected during the following year's community wide outbreak also yielded sequences unrelated to the outbreak strain.

We conclude that sequence analysis of the PIV3 F gene is not only capable of defining the role of nosocomial transmission in outbreaks of PIV3 infection but also in developing policies for effective infection control.

## **Molecular Characterization and Severity of Symptoms Associated with Type of Respiratory Syncytial Virus Isolates**

**U. ILGERT<sup>1</sup>, U. WEGNER<sup>1</sup>, R. BRUNS<sup>2</sup>, L. GÜRTLER<sup>1</sup> & R. MENDEL<sup>1</sup>**

**<sup>1</sup>Friedrich Loeffler Institute for Medical Microbiology, <sup>2</sup>Dept of Paediatrics, University Hospital, Ernst-Moritz-Arndt-University Greifswald, Martin-Luther-Straße 6, D-17487 Greifswald, Germany**

RSV belongs to the leading viral cause of severe lower respiratory tract illness in children as well as in the elderly and in immunocompromised bone marrow recipients. This patient group would benefit from effective antiviral options for RSV, antiviral drugs and/or immunotherapy. Therefore a sensitive and rapid diagnosis of type and subtype of this viral pathogen, partially associated with a severe course of the disease, is necessary.

From January 2000 to May 2001 356 clinical samples of patients which were hospitalised with respiratory tract infection in the university children hospital were evaluated for RSV using antigen ELISA, RT-PCR, subgroup PCR and partially sequencing. The primer set for screening PCR was derived of the F gene. The subtype PCR was performed with primers placed in the N and P region of the RSV genome. In 94 (26.4%) samples RSV was detected by PCR and only in 23 (6.5%) samples by antigen ELISA. Thus the RT-PCR was very efficient in detection and superior to the antigen assay. Subtype analysis showed that both subgroups A and B were cocirculating in the evaluated period. Most isolates were characterized as subgroup A (90.2%). Remarkably was the severe course of diseases observed for type B, in contrast to previous reports.

Analysis of nucleotide and deduced amino acid sequences showed that all isolates of type A were closely related to strain MAD-6-92. The lowest homology was found with strain Long.

### **Yellow Fever Virus is Enzootic in Peru and Bolivia**

**J.E. BRYANT<sup>1</sup>, H. WANG<sup>1</sup>, C. CABEZES<sup>2</sup>, P.C. VASCONCELOS<sup>3</sup>, A. GIANELLA<sup>4</sup>, K. RUSSELL<sup>5</sup>  
D.M. WATTS<sup>5</sup> & A.D.T. BARRETT<sup>1</sup>**

<sup>1</sup>Center for Tropical Diseases, University of Texas Medical Branch, Galveston, TX, USA; <sup>2</sup>Instituto Nacional Salud, Lima, Peru, <sup>3</sup>Instituto Evandro Chagas, Belem, Brazil; <sup>4</sup>CENETROP, Santa Cruz, Bolivia; <sup>5</sup>U.S. Naval Medical Research Center Detachment, Lima, Peru

Yellow fever (YF) virus is an important reemerging disease. The natural transmission cycle of the virus remains poorly understood, however it has long been assumed that inter-epidemic maintenance involves transmission within primate populations. The virus is believed to move continually through the jungle in epizootic waves of infection. Our studies of the geographic distribution of 68 viral from South America suggest that this paradigm of transmission may not be true. Phylogenetic analyses indicate there are two major genotypes circulating within South America; one genotype (I) is found exclusively in Peru and Bolivia while the second genotype (II) is found in all other areas of South America, including Brazil, Colombia, Ecuador, Panama, Trinidad and Venezuela. Peru and Bolivia account for over 85% of all YF cases reported from South America; the largest recent epidemic occurred in 1995, with approximately 700 cases occurring throughout the eastern foothills of the Peruvian Andes. Nucleotide sequencing of 12 strains from the 1995 epidemic revealed up to 7% nucleotide variation. Repeated virus isolations from the same geographic areas at different time points suggest that particular variants are locally maintained. In addition, epidemiological data reveal that YF cases occur each year in the same areas. The combined evidence from prevalence data and the pattern of genetic diversity together strongly suggests the presence of multiple enzootic foci of YF virus genotype I in Peru and Bolivia.

### **Lack of Evidence for the Cross-Species Transmission Hypothesis for the Origin of Hepatitis B Virus in Humans**

**SOFIE STARKMAN & PETER SIMMONDS**

**Virus Evolution Group, Laboratories of Clinical and Molecular Virology, University of Edinburgh, Summerhall, Edinburgh EH9 1QH**

Hepatitis B Virus (HBV) shows geographic differences in genotype distribution, with genotypes A and E predominantly found in Sub-Saharan Africa. HBV is also found in both Old and New World primates in the wild. There is currently major uncertainty surrounding the origin of HBV in humans, and three main hypotheses have been proposed; a South American origin, co-evolution with man as he moved out of Africa, and cross-species transmission. We have been looking for evidence of this last hypothesis. The areas of high HBV infection rates in humans correspond with the areas where contact between humans and other primates is most likely, namely South America, Southeast Asia and Sub-Saharan Africa. In this study we screened 332 human serum samples from Sub-Saharan Africa as well as 163 primate serum samples using PCR. 92 of the human samples were found to be positive. None of the positive human samples correspond with chimpanzee HBV sequences, with 64.7% being genotype E, 23.5% genotype A, and 11.8% genotype B. Of the primate samples 4 chimpanzees and 5 gibbons were found to be positive. These sequences correspond to previously published chimpanzee and gibbon HBV genotypes.

The absence of chimp-like sequences within the human samples of this study group and the absence of human-like sequences within the primates provides no evidence so far for frequent cross-species transmission of HBV.

**Diagnosis of Flavivirus Infections by Immunofluorescence and Enzyme-Linked Immunosorbent Assay**  
**P. KORAKA<sup>1</sup>, H. ZELLER<sup>2</sup>, M. NIEDRIG<sup>3</sup>, A.D.M.E. OSTERHAUS<sup>1</sup> & J. GROEN<sup>1\*</sup>**

<sup>1</sup>Laboratory for Exotic Viral Infections, Institute of Virology, Erasmus Medical Centre Rotterdam, The Netherlands; <sup>2</sup>C.N.R des Arbovirus et des Fièvres Hémorragiques Virales, Institut Pasteur, Paris, France; <sup>3</sup>Robert Koch-Institut, Berlin, Germany

Flavivirus infections are a significant public health problem, since several members of the *Flaviviridae* family are highly pathogenic to humans. Accurate diagnosis and differentiation of the infecting virus is important especially in areas where more Flaviviruses are circulating. In this study we evaluated a newly developed commercially available immunofluorescence assay (IFA) (INDX, USA) for the detection of IgM and IgG antibodies against dengue virus (DEN), yellow fever virus (YFV), Japanese encephalitis virus (JEV) and West Nile virus (WNV). The IFA was compared with standard diagnostic enzyme immunoassays (EIAs) specific for these viruses. Forty-seven serum samples from patients with a defined Flavivirus infection were tested (n=13 from DEN patients, n=10 from YFV patients, n=12 from JEV patients and n=12 from WNV patients). As controls, serum samples from individuals with antibodies against tick-borne encephalitis virus (n=15), Hepatitis C virus (n=8) and from healthy individuals (n=5) were included. The results obtained from this study indicated that the IFA showed a significant better discrimination for Flavivirus specific IgM antibodies compared to the standard IgM specific EIAs. In contrast, the detection of Flavivirus specific IgG antibodies showed high cross-reactions in both the IFA and the EIAs. Therefore, the Flavivirus IFA is a useful tool for the identification of the infecting Flavivirus during the acute stage of disease. In particular, IFA can be an important diagnostic tool for testing samples from travellers that have accidentally been exposed to these viruses.

**Louping-ill In the UK: A Zoonosis with Unfulfilled Potential**

**H.W. REID & P.F. NETTLETON**

**Moredun Research Institute, Pentlands Science Park, Bush Loan, Edinburgh EH26 0PZ, UK**

In the UK disease caused by Tick-borne encephalitis (TBE) virus is primarily seen in domestic sheep and is known as louping-ill (LI). Although infection of humans can result in severe and even fatal disease this appears to occur rarely for reasons that remain speculative. During investigations to identify the native vertebrate host of LI it became progressively apparent that the only candidate was the red grouse (*Lagopus scoticus*). However, as both experimental and natural infection of this species resulted in very high mortality it is improbable that they represent a natural host for the virus since, as with the recent heavy mortality in native American birds following the introduction of West Nile virus, disease in wild species due to flaviviruses is indicative of recent introduction to their habitat. Through both a detailed historical analysis of the development of the sheep industry in the UK and molecular characterisation of the envelope gene of isolates from throughout the British Isles it is apparent that LIV has been introduced relatively recently. Thus, as with other flaviviruses, disease in free-living animals can be an early indicator of ecological perturbation. This phenomenon will be considered together with those factors which contribute to the low incidence of infection in humans.

### **Genetic Diversity of Hantaviruses Circulating in Slovenia**

**T. AVSIC-ZUPANC<sup>1</sup>, M. PETROVEC<sup>1</sup>, T. TRILAR<sup>2</sup>, K. PROSENC<sup>1</sup> & D. DUH<sup>1</sup>**

**Institute of Microbiology, Medical Faculty, Ljubljana, Slovenia; <sup>2</sup> Natural History Museum, Ljubljana, Slovenia**

Results of previous epidemiological, clinical and virological studies of hantavirus infection in Slovenia indicated the presence of different hantaviruses. To elucidate the existence and genetic variability of various hantaviruses spreading by their natural hosts, rodents from several geographical locations were examined. Animals were collected between 1990 and 1998 at known endemic HFRS regions. On overall 20 % of animals were seropositive. Out of 108 seropositive animals, hantavirus RNA was detected in 91 samples when the G1 region was examined. By using type-specific inner primers DOB virus was found in *A. flavicollis* (from 5,5% to 34,9%) and in *A. agrarius* (23,1% in a single locality). PUU virus was detected only in *C. glareolus* (from 0% to 50%). Representative 18 samples were proceeded for sequence analysis. Ten samples of DOB virus, originated in five localities, displayed G1 segment nucleotide (NT) sequence homology between 82% and 99%. The highest NT divergence (13,7%) was observed in DOB virus detected in *A. agrarius*. PUU samples varies the most (85% NT homology), indicating also the existence of two different PUU subtypes, with a regard of their geographical origin. Results of this study revealed that there is a substantial evidence of the existence of genetic interspecies diversity in DOB virus and a genetic intraspecies diversity of PUU virus. We conclude that genetic heterogeneity exists among two hantaviruses in Slovenia with a possible co-evolutionary relationship between the virus and the natural host reservoir.

### **Serological Evidence of Hantavirus in Humans and Rodents in Barbados**

**J. GROEN<sup>1</sup>, P. KORAKA<sup>1</sup>, C.N. EDWARDS<sup>2</sup>, S.L. BRANCH<sup>2</sup>, K.O. DOUGLAS<sup>2</sup>, A.D.M.E. OSTERHAUS<sup>1</sup> & P.N. LEVETT<sup>2</sup>**

**<sup>1</sup>Laboratory for Exotic Viral Infections, Institute of Virology, Erasmus Medical Centre Rotterdam, The Netherlands, <sup>2</sup>University of the West Indies, School of Clinical Medicine & Research, Queen Elizabeth Hospital, and Leptospira Laboratory, Ministry of Health, Barbados**

In order to determine the presence of hantavirus infections in Barbados, we studied patients admitted to the Queen Elizabeth Hospital, Barbados during the year 2000, with signs and symptoms suggestive of leptospirosis or dengue fever. Of 69 patients, nine were confirmed as leptospirosis cases and were not tested any further. From the 60 patients without leptospirosis, sera were investigated for the presence of hantavirus-specific IgM and IgG antibodies with a commercially available ELISA (Focus Technologies, Cypress, CA). Positive results were confirmed by immunofluorescence slides coated with Vero cells infected with Hantaan, Puumala or Seoul viruses. To investigate possible reservoir hosts of hantavirus in Barbados, 68 sera from *Rattus norvegicus*, three from *Rattus rattus* and four from *Herpestes auropunctatus* were tested for the presence of hantavirus-specific antibodies. Serology indicated an acute or recent infection with hantavirus in 18% patients (11/60). Seven patients (12%) had IgM antibodies in the absence of IgG antibodies, whereas five patients (8%) had both IgM and IgG antibodies. The majority of the sera reacted most strongly against Puumala and Seoul viruses; however, the different hantavirus serotypes causing HFRS have a relatively strong cross reactivity. Infection with Puumala and Seoul viruses cause mild HFRS symptoms. Among the rodent species, 28% *R.norvegicus* (19/68) were sero-positive, but none of the *R.rattus* or the *H.auropunctatus* were seropositive. These findings indicate that *R.norvegicus* is a possible reservoir host of hantavirus in Barbados. Seoul-like viruses are the most widely distributed hantaviruses and are frequently found in harbour cities throughout the world. Serological evidence of hantavirus infections in Barbados is important, since other infections with similar clinical features are present, such as leptospirosis and dengue. This is the first report of hantavirus infection in humans or animals from the southern Caribbean region. The differential diagnosis of acute febrile illnesses in this region should include hantaviruses, especially in patients that have been in contact with rodents or other small mammals.



**Poster no. 01**

**Emergence of Foot-and-Mouth Disease in North India**

**SHARAD K. YADAV, S.K. SHARMA & B.C. PAL**

**Dept of Epidemiology & Preventive Medicine, College of Veterinary Science & Animal Husbandry, Mathura U.P., India**

A systematic epidemiological study on foot-and-mouth disease was conducted to assess geographical distribution and seasonal occurrence of different types and subtypes of the virus associated with this disease and the factors associated with the maintenance and spread of infection in selected areas of North India. For FMD virus isolation and typing work, a total of 21 specimens of vesicular epithelium were collected during this year from different outbreaks of FMD. All of these were collected from buffaloes, the main species involved during the various outbreaks. While 11 of the strains were type "O" FMD virus.

Of these 25 outbreaks, 18 were subjected to detailed epidemiological analysis, which revealed an overall morbidity of 26.1%, the focal morbidity varied from as low as 1.0% as high as 73.2%. Amongst the different susceptible species, Pigs showed the highest overall attack rate of 41.0% followed by buffaloes (27.7%) cattle (24.3%) and goats (0.84%). Of the 191-recorded deaths, buffaloes shared the largest proportion with 171 adult animals deaths followed by cattle (19) & Pigs (1). A buffalo trembled and died instantly; autopsy revealed presence of a single small vesicular lesion on the dorsum linguae and pinpoint haemorrhages on the myocardium. The piece of myocardium yielded type "O" virus. Reports are also available from Mexico and Brazil, recording occurrence of malignant form of FMD. The zoonotic impotence of the disease was also studied.

**Poster no. 02**

**A Rapid RT-PCR Method to Differentiate Six Established Genotypes of Rabies and Rabies-Related Viruses Using TaqMan™ Technology**

**LORRAINE M. McELHINNEY, JEMMA SMITH & ANTHONY R. FOOKS**

**Rabies Research and Diagnostic Group, Dept of Virology, Veterinary Laboratories Agency (Weybridge), New Haw, Addlestone, Surrey KT15 3NB, UK**

The objective of this study was to develop a rapid and sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) assay incorporating TaqMan™ probes that will distinguish between the six established rabies and rabies-related virus genotypes. TaqMan™ probes were designed and validated against 106 rabies and rabies-related virus isolates, one isolate of the Australian bat lyssaviruses (genotype 7), and 18 other non-rabies viruses important in the veterinary field. The highly conserved nucleoprotein (N-gene) was used as the target for the probes. The N-gene region was chosen as it has been extensively used to genotype rabies isolates and was found to contain regions conducive to probe design. The RT-PCR assay described amplifies all rabies and rabies-related viruses tested. The inclusion of specific TaqMan™ probes allows for the rapid identification and classification of suspect rabies virus isolates in a closed tube system, thereby preventing potential PCR-product carry over contamination.

**Poster no. 03**

**Investigation of a Human Rabies Case within the UK**

**N. JOHNSON<sup>1</sup>, K. MANSFIELD<sup>1</sup>, J. SAWYER<sup>1</sup>, J. SMITH<sup>1</sup>, S.M. BROOKES<sup>1</sup>, G. RAO<sup>2</sup>, G. PARSONS<sup>1</sup>, L.M. McELHINNEY<sup>1</sup> & A.R. FOOKS<sup>1</sup>**

<sup>1</sup>The Rabies Research and Diagnostic Group, Veterinary Laboratories Agency - Weybridge, New Haw, Surrey KT15 3NB, <sup>2</sup>University Hospital Lewisham, London SE13 6LH

The UK is free of rabies, however, since 1977, nine cases of human rabies have been reported where infection occurred abroad. One such case was reported earlier this year in an individual visiting the UK from Nigeria (June, 2001). Antemortem tests were negative but both fluorescent antibody test (FAT) and reverse transcriptase polymerase chain reaction (RT-PCR) confirmed the diagnosis on post-mortem tissue. Phylogenetic analysis of two genomic segments of this isolate confirmed that it was a classical rabies virus (genotype 1) of the Africa 2 sub-group. Comparison with a previous UK rabies case of Nigerian origin (1996) shows that both viruses show remarkably close sequence homology (>99%) at both genomic and amino acid levels. Subsequent analysis of the tissue distribution of viral antigen and genome, identified virus in four compartments of the brain (cerebellum, cortex, pons and hippocampus), the skin and salivary glands. Virus could not be detected within heart tissue. Real time semi-quantitative PCR suggested that elevated levels of virus were found within the cerebellum and hippocampus. This could be explained by the proximity of these tissues to the spinal chord, the presumed entry point of the virus to the brain. Alternatively, it may demonstrate a tropism for the virus to tissues involved in behavioural control

**Poster no. 04**

**Viruses Associated with Canine Infectious Respiratory Disease**

**K. ERLS, C. TOOMEY, V.J. CHALKER, H.W. BROOKS, S. OPPERMAN & J. BROWNLIE**

**The Royal Veterinary College, Dept of Pathology and Infectious Diseases, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK**

Canine Infectious Respiratory Disease (CIRD) commonly called "kennel cough" is a disease complex that affects dogs housed in crowded conditions. It is highly contagious and symptoms range from mild cough to severe bronchopneumonia. In collaboration with a well-established kennel with a history of endemic CIRD we are investigating the causative agents of this disease.

Using tissue culture as well as PCR and RT-PCR, respiratory tract samples were tested for the presence of several viruses that have previously been reported to be a cause of CIRD.

Canine Parainfluenza was detected by RT-PCR in tracheal samples of 15% of all dogs tested, despite prior vaccination on entry into the kennel. Canine Adenovirus Type 2 however was not detected and does not seem to be present in this kennel.

Interestingly Canine Herpesvirus (CHV) was isolated and also detected by PCR in both tracheal and lung samples. Dogs with more severe respiratory symptoms showed a higher prevalence of Canine Herpesvirus than dogs with mild or no symptoms. The sequence of a section of the glycoprotein B gene of several CHV isolates was determined and compared to published sequences of CHV.

Furthermore as shown by a serum neutralisation test, a higher percentage of dogs with respiratory disease showed a seroconversion to CHV compared to dogs without symptoms.

Additional studies are required to determine the importance of Canine Herpesvirus infections in dogs with CIRD.

### **Poster no. 05**

#### **Host Restrictions for Transmission of Avian Influenza Viruses to Humans**

**WENDY BARCLAY<sup>1</sup>, YAO YONGXIU<sup>1</sup>, ANGIE LACKENBY<sup>1,2</sup> & JOHN McCAULEY<sup>2</sup>**

**<sup>1</sup>School of Animal and Microbial Sciences, University of Reading; <sup>2</sup>BBSRC Institute of Animal Health, Compton**

Influenza A viruses are widespread and heterogeneous in birds. Only rarely do avian influenza viruses cross the species barrier and infect mammals and the reason for this restriction is not clear. The outcome of virus infection in a new host is determined by the dynamics of the virus replication and the host antiviral response, both innate and acquired.

Most naturally occurring strains of avian influenza virus do not undergo fully competent replication and thus do not form plaques in mammalian cell lines. By multiple passage in mammalian cells, host range variants of avian have been selected which show increased replication in their adaptive hosts. Using reverse genetics we have shown that a region of the PB2 polypeptide controls replication in human and mouse cells. This region extends from 362 to 582 of PB2. Within this region residue 482 differed in the host range variant, 4H, compared to its parent (Dobson) and also compared to Rostock S3. Selection of engineered viruses was carried out in mouse L cells and all recombinant viruses able to grow in mouse L cells were also able to replicate in A549 cells. It seems likely that important variation in host range is controlled by this region in PB2. Interestingly, this region does not include residue 627 which previously shown to control replication in canine cells and virulence in the mouse. Thus PB2 may interact with the host cell and affect host range in several distinct ways.

### **Poster no. 06**

#### **High Prevalence of TT Virus Genome in Male HIV-1 Infected Patients and Blood Donors**

**DAVID REY<sup>2</sup>, ANNE FUCHS<sup>1</sup>, ELIANE FRICK-MICHOT<sup>2</sup>, JEAN-MARIE LANG<sup>2</sup>, PIERRE MEYER<sup>2</sup>, EVELYNE SCHVOERER<sup>1</sup> & FRANÇOISE STOLL-KELLER<sup>1</sup>**

**<sup>1</sup>Institut de Virologie, 3 rue Koeberlé, 67000 Strasbourg, France, <sup>2</sup>CISIH, Clinique Médicale A, HUS**

The prevalence of TTV in HIV-1 infected patients and blood donors was assessed by PCR using two primer sets: (i) T primers derived from the ORF1 region N22 detecting essentially genotype 1 or viral strains associated with hepatitis of unknown etiology, (ii) B primers derived from the untranslated region localized upstream of ORF-2 detecting genotype 1, 2 and 3. HIV infected patients (383) were prospectively included and 105 healthy blood donors.

Using T primers, TTV was detected in 5.8 % healthy individuals as compared to 51.4 % with B primers. The prevalence of TTV was 57% in male and 37% in female (p=0.056) with B primers.

In HIV infected patients, results based on T primers show a prevalence of 9.8%. There was no differences in terms of sex, age, way of contamination, immunosuppression, CDC clinical classification. However the TTV was detected in 29.2% Africans (Sub-Sahara), versus 8.3% non Africans (p=0.001).

With B primers, 67% of patients were infected by TTV. The difference between male and female was 70.5% versus 58.3% (p=0.033). Interestingly TTV DNA was detected in 95.6% Africans versus 64.8% non Africans (p=0.002).

The presence of TTV genome was examined in the PBMC of 23 patients with a positive PCR in their serum (T primers) after washing the cells with trypsin. The viral genome was detected in 20 PBMC samples.

As described in immunocompetent patients no relationship between hepatitis and TTV infection was observed.



**Poster no. 07**

**A Study of Cellular Adhesion, Structural, Transport Proteins, and Apoptosis in Human and Mouse Japanese Encephalitis**

**P.M. WINTER<sup>1,2</sup>, L.T. THAO<sup>3</sup>, N.M. DUNG<sup>3</sup>, R. KNEEN<sup>4</sup>, K.S. MYINT<sup>5</sup>, J. FARRAR<sup>4</sup>, M.J. CARDOSA<sup>6</sup>, M. ROSSI<sup>1</sup>, A.D.T. BARRETT<sup>7</sup>, G.D. TURNER<sup>4</sup>, C.A. HART<sup>2</sup> & T. SOLOMON<sup>1,2</sup>**

<sup>1</sup>Depts of Neurological Sciences, and of <sup>2</sup>Medical Microbiology and Genitourinary Medicine, University of Liverpool, UK, L69 3GA; <sup>3</sup>Centre for Tropical Diseases and <sup>4</sup>Wellcome Trust Clinical Research Unit and The Centre for Tropical Diseases Ho Chi Minh City, Vietnam, <sup>5</sup> Armed Forces Research Institute for Medical Science, Bangkok, Thailand; <sup>6</sup>University Malaysia, Kota Samarahan, Sarawak; <sup>7</sup>Centre for Tropical Diseases, University of Texas Medical Branch, Galveston, Texas, USA

Japanese encephalitis (JE) is a CNS infection caused by Japanese encephalitis virus (JEV), a single stranded positive sense RNA enveloped mosquito-borne flavivirus. JE is the most common epidemic viral encephalitis worldwide, causing approximately 35-50,000 cases and 10,000 deaths per year. A mouse model has provided useful insights, but the pathogenesis of JE is not completely understood. Recruitment of host inflammatory cells, including; neutrophils, CD8+ and CD8- T cells is thought to be important in humans, but the roles of cellular adhesion, structural and transport proteins are unknown. In some CNS infections apoptosis is important, but its importance in JE is unknown.

The aim of the work was to investigate, using immunohistochemistry the effect of JEV infection upon the central nervous system (CNS). This was achieved by the assessment of post-mortem samples obtained from 13 Vietnamese JE patients, mice infected intracerebrally inoculated with JEV (a neurovirulent strain SA14, or the attenuated Nakayama strain). All samples were fixed in formalin and paraffin embedded. Bcl-2, GFAP, N-CAM, CD11c, CD68 were analysed immunohistochemically using monoclonal antibodies (ARP, USA), combined with the LSAB+ (DAKO, UK) detection system. Apoptosis was directly measured using a neuro-specific *in situ* apoptotic DAB detection system – NeuroTACS (R&D systems, UK).

In summary the results showed apoptosis occurs in human JE and the mouse model, with some up-regulation of adhesion, structural and transport proteins. However the staining of the individual proteins and levels of apoptosis were tissue specific, with focal staining in some of these tissues.

**Poster no. 08**

**Elevated Levels of Total and Dengue Virus Specific Immunoglobulin E in Patients with Varying Disease Severity**

**P. KORAKA<sup>1</sup>, B. MURGUE<sup>2</sup>, T.E. SETIATI<sup>3</sup>, C. SUHARTI<sup>3</sup>, E.C.M. VAN GORP<sup>4</sup>, C.E. HACK<sup>5</sup>, A.D.M.E. OSTERHAUS<sup>1</sup> & J. GROEN<sup>1</sup>**

<sup>1</sup>Laboratory for Exotic Viral Infections, Institute of Virology, Erasmus Medical Centre Rotterdam, The Netherlands; <sup>2</sup>CNR des Arbovirus et des Fievres hemorrhagiques Virales, Institut Pasteur, Paris, France; <sup>3</sup>Dept of Internal Medicine and Pediatric Dept University of Diponegoro, Semarang, Indonesia; <sup>4</sup>Dept of Internal Medicine, Slotervaart Hospital, Amsterdam, The Netherlands; <sup>5</sup>Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and Department Clinical Chemistry, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands

The kinetics of total and dengue virus (DEN) specific immunoglobulin E (IgE) were studied in serial serum samples obtained from 168 patients, 41 of which suffered from primary DEN infection and 127 suffered from secondary DEN infection. Seventy-one patients were classified as dengue fever (DF), 30 as dengue haemorrhagic fever (DHF), and 67 as dengue shock syndrome (DSS). A control group included single serum samples from patients with a herpes virus infection (n=14), non-dengue febrile patients (n=10), and healthy blood donors (n=10). Patients with secondary DEN infections had significantly increased levels of both total and DEN specific IgE in the acute phase of disease compared to patients with primary DEN infection (P<0.05) and non-dengue patients (P<0.05). DEN specific IgE was significantly higher in DHF and/or DSS patients compared to DF and non-dengue patients (P<0.05). In the convalescent phase of DEN disease total and DEN specific IgE serum antibodies decreased in almost all patient groups. In conclusion, we have shown that elevated total and DEN specific IgE serum antibody levels follow mainly secondary DEN infections in the acute stage of disease. Therefore, measurement of both total and DEN specific IgE serum antibodies can be used as prognostic marker in the development of severe complications in DEN infections. In addition, the presence and increase of DEN specific IgE serum antibodies in patients with primary and secondary DEN infections, is suggestive of the pathogenetic role that IgE may play in the hemostatic disorders observed in DHF and DSS.

**Poster no. 09**

**HSV2 Antibody Detection in African Sera-Comparison between rgG2 ELISA and Western Blot**

**WAYNE HOGREFE<sup>1</sup>, XIN SU<sup>1</sup>, JAMES SONG<sup>1</sup>, RHODA ASHLEY<sup>2</sup> & LILLY KONG<sup>1</sup>**

**<sup>1</sup>Focus Technologies, Cypress, CA, <sup>2</sup>University of Washington, Seattle, WA, USA**

Recent HSV2 seroprevalence studies in various countries have demonstrated a possible association between genital herpes and the acquisition of HIV. Some HSV seroprevalence studies conducted in Africa have raised concern that the gG2 ELISA may give falsely positive results in African sera. The present study was undertaken to confirm the HSV2 antibody results obtained with a recombinant gG2-based ELISA by using the Western blot (WB) in sera obtained from four African locations (Kenya, Uganda, South Africa, and Zimbabwe). The sera (N=609) were assayed for the presence of HSV2 antibody using HerpeSelect HSV-2 ELISA (Focus Technologies, Cypress, CA). All ELISA positive samples and 68 ELISA negative samples were subsequently tested in a blinded fashion by WB. All ELISA negative samples were negative by WB. Of 368 samples positive for HSV2 antibody by ELISA, 342 (93%) were WB positive, 7 (2%) had atypical HSV2 patterns by WB, and 19 (5%) were negative by WB. No discrepant results were found in the South African or Zimbabwe samples. Twelve (63%) of the 19 discrepant sera had low antibody levels with ELISA Index values between 1.1 and 2.0. When the 19 discrepant sera were further evaluated by a HSV inhibition assay, 12 confirmed as HSV2 positive. The Focus HerpeSelect ELISA is a sensitive and specific method for detecting HSV2 antibody in African populations. Apparent false positive results may be due to the ability of the HerpeSelect assay to detect low level HSV2 antibodies not easily detected by other methods.

**Poster no. 10**

**HSV2 Antibody Detection in African Sera - Investigation of the Discordance between Recombinant gG2 (rgG2) ELISA and Western Blot**

**XIN SU, JAMES SONG, WAYNE HOGREFE & LILLY KONG**

**Focus Technologies, Cypress, CA, USA**

Recent seroprevalence studies in Africa have suggested a rgG2 based ELISA (HerpeSelect, Focus Technologies) may give high false positive results for HSV-2 antibody detection. The present study was designed to investigate the discordance between rgG2 ELISA and Western blot (WB) by devising an inhibition assay. Specificity of the antibodies detected by the rgG2-ELISA was examined by measuring the differential abilities of native HSV-1 and HSV-2 Vero cell lysates to neutralize the immunoreactivity of the patient sample to rgG2. A population of 526 African sera from Kenya, Uganda, South Africa, and Zimbabwe were assayed for HSV2 IgG with the ELISA, and 286 were positive, among which 260 (91%) were confirmed by WB. The 260 ELISA/WB concordant samples were used to establish the cutoff value (% inhibition) of the inhibition assay. After HSV2/HSV1 lysate absorption, 253 of the 260 samples had Index values of <1.0. For the remaining 7 samples, the mean % inhibition with HSV2/HSV1 lysate absorption was 78% (SD=11%) with a range from 59% to 90%. Therefore, 56% (mean-2SD) was used as the cutoff for true positives in the inhibition assay. Applying this criterion, 279 of 286 samples (98%) were confirmed positive by the inhibition assay. We conclude that the inhibition assay is sensitive and specific for verifying the specificity of HSV2 antibody detected by recombinant gG2 antigen. The high level concordance between the ELISA and inhibition assay indicates that HerpeSelect is a sensitive and specific method for detecting HSV2 IgG in the African populations.

**Poster no. 11**

**Kissed by a Sheep**

**C.E.VISSER<sup>1</sup>, R.N. PATTISELANNO<sup>1</sup>, H.L. LIM<sup>3</sup> & F.A. TJEBBES<sup>2</sup>**

**Depts. Medical Microbiology<sup>1</sup> and Surgery<sup>2</sup>, Reinier de Graaf Hospital, Reinier de Graafweg 3-11, 2625 AD Delft, and general practitioner<sup>3</sup>, Zuideindseweg 6, 2645 BG Delfgauw, The Netherlands**

Three weeks before admission to the outpatient department of surgery a boy, aged 13 years old, was hit in the face by a sheep lifting its head. His upper lip was slightly damaged. During the following week, the superficial wound developed into an ulcer that did not react to antibiotics (amoxycillin/clavulanic acid and fucidic acid ointment). No regional lymph nodes were palpable and no systemic symptoms were observed.

The patient's grandfather had told the GP that his sheep sometimes had contagious ecthyma. Therefore, a parapox infection was high in our differential diagnosis. Viral cultures of the lesions were taken and parapox virus was identified by electron microscopy. Bacterial culture yielded only skin flora. Since parapox virus infection is self-limiting, we advised to stop all antibiotics.

Orf or contagious ecthyma is an infection that is incidentally diagnosed in Dutch patients who have had contact with infected animals. Since the incidence is very low in humans, the diagnosis is relatively difficult and the number of infections might be underestimated.

**Poster no. 12**

**The Hunt for HPV DNA in Skin**

**J. BREUER<sup>2</sup>, C.A. HARWOOD<sup>1</sup>, T. SURENTERAN<sup>2</sup>, C.M. PROBY<sup>1</sup> & J.M. MCGREGOR<sup>1</sup>**

**<sup>1</sup>Dept of Dermatology, Barts & The London, Queen Mary's School of Medicine & Dentistry, University of London, 2 Newark Street, London E1 2AT; <sup>2</sup>Dept of Virology, Barts & The London, Queen Mary's School of Medicine & Dentistry, University of London, 37 Ashfield Street, London E1 1BB**

Clinicopathological and epidemiological evidence points to a role for human papillomavirus (HPV) in the pathogenesis of non-melanoma skin cancer, the commonest of all malignancies worldwide, providing the impetus for current intensive research into HPV and cutaneous carcinogenesis. Epidemiological studies have relied upon detection of HPV DNA since HPV culture is difficult and serological studies less informative than for other viruses. However, over 80 HPV types are recognised and their considerable genetic diversity has caused significant methodological difficulties. Early DNA hybridisation methods were less specific than more recent type-specific or consensus PCR, but the latter are often insufficiently comprehensive to detect all HPV types potentially present in skin. This has resulted in discrepancies in the reported prevalence and spectrum of HPV in skin cancers.

We describe the development of a degenerate nested PCR technique for detection and genotyping of HPV in skin. Sensitivity and specificity of this method has been validated by analysing representative HPV plasmids and a series of viral warts, and has been compared with alternative typing methodologies. Of particular importance, this technique allows detection of multiple HPV infections within individual lesions, an event commonly observed in lesions from immunosuppressed patients. This methodology has thus proved sufficiently sensitive and comprehensive to undertake accurate epidemiological assessment of the role of HPV in non-melanoma skin carcinogenesis.

**Poster no. 13**

**Investigation of Varicella Zoster Virus Genotypes in the United Kingdom Population since 1900**

**M.L. QUINLIVAN, K. HAWRAMI, F. SCOTT, M. LEEDHAM-GREEN & J. BREUER**

**Dept of Virology, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London, 37 Ashfield Street, London E1 1BB**

We have shown Varicella zoster virus (VZV) can be grouped into at least 3 distinct genotypes, which are unique to certain geographical locations. One is associated with a Bgl I restriction site in gene 54. In Africa, Asia, the Indian Subcontinent and South America, Bgl I positive strains are highly prevalent in varicella and zoster cases, whilst in the UK currently account for 20% of VZV infections. We have previously shown an increase in the prevalence of Bgl I positive strains in the UK. In order to investigate this further we typed samples from a community study of zoster cases in London. Virus from patients with zoster in East London was typed for Bgl I. The country of acquisition of varicella of the patients was determined. The study group consisted of 170 Caucasians and 15 non-Caucasians with a history of varicella in the UK. 17 were non-Caucasians who either gave a history of varicella in the countries with a high prevalence of Bgl I positive cases of varicella and zoster, or who had no history of varicella but had immigrated to the UK as adults (>19 years of age). 30% of Non-Caucasians who acquired varicella in the UK reactivated Bgl I positive zoster, compared to only 10% of Caucasians who acquired varicella in the UK. 30% of non-Caucasians who acquired varicella in a country of high Bgl I positive prevalence reactivated Bgl I negative zoster compared to 0% of similar subjects who remained in and reactivated zoster in the country of high Bgl I prevalence.

**Poster no. 14**

**Development of an Enzyme Linked Immunosorbent Assay for the Detection of IgG Antibodies to Varicella Zoster Virus in Oral Fluid Samples**

**Y.S. TALUKDER<sup>1</sup>, R. GOPAL<sup>1</sup>, D.W.G. BROWN<sup>1</sup> & J. BREUER<sup>2</sup>**

**<sup>1</sup>Dept of Medical Microbiology, Queen Mary College and Enteric, Respiratory and Neurological Virus Laboratory, Central Public Health Laboratory, 61 Colindale Avenue, London NW9 5HT, <sup>2</sup>Dept of Virology, Barts and The London, Queen Mary's School of Medicine and Dentistry, University of London, 37 Ashfield Street, London E1 1BB**

An Indirect ELISA was developed to detect IgG antibody to varicella zoster virus (VZV) in oral fluid samples. Samples were obtained using a sponge swab and eluting the fluid into a buffer. Three hundred and thirty seven samples were obtained from children aged 1-5 years and 205 samples from adults aged 20-50 years. The ELISA is based on VZV infected cell antigens and with uninfected cell antigen as a control. Samples were incubated with antigen; bound IgG was detected by anti-IgG enzyme conjugate followed by a chromogenic substrate. The difference in absorbance between antigen and control coated wells was used as a measure of VZV specific antibody. The distribution of results was assessed using the Mixture Model to define the performance of the assay. The predicted sensitivity of the Oral fluid assay is 93.7% and specificity 99.7%. Assay sensitivity and specificity by comparing matched serum and saliva samples, using the serum result as a gold standard, were 93% and 95.7% respectively. We conclude that the oral fluid ELISA described here can be used in population based surveys on VZV immunity.

**Poster no. 15**

**Performance of a HIV-1 Genotyping Assay with Non-B Subtypes - The East London Experience**

**I. USHIRO-LUMB<sup>1</sup>, J. NORMAN<sup>1</sup>, C. SKINNER<sup>2</sup>, M. MURPHY<sup>2</sup>, J. BREUER<sup>1</sup> & C. AITKEN<sup>1</sup>**

<sup>1</sup>Dept of Virology, Barts and the London NHS Trust, 3<sup>rd</sup> Floor, 51-53 Bartholomew Close, West Smithfield, London EC1A 7BE, <sup>2</sup>Dept of Infection and Immunity, Barts and the London NHS Trust, West Smithfield, London EC1A 7BE

**Background:** HIV resistance testing has become standard of care in many UK centres. Current commercial assays have been developed using the HIV-1, group M, subtype B, with potential lack of sensitivity for non-B subtypes.

**Objective:** To assess the clinical utility of a genotypic resistance system in a genetically diverse cohort of HIV-infected patients.

**Methods:** Data from 93 samples tested by the TruGene™ Assay (VGI Inc.) between September 1999 and May 2000 was analysed. HIV-1 subtypes were determined through the Stanford HIV RT/Protease and NCBI HIV databases.

**Results:** 87 (93.5%) samples were successfully genotyped in our laboratory. All but one of the White patients (64.2%) had subtype B virus; that strain clustered as a possible A/C recombinant. Amongst Black/Africans (27.2%), subtypes A (36%), B (4%), C (20%) and D (32%) were detected, with two samples showing chimeric sequences. Black/Caribbeans (4%) harbored subtype B only. Three Black/European individuals had subtype B virus. Six initial sequence failures occurred, followed by successful genotyping by the manufacturer. The subtypes for those samples were B (4), A (1), and D (1).

**Conclusion:** The TruGene™ Assay is a robust HIV-1 genotyping system, which is easily incorporated into a diagnostic laboratory. There is no suggestion that failure to obtain sequence data was due to inability of the assay to amplify non-B targets. With up to 27% of our samples belonging to non-B subtypes, we have demonstrated that the VGI system can reliably detect mutations in non-B subtypes.

**Poster no. 16**

**Nosocomial Transmission of Rubella on a Special Care Baby Unit : Case Report and Results of a Look Back Exercise**

**E.A. SHERIDAN, M. HIRD & C. AITKEN**

**Depts of Virology and Paediatrics, Barts and the London NHS Trust, 37 Ashfield Street, London E1 1BB**

Congenital Rubella Syndrome is rare in the UK. Delay in diagnosis may result in nosocomial transmission as large amounts of virus are excreted in the urine of affected infants. We report the investigations and infection control measures implemented following the identification of a case of CRS in a pre-term small for dates infant in our SCBU with secondary spread to a further infant.

**Methods:** A female infant was born at 31 weeks with symmetrical IUGR, persistent jaundice and thrombocytopenia. Her 20 year old mother was a primigravida who had arrived in the U.K from Bangladesh when she was 20 weeks pregnant. IUGR was identified on a scan at 22 weeks gestation. A maternal serum sample from this time was positive for rubella IgG and negative for IgM. The infant was identified (rubella IgM positive) at 11 weeks of age, and immediately isolated. Lists of patients and staff contacts were obtained and antibody testing arranged. Infant and pregnant staff contacts were tested again 3 weeks later.

**Results:** 33 of the 46 nurses in contact with the infant were either known to be/or tested positive for rubella antibodies. 9 of the 13 doctors were also positive. Of the babies in contact 12 were IgM negative, 1 was IgM positive and 5 were discharged and lost to follow -up.

**Conclusions:** 1.CRS should always be suspected in babies with compatible clinical features particularly if their mothers have recently arrived in the UK / 2. Good infection control practices including handwashing are essential to stop spread within a clinical area.

**Poster no. 17**

**Intravenous Immunoglobulin (IVIG) Therapy for Parvovirus B19-associated Chronic Fatigue Syndrome (CFS)**

V.S. CUNNIFFE<sup>1</sup>, I.N. BRUCE<sup>2</sup>, R.M. BERNSTEIN<sup>2</sup> & J.R. KERR<sup>1</sup>

<sup>1</sup>Dept of Microbiology, Royal Brompton Hospital, Imperial College School of Medicine, Sydney Street, London SW3 6NP, UK; <sup>2</sup>Rheumatism Research Centre, Central Manchester Healthcare Trust, Oxford Road, Manchester M13 9WL, UK

Human parvovirus B19 is associated with a wide variety of clinical manifestations, including chronic fatigue syndrome (CFS) and B19-associated CFS has been associated with detectable circulating tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ) and B19 viraemia (Kerr et al. J Gen Virol 2001;82:3011-3019). Here we report three cases of B19-CFS whose clinical details meet the CDC criteria for a diagnosis of CFS, and whose fatigue and associated symptoms began at the time of detection of serum anti-B19 IgM and then persisted for more than a year. Each was treated with a 5-day course of intravenous immunoglobulin (IVIG), the only specific treatment for B19 infection. Serial sera were taken at intervals both before and after IVIG therapy and for up to 2-3 years following acute infection and were tested for B19 markers, autoantibodies and circulating cytokines / chemokines using the Bioplex protein array system (Bio-Rad) (IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNF- $\alpha$ , IFN- $\gamma$ , GM-CSF, MCP-1). IVIG therapy led to a prompt and marked clinical recovery, clearance of B19 virus from the circulation and normalisation of cytokine / chemokine dysregulation. Unfortunately, a B19-related aetiology for CFS cannot be determined with certainty unless the onset of fatigue is coincident with detection of serum anti-B19 IgM (Kerr et al. J Gen Virol 2001;82:3011-3019). However, if a case of CFS is known to be due to B19 infection, then IVIG appears to be a very effective treatment.

**Poster no. 18**

**Evidence for Widespread Infection of Wild Rats with Hepatitis E Virus in Ukraine**

**O. KORZH, T. BONDARENKO & O. ZHMURO**

**Ukrainian Research Institute of Microbiology, Pr. Postysheva-2A, 61002 Kharkov, Ukraine**

**Background:** Hepatitis E is an important medical pathogen in many developing countries but is rarely reported from Ukraine, although antibody to hepatitis E virus (anti-HEV) is found in >2% of Ukrainian citizens. Sporadic cases of clinical hepatitis E not only occur in these countries but also occur uncommonly in patients with no known epidemiological exposure to HEV in industrialized countries. The source of infection in industrialized countries is unknown but it has been suggested that animals might serve as a reservoir for HEV in both settings. We recently identified and characterized an HEV strain (rat HEV) that infects large numbers of rats in Ukraine.

**Methods:** Sera obtained from 239 wild rats trapped in widely separated regions of Ukraine were tested for anti-HEV. Tissues were examined by light microscopy for detection of histopathological changes and by direct immunofluorescence for detection of HEV antigens.

**Results:** Seventy-two percent of rats from South Ukraine, 90% from Western, and 44% from Eastern Ukraine were seropositive for anti-HEV. Rats from urban as well as rural areas were seropositive and the prevalence of anti-HEV IgG increased in parallel with the estimated age of the rats, leading to speculation that they might be involved in the puzzling high prevalence of anti-HEV among some Ukrainian city dwellers. We found HEV antigens in liver, peripheral blood mononuclear cells, spleen, mesenteric lymph nodes, and small intestine. We detected histopathology attributable to the inoculum in liver, spleen, and lymph nodes.

**Conclusion:** The results from this study suggest that hepatitis E is enzootic in rats regardless of whether HEV is endemic in the respective human population. The results confirm that HEV can replicate in laboratory rats and suggest new tissue sites for HEV replication. The discovery of a HEV in rats in Ukraine and the recently reported discovery that HEV is endemic in Ukraine swine raise many questions about transmission, reservoirs, and strains of HEV in developed countries.

**Poster no. 19**

**Clinical and Epidemiological Implications of Swine Hepatitis E Virus Infection**

**I. RAYNINA-KORZH, V. NEMTSOVA & P. KRAVCHUN**

**Kharkov Medical University, Pr. Lenina-4, 61022 Kharkov, Ukraine**

**Background:** Hepatitis resulting from HEV infection is a moderately severe jaundice that is self-limiting in most patients. Hepatitis E virus is found in both wild and domestic animals; thus, HEV is a zoonotic virus. In nonendemic areas, most patients with acute hepatitis E were infected through traveling to endemic areas. However, some patients did not have a history of foreign travel before infection. Furthermore, high seroprevalence rates of antibody to hepatitis E virus (anti-HEV) were found in the general adult population in some countries without any recorded outbreak of hepatitis E. The significance of anti-HEV assay in these subjects remains obscure.

**Methods:** To study if swine might be a source of HEV infection, HEV was tested in sera of 235 pigs in Ukraine, and from 5 patients with acute HEV infection who either denied or did not provide any foreign travel history.

**Results:** Three (1.3%) pigs had detectable swine HEV RNA. The swine and human HEV strains from Ukraine formed a monophyletic group, distinct from three previously reported groups: the United States human and swine HEV strains, the Mexico strain, and the largest group composed of the Asian and the African strains. The identity of nucleotide sequences was 81-92% between swine and human HEV strains in Ukraine, and 68-73% between Ukraine strains and those from different areas. The predicted amino acid sequence of a Ukraine swine HEV strain within the peptide 3-2 used in commercial anti-HEV assay showed a high identity (92-95%) with those of other human and swine HEV strains.

**Conclusion:** The close genetic relationship of the swine and human virus suggests that swine may be a reservoir of HEV and subclinical swine HEV infection may occur. Cross-reactivity of current anti-HEV assay may account for the high prevalence rate of anti-HEV in the general population in nonendemic areas. In areas where swine are raised, swine manure could be a source of HEV contamination of irrigation water or coastal waters with concomitant contamination of produce or shellfish. Increasing globalization of food markets by industrialized countries has the potential of introducing HEV into new areas of the world.

**Poster no. 20**

**Serologic Evidence of Ehrlichiosis among Humans and Wild Animals in The Netherlands**

**J. GROEN<sup>1</sup>, P. KORAKA<sup>1</sup>, Y.A. NUR<sup>1</sup>, T. AVSIC-ZUPANC<sup>2</sup>, W.H.F. GOESSENS<sup>3</sup>, A. OTT<sup>3</sup>, A.D.M.E. OSTERHAUS<sup>1</sup>**

**<sup>1</sup>Laboratory of Exotic Viral Infections, University Hospital Rotterdam; <sup>2</sup>Institute of Microbiology and Immunology, Medical Faculty, Zaloska 4, 1000 Ljubljana, Slovenia; <sup>3</sup>Dept of Bacteriology, University Hospital Rotterdam, Rotterdam, The Netherlands**

A serological survey for the prevalence of antibodies against the causative agent of human granulocytic ehrlichiosis (HGE) and human monocytic ehrlichiosis caused by *Ehrlichia chaffeensis* in The Netherlands was conducted on a total of 721 recently collected serum samples from febrile patients with unresolved aetiology (n=108), patients suspected of Lyme disease (n=174), forestry workers (n=154), healthy controls (n=54) and from wild deer (n=96), hare (n=60), wild boar (n=15) and red foxes (n=60). Specific antibodies against the agent of HGE were detected in 4% of febrile patients with unresolved aetiology, and in 4% of patients suspected of lyme disease. Among the forestry workers 1% tested positive for antibodies against the agent of HGE, whereas all the healthy controls were negative. Antibodies against *E. chaffeensis* were only detected in 2% of the febrile patients. HGE and *E. chaffeensis* specific serum antibodies were detected in 22% and 3% of the deer samples, respectively and in 2% of the hares. In wild boars and in red fox only serum antibodies against *E. chaffeensis* were detected in 13% and 7%, respectively. The demonstration of the presence of both HGE and *E. chaffeensis* specific serum antibodies among humans and wild animals in The Netherlands, indicates that patients suspected of lyme disease and febrile patients with unresolved aetiology should be tested for the presence of HGE and *E. chaffeensis* antibodies. Furthermore, we demonstrated that HGE is the most prevalent ehrlichiosis in The Netherlands.

**Poster no. 21**

**Human metapneumovirus detected in community-acquired illness in winter 2000-01 in England**

**J.D. STOCKTON<sup>1</sup>, I. STEPHENSON<sup>2</sup>, D.G. FLEMING<sup>3</sup> & M.C. ZAMBON<sup>1</sup>**

**<sup>1</sup>Central Public Health Laboratory, <sup>2</sup>Leicester Royal Infirmary, <sup>3</sup>RCGP Birmingham**

**Background:** Acute respiratory tract (ART) infections cause a substantial burden of illness in the general community every year. We looked for evidence that the newly discovered human metapneumovirus contributed to these infections along with RSV and influenza.

**Methods:** General practitioners collected combined nose and throat swabs from patients presenting with influenza like illness (ILI) as part of the Royal College of General Practitioners (RCGP) national sentinel surveillance scheme. Swabs were posted to the laboratory for PCR analysis.

**Results:** A total of 700 swabs were submitted for testing. RSV was detected in 43 (6.1%) of samples; influenza was detected in 249 (35.4%) leaving a total of 408 samples negative samples. Of these 405 (99.3%) were analysed for hMPV with 9 (2.2%) being found positive. HMPV positive swabs were from all ages (range 1-74). RSV, influenza and hMPV were all found cocirculating during the winter season.

**Conclusion:** RSV, influenza and hMPV cocirculate in the community throughout the winter season. hMPV can cause infections in all age groups of the general community.





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 Stewart J.P. p5, 18  
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 Stoll-Keller F. p29  
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 Vasconcelos P.C. p9, 23  
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 Vera M. p5, 18  
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 Yongxiu Y. p29  
 Yoon K.-J. p3, 15  
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## LIST OF PARTICIPANTS

Dr Dennis Alexander  
Department of Virology  
VLA Weybridge  
Addlestone, Surrey KT15 3NB  
d.j.alexander@vla.defra.gsi.gov.uk

Dr Sandy Anderson  
Consultant Microbiology  
York Health Services  
York District Hospital  
Wigginton Road  
York, North Yorkshire YO31 8HE

Dr Pertti Arstila  
Department of Virology  
University of Turku  
Kllnamyllynkatu 13  
Fin - 20520 Turku  
Finland  
parstila@utu.tn

Dr Barbara Bannister  
Consultant for Infectious / Tropical Diseases  
Royal Free Hospital  
Hampstead, London NW3 2QG  
Barbara.Bannister@rfh.nthames.nhs.uk

Dr Wendy Barclay  
School of Animal and Microbial Sciences  
University of Reading  
Whiteknights, PO Box 288  
Reading RG6 6AJ  
w.s.barclay@reading.ac.uk

Professor Alan Barrett  
Dept of Pathology / Centre for Tropical Diseases  
University of Texas Medical Branch  
301 University Boulevard  
Galveston,  
Texas 77555-0609  
USA  
abarrett@utmb.edu

Dr Justin Bendig  
Consultant Microbiologist  
Epsom & St Helier NHS Trust  
West Park Hospital, Epsom  
Surrey KT19 8PB

Dr C A Benne  
Clinical Virologist  
Regional Public Health Laboratory  
Van Ketwich Verschuurlaan 92  
Groningen, NL-9721 SW  
The Netherlands  
benneclg@compuserve.com

Dr Louise Berndtsson  
Head of Section / Dept of Virology  
SVA  
SE - 75189, Uppsala  
Sweden  
louise.t.berndtsson@sva.se

Dr Jenny Best  
Reader in Virology  
Kings College London  
Dept of Virology  
St Thomas' Hospital  
London SE1 7EH  
jenny.best@kcl.ac.uk

Miss Angela Birchill  
Biochemistry Section Manager  
Bio Products Laboratory  
Dagger Lane, Elstree  
Herts WD6 3BX

Professor Merete Blixenkronne - Moller  
Dept of Veterinary Microbiology  
The Royal Veterinary and Agricultural University  
Stiebojlen 7, 1870 Frederiksberg  
Denmark

Professor Letterio Bonina  
Virology - Infectious Diseases  
University of Messina  
Faculty of Medicine  
Viale Liberta 175  
Messina  
Italy

Dr Chris Bosman  
Consultant Physician / Private Practice  
Rietfontein (SIZWE) Infectious Diseases Hospital  
University Witwatersrand  
PO Box 795, Bedfordview 2008  
South Africa

Ms Amanda Brass  
Department of Virology  
University of Edinburgh  
Royal School of Vet. Studies  
Summerhall  
Edinburgh EH9 1QH  
a.f.brass@sms.ed.ac.uk

Dr John Bremner  
Consultant Virologist  
Sheffield Teaching Hospitals  
Royal Hallamshire Hospital  
Glossop Road

Sheffield S10 2JF  
john.bremmer@sth.nhs.uk  
Dr Judith Breuer  
Reader in Virology, Dept Medical Microbiology  
St Barts & The Royal London Hospitals Medical School  
Queen Mary Westfield College  
25 - 29 Ashfield Street  
London E1 1BB  
j.breuer@mds.qmw.ac.uk

Dr Janice Bridger  
Senior Lecturer  
Royal Veterinary College  
Royal College Street  
London NW1 0TU  
jbridger@rvc.ac.uk

Dr Nicola Brink  
Consultant / Honorary Senior Lecturer / Virology  
University College London Hospitals  
Windeyer Building  
46 Cleveland Street  
London W1T 4JF  
n.brink@ucl.ac.uk

Dr Ian Brown  
Virology Department  
Veterinary Laboratories Agency  
Woodham Lane  
New Haw  
Addlestone, Surrey KT15 3NB  
i.h.brown@vla.defra.gsi.gov.uk

Dr David Brown  
Laboratory Director  
Central Public Health Laboratory  
Enteric, Respiratory & Neurological Virus Laboratory  
61 Colindale Avenue  
London NW9 5HT  
dbrown@phls.org.uk

Professor Joe Brownlie  
Head of Department of Pathology & Infectious Diseases  
Royal Veterinary College  
Hawkshead Lane  
North Mymms  
Hatfield, Herts AL9 7TA  
jbrownlie@rvc.ac.uk

Dr Maria Bruckova  
Head, National Reference Lab on AIDS  
National Institute of Public Health  
Srobarova 48  
100 42 Prague 10  
Czech Republic  
brucaids@niph-prague.anet.cz  
Dr Sylvia Bruisten  
Dept of Municipal Health Lab  
GG & GD, Amsterdam

Nieune Achtergracht 100  
1018 WT Amsterdam  
The Netherlands  
sbruisten@ggga.amsterdam.nl

Dr Sheila Burns  
Consultant Virologist / Regional Virus Laboratory  
Lothian Acute University NHS Trust  
City Hospital, Greenbank Drive  
Edinburgh EH10 5SB  
sm.burns@luht.scot.nhs.uk

Dr Kathryn Cann  
Consultant in Microbiology  
John Radcliffe Hospital  
Headley Way, Headington  
Oxford OX 3 9DU  
kjcann@zircon.co.uk

Dr Ilaria Capua  
Laboratorio Virologia  
Istituto Zooprofilattico Sperimentale delle Venezie  
Via Romea 14/A  
Legnaro, Padova, 35020  
Italy  
icapua@izsvenezie.it

Dr Bill Carman  
Regional Virus Laboratory  
Gartnavel General Hospital  
1053 Great Western Road  
Glasgow G12 0YN  
w.carman@vir.gla.ac.uk

Dr John Carter  
Senior Lecturer  
Liverpool John Moores University  
School of Biomolecular Sciences  
Byrom Street  
Liverpool L3 3AF  
j.b.carter@livjm.ac.uk

Miss Cecile Chaput  
Department of Virology  
NIBSC  
Blanche Lane, South Minns  
Potters Bar  
Herts EN6 3QG  
cchaput@nibsc.ac.uk

Dr Anuradha Chawla  
Department of Virology  
Royal Free Hospital  
Pond Street  
London NW3 2QG  
anuradha.chawla@rft.nthames.nhs.uk

Ms Victoria Chesters  
Senior Scientist, Virology

GlaxoSmithKline  
Bld 113  
South Eden Park Road  
Beckenham BR3 3BS  
vjc48906@glaxowellcome.co.uk

Dr Laurids Siig Christensen  
Dept of Clinical Microbiology  
Rigshospitalet  
Juliane Maries Vej 22  
DK -2100 Copenhagen East  
Denmark  
sigg@biobase.dk

Dr Berwyn Clarke  
Research Director  
Visible Genetics UK  
184 Cambridge Science Park  
Milton Road  
Cambridge CB4 0GA  
bclarke@visgen.com

Dr Julie Clayton  
Freelance Science Writer  
18 Highbury Villas  
Bristol BS2 8BX  
julie.p.clayton@blueyounder.co.uk

Dr Bernard Cohen  
Virus Reference Division  
PHLS  
Central Public Health Laboratory  
61 Colindale Avenue  
London NW9 5HT  
bcohen@phls.org.uk

Miss Samantha Cooray  
Infection, Dept of Virology  
Kings College London  
5th Floor, North Wing  
St Thomas' Hospital  
London SE1 7EH  
samantha.cooray@kcl.gc.uk

Miss Karen Coyne  
Veterinary Pathology  
University of Liverpool  
Leahurst, Neston  
Chester High Road  
South Wirral CH64 7TE  
kpcoyne@liv.ac.uk

Dr David Cubitt  
Consultant Virologist  
Gt Ormond Street Hospital  
Virology, Camelia Botnar Labs  
London WCN1 3JM  
cubitd@gosh.nhs.uk

Miss Victoria Cunniffe  
Department of Microbiology  
Imperial College  
Royal Brompton Campus  
Sydney Street  
London SW3 6NP  
v.cunniffe@ic.ac.uk

Ms Roxana Curtis  
Student, Biological Sciences  
University of Manchester  
4 Hillfield Road  
London NW6 1QE  
lillycurtis@hotmail.com

Dr Judy Daly  
Professor of Pathology/Director - Microbiology Labs  
University of Utah  
Primary Children's Medical Center  
100 North Medical Drive  
Salt Lake City Utah 84098  
USA  
jald2@msn.com

Dr Janet Daly  
Centre for Preventive Medicine  
Animal Health Trust  
Lanwades Park  
Kentford, Newmarket  
Suffolk CB8 7UU  
janet.daly@aht.org.uk

Dr Jan De Jong  
Erasmus University Rotterdam  
Krugerlaan 205  
2806 EH Gouda  
The Netherlands  
jc.de.jong@wxs.nl

Dr Ulrich Desselberger  
Public Health & Clinical Microbiology Laboratory  
Addenbrookes Hospital  
Level 6  
Hills Road  
Cambridge CB2 2QW  
ulrich.desselberger@addenbrookes.nhs.uk

Mr Robert Diepersloot  
Medical Microbiology  
Diakonessen Hospital  
Bosboomstraat 1  
3582 KE Utrecht  
The Netherlands  
rdieprsllot@diakhuis.nl

Dr Angela Dyer  
Post-Doctoral Scientist / Infectious Tropical Diseases  
London School of Hygiene & Tropical Medicine  
Keppel Street  
London WC1E 7HT  
Angela.dyer@Ishtm.ac.uk

Dr Juan E. Echevarra  
Servicio de Microbiología Diagnóstica  
Instituto de Salud Carlos III  
Centro Nacional de Microbiología  
Ctra. Majadahonda-Pozuelo s/n  
28220 Majadahonda - Madrid  
Spain  
jeecheva@isciii.es

Professor Steve Edwards  
Chief Executive  
Veterinary Laboratories Agency  
New Haw  
Addlestone  
Surrey KT15 3NB  
s.edwards@vla.defra.gsi.gov.uk

Dr Fredrik Elgh  
Director / Centre for Microbiological Preparedness  
Swedish Institute for Infectious Disease Control  
SF – 17182 Solna  
Sweden  
fredrik.elgh@foi.se

Dr Joanna Ellis  
Clinical Scientist  
PHLS  
61 Colindale Avenue  
Colindale  
London NW9 5HT  
jellis@phls.org.uk

Dr Anne-Marie Elsacker-Niele  
Clinical Microbiologist / Medical Microbiology Dept  
Public Health Laboratory  
PO Box 21020  
8900 Ja Leeuwarden  
The Netherlands  
a.van.elsacker-niele@lvf.nl

Dr Kerstin Erles  
Department of Pathology & Infectious Diseases  
Royal Veterinary College  
Hawkshead Lane  
North Mimms  
Hatfield, Herts AL9 7TA  
kerles@rvc.ac.uk

Dr Teuku Reza Ferasyi  
Department of Veterinary Epidemiology  
Utrecht University  
Ijsselsteinlaan 6  
3525 EW Utrecht  
The Netherlands  
t.r.ferasyi@vet.uu.nl

Dr Hugh J Field  
Senior Lecturer in Virology  
Cambridge University  
Centre for Veterinary Science  
Maddingley Road  
Cambridge CB3 0ES  
hjf10@cam.ac.uk

Dr Tony Fooks  
Head of Group / Virology Dept  
Veterinary Laboratories Agency  
New Haw, Addlestone  
Surrey KT15 3NB  
t.fooks@vla.maff.gsi.gov.uk

Dr Jeremy Garson  
Senior Lecturer / Dept of Virology  
Royal Free & University College Medical School London  
Windeyer Building  
46 Cleveland Street  
London W1T 4JF  
j.garson@ucl.ac.uk

Dr Markus Glatzel  
Institute of Neuropathology  
University Hospital of Zurich  
Schmelzbergstrasse 12  
CH-8091 Zurich  
Switzerland  
markus.glatzel@pty.usz.ch

Professor Patrick Goubau  
Head of Virology Unit  
U.C.L.  
Avenue Hippocrate 54/92  
Brussels  
B-1200 Belgium  
goubau@mblg.ucl.ac.be

Miss Vicki Gregory  
Department of Virology  
National Institute for Medical Research  
The Ridgeway, Mill Hill  
London NW7 1AA  
vgregor@nimr.mrc.ac.uk

Dr Jim Greig  
Consultant Microbiologist

PHLS  
Level 5, Derrifod Hospital  
Derriford PL8 6DH

Castle Road  
Hull HU16 5JQ

Miss Rhoswyn Griffiths  
Intercalated Year Student / Virology  
GlaxoSmithKline  
Biopharmaceutical Analytical Development  
South Eden Park Road  
Beckenham, Kent BR3 3BS  
ryg26063@gsk.com

Miss Ruth Harvey  
Student  
University of Reading  
PO Box 228  
Whiteknights  
Reading, Berks RG6 6AJ

Professor Lena Grillner  
Dept of Clinical Microbiology  
Karolinska Hospital  
Stockholm  
SE 171 76  
Sweden  
lena.grillner@ks.se

Dr Wayne R. Hogrefe  
Director, Licensing and Acquisitions  
Focus Technologies  
5785 Corporate Avenue  
Cypress, CA 90630  
USA  
whogrefe@focusanswers.com

Dr Jan Groen  
Laboratory for Exotic Viral Infections  
Erasmus Medical Centre Rotterdam  
Insitute of Virology  
Dr. Molewaterplein 50  
NL-3015, Rotterdam  
The Netherlands  
groen@viro.fgg.eur.nl

Professor Heidi Holzmann  
Institute of Virology  
University of Vienna  
Kinderspitalgasse 15  
A-1095 Vienna  
Austria  
heidemarie.holzmann@univie.ac.at

Professor Keith Gull  
School of Biological Sciences  
University of Manchester  
2.205 Stopford Building  
Oxford Road  
Manchester M13 9PT  
k.gull@man.ac.uk

Professor Allan Hornsleth  
Head, Dept of Clinical Virology  
Rigshospital  
Dept no 9301  
2100 - Copenhagen  
Denmark

Professor Otto Haller  
Department of Virology  
University of Freiburg  
Hermann Herder Str. 11  
79104 Freiburg  
Germany  
haller@ukl.uni-freiburg.de

Dr Hendrik Huedig  
Head of Infectious Diseases  
Roche Diagnostics  
Nommenwald 2  
D - 82377 Penzberg  
Germany  
hendrik.huedig@roche.com

Dr Dave Harbour  
Dept Clinical Veterinary Science  
University of Bristol  
Langford House  
Langford  
Bristol BS40 5DU  
dave.harbour@bristol.ac.uk

Mr Ulrike Ilgert  
Medical Student  
University of Greifswald  
Bleichstr 49  
17489 Greifswald  
Germany  
renate.mentel@mail.uni-greifswald.de

Mrs Dale Harman  
Biomedical Scientist, Virology Dept  
Public Health Laboratory Service  
Castle Hill Hospital

Dr William Irving  
Dept of Microbiology  
University of Nottingham  
University Hospital  
Queens Medical Centre  
Nottingham NG7 2UH  
will.irving@nottingham.ac.uk



Mr David Jackson  
AMS  
University of Reading  
PO Box 228  
Whiteknights  
Reading, Berkshire RG6 6AJ  
d.jackson@reading.ac.uk

Dr Vivienne James  
Deput Director Quality Assurance Laboratory  
Central Health Public Laboratory  
61 Colindale Avenue  
London NW9 5HT  
vjames:phls.org.uk

Professor Donald Jeffries  
Head, Virology / Microbiology  
St Bartholomew s & Royal London Hospital  
48-53 Bartholomew Close  
London EC1A 7BE  
d.j.jeffries@nds.qmw.ac.uk

Dr Lin Jin  
Virus Reference Division  
Central Public Health  
61 Colindale Avenue  
London NW9 5HT  
ljin@phls.org.uk

Dr Nick Johnson  
Rabies Research Group  
Veterinary Laboratories Agency - Weybridge  
Addlestone  
Surrey KT15 3NB  
N.Johnson2@vla.defra.gsi.gov.uk

Dr Pam Johnstone  
Head of Science Funding (Laboratories)  
The Cancer Research Campaign  
10 Cambridge Terrace  
London NW1 4JL  
pjohnstone@crc.org.uk

Dr Vaira-Irisa Kalnina  
Head, Laboratory of Virology  
National Environmental Health Center  
no. 7 Klijanu Str  
Riga LV-1012  
Latvia  
kalnina@nvvc.org.lv

Professor Adeeba Kamarulzaman  
Head, Infectious Disease Unit, Dept of Medicine  
University Malaya Medical Centre  
Kuala Lumpur - 59100  
Malaysia  
adeeba@ummc.edu.m

Dr Aino Karvonen  
Department of Virology  
University of Tampere  
University of Tampere, Medical School  
Lenkeilijankatu 10, FM3  
Tampere  
Finland  
aino.karvonen@uta.fi  
Professor Berndt Klingeborn  
Department of Virology  
National Veterinary Institute  
BMC Box 585  
SE 75123 Uppsala  
Sweden  
Berndt.klingeborn@bmc.uu.se

Dr Wendy Knowles  
ERNVL  
Central Public Health Laboratory  
61 Colindale Avenue  
London NW9 5HT  
wknowles@phls.org.uk

Miss Penelopie Koraka  
Dept of Virology  
Erasmus Medical Centre  
Dr Molewaterplein 50  
3015 GD ROTTERDAM  
The Netherlands  
koraka@viro.fgg.eur.nl

Dr Louise Genevieve Labrecque  
Department of Medical Microbiology & Infectious Diseases  
Hotel-Dieu  
3840 St-Urbain  
Montreal  
Quebec H3W 1T8  
Canada  
louise.labrecque.chum@ssss.gouv.qc.ca

Miss Angie Lackenby  
Department of Molecular Biology  
Institute for Animal Health  
Compton  
Newbury  
Berkshire RG20 7NN  
angie.lackenby@bbsrc.ac.uk

Dr Pauli Leinikki  
Director / Infectious Disease Epidemiology  
National Public Health Institute  
Mannerheimintie 106  
FIN-00300 Helsinki  
Finland  
pauli.leinikki@ktl.fi

Dr Yi Pu Lin  
Assistant Director of World Influenza Center  
National Institute for Medical Research

The Ridgeway  
Mill Hill  
London NW7 1AA  
lyipu@nimv.mvc.ac.uk

Professor Bruno Lina  
Head of Department  
Unite de Virologie Medicale EA 3085  
Domaine Rockefeller  
Lyon Cedex 08 - 69373  
France  
lian@univ-lyon1.fr

Professor Annika Linde  
Dept of Virology  
Swedish Institute for Infection Disease Control  
Se - 17182  
Sweden  
annika.linde@si.ki.se

Professor Erik Lycke  
Department of Clinical Virology  
University of Gothenburg  
Torphagenbacken 3  
44338 Lerum  
Sweden

Miss Katie Lyne  
Scientist  
GlaxoSmithKline  
South Eden Park Road  
Beckenham  
Kent BR3 3BS  
kcl75464@gsk.com

Dr Eithne MacMahon  
Consultant / Virology Section / Dept of Infection  
Guys & St Thomas' NHS Trust  
5th Floor, North Wing, St Thomas Hospital  
Lambeth Palace Road  
London SE1 7EH  
eithne.macmahon@kcl.ac.uk

Professor Dick Madeley  
Burnfoot  
Stocksfield  
Northumberland NE43 7TN  
dickmadeley@aol.com

Dr Brian Mahy  
Senior Scientist  
Centers for Disease Control and Prevention  
National Center for Infectious Diseases  
Mailstop C12  
1600 Clifton Road Atlanta, GA  
USA  
bxm1@cdc.gov

Dr Susan Mason  
MLSO 3  
Public Health Laboratory  
Level B, South Block  
Southampton General Hospital  
Southampton SO16 6YD  
sue.mason@suht.swest.nhs.uk

Dr Pascale Massin  
Unite de Genetique moleculaire des virus respiratoires  
Institut Pasteur  
URA CNRS 1966,  
25 rue du Dr Roux,  
75724 Paris cedex 15  
France  
pmassin@pasteur.fr

Dr Frank Mattes  
Clinical Research / Virology  
Royal Free Hospital / University College Medical School  
Rowland Hill Street  
London NW3 2PI  
fmahes@yahoo.com

Professor Myra McClure  
Department of G U Medicine  
Imperial College School of Medicine  
St Mary's Campus, Norfolk Place  
Paddington, London W2 1PG  
m.mcclure@ic.ac.uk

Dr Liz McCrudden  
Senior Lecturer  
University of Glasgow  
Institute of Virology  
Church Street, Glasgow G11 5JR  
e.mccrudden@vir.gla.ac.uk

Dr Paul McIntyre  
Medical Microbiology  
Ninewells Hospital  
Dundee DD1 9SY  
paul.mcintyre@tuthtscto.nhs.uk

Dr Ella Mendelson  
Director / Ministry of Health  
Central Virology Laboratory  
Chaim Sheba Medical Center  
Tel-Hashomer 52621  
Israel  
ellamen@sheba.health.gov.il

Professor Renate Mentel  
Friedrich Loeffler Institute for Medical Microbiology  
University of Greifswald  
Martin-Luther-Strae 6  
D 17487 Greifswald  
Germany  
renate.mentel@mail.uni-greifswald.de  
Dr Jane Minton  
Consultant / Infectious Diseases  
Leeds Teaching Hospitals NHS Trust  
Seacroft Hospital  
York Road  
Leeds LS14 6UH  
e.j.minton@leeds.ac.uk

Dr Valerie Mioulet  
Special Pathogens  
CAMR  
Porton Down  
Salisbury  
Wiltshire SP4 0JG  
valerie.mioulet@camr.org.uk

Dr Pamela Molyneaux  
Consultant Virologist  
Aberdeen Royal Infirmary  
Foresterhill  
Aberdeen AB25 22N  
P.Molyneaux@arh.grampian.scot.nhs.uk

Professor John Morris  
Research Director  
Veterinary Laboratories Agency  
Woodham Lane  
New Haw  
Addlestone, Surrey KT15 3NB  
j.a.morris@vla.defra.gsi.gov.uk

Dr Philip Mortimer  
Virus Reference Division  
Central Public Health Laboratory  
61 Colindale Avenue  
London NW9 5HT  
pmortimer@phls.nhs.uk

Dr Nadia Naffakh  
Genetique moleculaire des virus respiratoires  
Institut Pasteur  
25 rue de Docteur Roux  
75 724, Paris Cedex 15  
France  
naffekh@pasteur.fr

Dr Saloua Najjam  
Post Doctoral Scientist  
IAH  
Ash Road, Pirbright  
Woking, Surrey GU24 0NF  
saloua.najjam@bbsrc.ac.uk

Dr Vratislav Nemecek  
Head, Dept of Viral Hepatitis  
National Institute of Public Health  
Srobarova 48  
10042 Prague 10  
Czech Republic  
nemecekv@anet.cz  
Dr Peter Nettleton  
Moredun Research Institute  
Pentlands Science Park  
Bush Loan, Penicuik  
Edinburgh EH26 0PZ  
nettp@mri.sari.ac.uk

Mr Philip Noone  
European Sales Manager  
Focus Technologies  
10703 Progress Way  
Cypress  
California 90630-4717  
USA  
pnoone@focusanswers.com

Dr Malila Noone  
Consultant Microbiologist  
North Tees General Hospital  
Harwick  
Stockton-on-Tees TS19 8PE

Professor Norbert Nowotny  
Institute of Virology  
University of Veterinary Sciences, Vienna  
Veterinaerplatz 1, A-1210  
Austria  
Norbert.Nowotny@vu-vien.ac.at

Mr Ronan O'Neill  
Research Officer  
Department of Agriculture  
Virology Division, Abbotstown CVRL  
Castleknock  
Dublin  
Ireland  
oneillronan@eircom.net

Dr Marie Ogilvie  
Dept of Medical Microbiology  
University of Edinburgh  
Medical School, Teviot Place  
Edinburgh EH8 9AG  
marie.ogilvie@ed.ac.uk

Dr Husam Osman  
Consultant Virologist  
Birmingham Heartlands Hospital  
Bordesley Green East  
Birmingham B9 5SS  
osmanh@heartsol.wmids.nhs.uk

Professor Ab Osterhaus  
Institute of Virology Building  
Erasmus University Rotterdam  
Room Ee 1726  
Dr. Molewaterplein 50  
NL-3015, Rotterdam  
The Netherlands  
osterhaus@viro.fgg.eur.nl

Mrs Carol Porter  
Department of Veterinary Pathology  
University of Liverpool  
Leahurst, Neston  
Wirral  
Merseyside CH64 7TE  
c.j.porter@liv.ac.uk.

Professor John Oxford  
Retroscreen Virology  
64 Turner Street  
Whitechapel  
London E1 2AD  
j.s.oxford@retroscreen.com

Miss Caroline Powell  
NIBSC  
Blanche Lane  
South Mimms  
Potters Bar EN6 3QG  
clpowell@nisbc

Mr Simon Parker  
Department of Virology  
NIBSC  
Blanche Lane, South Minns  
Potters Bar  
Herts EN6 3QG  
sparker@nibsc.ac.uk

Dr med Wolfgang Preiser  
Consiliaroberarzt, Institut f. Medizinische Virologie  
J W Goethe-Universit?t Frankfurt am Main  
Reisemedizinische Impfabulanz  
Paul Ehrlich-Str. 40  
D-60596 Frankfurt am Main  
Germany  
w.preiser@em.uni-frankfurt.de, preiser@wildmail.com

Dr David Paton  
Head, Exotic Diseases Dept  
Institute for Animal Health  
Pirbright Laboratory  
Ash Road, Pirbright  
Woking, Surrey GU24 0NF  
david.paton@bbsrc.ac.uk

Dr Ludmilla Priimagi  
Head of the Virology Dept  
Estonian Institute of Experimental & Clinical Medicine  
Hiiu 42  
Tallinn 11619  
Estonia  
dr.priimagi@mail.ee

Mr Adrian Philbey  
Moredun Research Institute  
Bush Loan  
Penicuik  
Edinburgh EH26 0PZ  
adrian.philbey@mri.sari.ac.uk

Dr Simon Pugh  
Consultant Virologist  
PHLS  
Microbiology & PHL  
University Hospital  
Nottingham NG7 2UH  
spugh@trent.phls.nhs.uk

Dr Deenan Pillay  
Department of Infection  
University of Birmingham  
Medical School  
Edgbaston  
Birmingham B15 2TT  
d.pillay@bham.ac.uk

Miss Jane Rosbottom  
PhD Student / Dept of Clinical & Molecular Virology  
University of Edinburgh  
Royal School of Veterinary Studies  
Summerhall  
Edinburgh EH9 1QH  
j.rosbottom@sms.ed.ac.uk

Dr Christopher Pipkin  
Consultant in Medical Microbiology  
Royal Hospital Haslar  
Gosport  
Hampshire PO12 2AA

Dr Cathy Roth  
Global Alert and Response  
CSR / WHO  
20 Av Appia  
1211 Geneva

Dr Walter Plowright  
Whitehill Lodge  
Reading Road  
Goring RG8 0LL

Switzerland  
rothc@who.ch

Mr Claude Sabeta  
Lecturer, Biological Sciences Dept  
University of Zimbabwe  
MD 167, Mt Pleasant  
Harare  
Zimbabwe  
taurai30@yahoo.com

Dr Agneta Samuelson  
Division Clinical Virology  
Huddinge University Hospital  
F 68  
S-141 86  
Stockholm  
Sweden  
agneta.samuelson@viruslab.hs.sll.se

Dr Jurjen Schirm  
Department of Virology  
Regional Public Health Laboratory  
Van Ketwich Verschuurlaan 92  
9721 SW Groningen  
Netherlands  
schirmjsg@compuserve.com

Professor Herbert Schmitz  
Department of Virology  
B N J  
Hamburg 20359  
Bernhard - Nocht SH 74  
Germany  
schmitz@bni.uni-hamburg.de

Miss Fiona Scott  
Dept of Virology / Barts & The London  
University of London  
Queen Mary's School of Medicine & Dentistry  
37 Ashfield Street  
London E1 1BB  
lmsimmondss@lhmc-fs.mds.qmw.ac.uk

Mr Jim Scudamore  
Chief Veterinary Officer  
State Veterinary Service  
Room 303  
1A Page Street  
London SW14 4PQ  
jim.scudamore-official@defra.gsi.gov.uk

Professor Dr Gunter Siegl  
Head of the Institute  
IKMI Inst for Clinical Microbiology & Immunology

Frohbergstr 3  
CH -9001, St Gallen  
Switzerland  
guenter.siegl@gd-ikmi.sg.ch

Ms Rhiannon Silk  
Research Assistant  
IAH  
Pirbright Laboratory  
Ash Road, Pirbright  
Woking, Surrey GU24 0NF  
rhiannon.silk@bbsrc.ac.uk

Professor Peter Simmonds  
Laboratory for Clinical & Molecular Virology  
University of Edinburgh  
Summerhall  
Edinburgh EH9 1QH  
peter.simoonds@ed.ac.uk

Dr Cate Sims  
Virologist Specialist  
Bio Products Laboratory  
Dagger Lane, Elstree  
Herts WD6 3BX  
cs22255@bpl.co.uk

Dr Sue Skidmore  
Grade C Clinical Scientist  
Public Health Laboratory Service  
PHLS  
Princess Royal Hospital  
Telford TF6 6TF  
sskidmore@mids.phls.nhs.uk

Professor Peter Sneath  
Department of Microbiology & Immunology  
University of Leicester  
PO Box 138  
Leicester LE1 9HN  
phas1@le.ac.uk

Mr Philip Spearpoint  
Department of Biological Sciences  
University of Manchester  
3 McKee Square  
RAF Benson  
Wallingford, Oxon OX10 6EE  
philip.a.spearpoint@stud.man.ac.uk

Miss Lynn Spencer  
Centre for Preventive Medicine  
Animal Health Trust  
Lanwades Park, Kentford  
Newmarket  
Suffolk CB8 7UU  
lynn.spencer@aht.org.uk

Mrs Annette Stannard  
BMS 3, Virology  
UCLH  
Windeyer Building  
46 Cleveland Street  
London W1T 4JF  
annette.stannard@uclh.org

Miss Sofie Starkman  
Virus Evolution Group  
University of Edinburgh  
Laboratories of Clinical and Molecular Virology  
Summerhall  
Edinburgh EH9 1QH  
sstarkma@srv1.med.ed.ac.uk

Dr Iain Stephenson  
Specialist Registrar  
Leicester Royal Infirmary  
Respiratory Unit, CPHL  
61 Colindale Ave  
London NW9 8HT  
istephenson@phls.org.uk

Dr Peter Stevenson  
G6, Science Directorate  
DEFRA  
Cromwell House, Dean Stanley Street  
Westminster  
London SW1P 3JH  
peter.stevenson@defra.gsi.gov.uk

Professor James Stewart  
Department of Medical Microbiology  
University of Liverpool  
Duncan Building  
Daulby Street  
Liverpool L69 3G A  
j.p.stewart@liv.ac.uk

Miss Nicola Stock  
PHD Student / Biomolecular Sciences  
University of St Andrews  
BMS Building  
North Haugh  
Fife KY16 9ST  
ns22@st-andrews.ac.uk

Dr Joanne Stockton  
ERNVL  
Central Public Health Laboratory  
61 Colindale Avenue  
Colindale  
London NW9 5HT  
jstockton@phls.org.uk

Professor Françoise Stoll-Keller  
Institut de Virologie  
3, rue Koeberl  
67000 STRASBOURG

FRANCE  
francoise.stoll@viro-ulp.u-strasbg.fr

Dr Gunnar Storvold  
Department of Microbiology  
Ullevål University Hospital  
Kirkev. 166  
Oslo 0407  
Norway  
gstorvold@hotmail.com

Dr Thiru Suretheran  
Clinical Virology  
Barts & The London School of Medicine & Dentistry  
25-29 Ashfield Street  
Whitechapel  
London E1 1BB  
TSuretheran@mds.qmw.ac.uk

Dr Julian Tang  
Virology, Specialist Registrar  
University College London  
Windeyer Building  
46 Cleveland Street  
London W1T 4JF  
jwang49@hotmail.com

Dr Catherine Tarbatt  
Staff Editor  
SGM - Journal of General Virology  
Marlborough House  
Basingstoke Road, Spencers Wood  
Reading, Berks RG7 1AG  
c.tarbatt@sgm.ac.uk

Dr Giulio Tarro  
Division Head  
D. Cotugno Hospital  
via Posillipa 286  
80123 Naples  
Italy  
gitarro@tix.it

Mr Paul Taylor  
Consultant Clinical Scientist  
Royal Brompton Hospital  
Microbiology Dept  
Sydney Street  
London SW3 6NP  
p.taylor@rbh.nthames.nhs.uk

Dr Clive E Taylor  
Consultant Clinical Scientist  
Public Health Laboratory Service

Public Health Laboratory  
Institute of Pathology, Newcastle General Hospital  
Newcastle upon Tyne NE4 6BE  
newctaylo@norbh.phls.nhs.uk

Dr Samuel Thevasagayam  
Principal Scientist, Vet Med Clinical Development  
Pfizer Global R&D  
IPC A837, Pfizer Ltd  
Ramsgate Road  
Sandwich, Kent CT13 9NJ  
samuel.Thevasagayam@sandwich.pfizer.com

Dr Alero Thomas  
Dept of Infectious & Tropical Diseases  
London School of Hygiene & Tropical Medicine  
Keppel Street  
London WC1E 7HT  
alero.thomas@lshtm.ac.uk

Dr William Tong  
Consultant / Dept of Infection  
Guys & St Thomas' Hospital Trust  
Virology Section  
5th Floor, North Wing, St Thomas Hospital  
London SE1 7EH  
william.tong@sstt.sthames.nhs.uk

Miss Crista Toomey  
Department of Pathology & Infectious Diseases  
Royal Veterinary College  
Hawkshead Lane  
North Mimms  
Hatfield, Herts AL9 7TA  
ctoomey@rvc.zc.uk

Dr Noel Tordo  
Laboratoire des Lyssavirus  
Institut Pasteur  
25 rue du Dr Roux  
75724 Paris Cedex 15  
France  
ntordo@pasteur.fr

Dr Gill Underhill  
Consultant Virologist  
St Marys Hospital  
Public Health Laboratory  
Milton Road  
Portsmouth, Hampshire PO3 6AQ  
gill.underhill@smail01.porthosp.swept.nhs.uk

Dr Daniele Van Beers  
Hopital St. Pierre Microbiologie  
Rue Haute 322  
B 1000 Brussels

Belgium  
daniele\_vanbeers@stpierre.bru.be

Dr Wim van der Poel  
Viral Zoonoses and Foodborne Virus Infections  
RIVM National Institute of Public Health and the  
Environment  
Microbiological Laboratory for Health Protection  
P.O. box 1, A. van Leeuwenhoeklaan 9  
3720 BA Bilthoven  
The Netherlands  
Wim.van.der.Poel@rivm.nl

Dr Gerard van Doornum  
Dept of Virology  
Erasmus MC  
Dr Molewaterplein 40  
3015 GD Rotterdam  
The Netherlands  
vandoornum@viro.a2r.nl

Dr E P M van Elzakker  
Medical Microbiology  
Reinier de Graaf Group  
PO Box 5011  
Delft, 2600 GA  
The Netherlands  
elzakker@rdgg.nl

Professor Dr Jan van Oirschot  
Head, Virus Discovery Unit  
ID-Lelystad  
Edelhertweg 15  
PO Box 65  
8200 AB Lelystad  
The Netherlands  
j.t.vanoirschot@id.wag-ur.nl

Dr Jana Vandasova  
Scientific Worker, Ntl Ref Lab on AIDS  
National Institute of Public Health  
Srobarova 48  
100 42 Prague 10  
Czech Republic  
brucaids@niph-prague.anet.cz

Dr Cheryl Vella  
Senior Lecturer, Faculty of Science  
University of North London  
166-220 Holloway Road  
London N7 8DB  
c.vella@unl.ac.uk

Dr Caroline Visser  
Dept of Medical Microbiology  
Reinier de Graaf Hospital  
Reinier de Graafweg 3-11  
Delft 2625AD

The Netherlands  
VisserC@rdgg.nl

Professor Carl - Henrik von Bonsdorff  
Department of Virology, Haartman Institute  
HUCH Laboratory Diagnostics  
Haartmanink 3  
00029 HUCH  
Finland  
carl-henrik.vonbonsdorff@helsinki.fi

Dr Kate Ward  
Department of Virology  
Windever Institute, University College  
46 Cleveland Street  
London W1T 4JG  
k.n.ward@ucl.ac.uk

Dr Mary Warrell  
Centre for Tropical Medicine  
John Radcliffe Hospital  
Headington  
Oxford OX3 9DU  
mary.warrell@ndm.ox.ac.uk

Dr Ruth Watkins  
Pen y Graid Goch Farm  
Llanddeusant  
Llangadog, Carmarthen SA19 9TH  
ruthwatkins@supanet.com

Mr Peter Watts  
Clinical Scientist  
UCLH  
Windeyer Building  
46 Cleveland Street  
London W1T 4JF  
p.watts@ucl.ac.uk

Dr Manfred Weidmann  
Inst. F. Med. Mikrobiol. U. Hygiene Ast. Virologie  
Universitäts Kliniken Freiburg  
Hermann - Herder - Str - 11  
73104 Freiburg  
Germany  
weidmann@ukl.uni-freiburg.de

Professor Robin Weiss  
Prof Viral Oncology / Dept Molecular Pathology  
Windeyer Institute of Medical Sciences  
University College London  
46 Cleveland Street  
London W1T 4JF  
r.weiss@ucl.ac.uk

Dr Manfred Weitz  
Division of Molecular Biology  
Institute of Clinical Microbiology & Immunology  
Frohbergstr. 3  
CH - 9001 , St Gallen  
Switzerland  
manfred.weitz@gd-ikmi.sg.ch

Dr Sytske Welling-Wester  
UHD / Medical Microbiology  
University Medical Microbiology  
Hanzeplein 1  
9713 GZ Groningen  
The Netherlands  
S.Welling-Wester@Med.RUG.NL  
Dr Diana Westmoreland  
Consultant Virologist, Public Health Laboratory  
University Hospital of Wales  
Heath Park  
Cardiff CF4 4XW  
diana.westmoreland@phls.wales.nhs.uk

Dr Jan Whitby  
Programme Manager Centres & Veterinary Sciences  
The Wellcome Trust  
183 Euston Road  
London NW1 2BE  
j.whitby@wellcome.ac.uk

Dr Philippa White  
Group Director  
PHLS East  
Institute of Food Research  
Norwich Research Park, Colney Lane  
Norwich NR4 7UA  
pwhite@phls.nhs.uk

Dr Ailsa Wight  
Department of Health  
Skipton House, Room 640B  
80 London Road  
London SE1 6LW  
awight@doh.gsi.gov.uk

Dr Roseanne Wilkinson  
Department of Retrovirology  
National Institute for Biological Standards & Control  
Blanche Lane, South Mimms  
Potters Bar  
Hertfordshire EN6 3QG  
rwillkinson@nibsc.ac.uk

Professor Bob Will  
Dept of Clinical Neurosciences  
Western General Hospital  
National Creutzfeldt-Jakob Disease Surveillance Unit  
Crewe Road  
Edinburgh EH4 2XU  
rjw@srvo.med.ed.ac.uk



Mr Peter Winter  
Dept of Medical Microbiology and G.U.M.  
University of Liverpool  
Duncan Building  
Daulby Street  
Liverpool L69 3GA  
pmw@liverpool.ac.uk

Mr Franc Zerjav  
Virological Laboratory  
Institute for Infectious Diseases  
Bulevar JNA 16, 11000 Belgrade  
Jugoslavija  
franc@www.yu

Dr Mark Zuckerman  
South London PHL & Dept Infection  
Kings College Hospital (Dulwich Site)  
East Dulwich Grove  
London SE22 8QF  
mark.zuckerman@kcl.ac.uk

Dr Tim Wreghitt  
Deputy Director  
Addenbrookes Hospital  
Clinical Microbiology & Public Health Laboratory  
Box 236  
Cambridge CB2 2QW  
tim.wreghitt@msex.addenbrookes.anglox.nhs.uk

Dr Werner Wunderli  
Central Laboratory of Virology  
University Hospital  
24 rue Micheli-du-Crest  
CH-1211 Geneve 14  
Switzerland  
werner.wunderli@hcuge.ch

Dr Su Xin  
Sr Scientist, Research & Development  
Focus Technologies Inc  
10703 Progress Way  
Cypress, CA 90630  
USA  
xsu@focusanswers.com

Professor Zichria Zakay-Rones  
Faculty of Medicine  
Hebrew University of Jerusalem  
POB 12272, Jerusalem, 91120  
Israel  
rones@cc.huji.ac.il

Mr Itzhak Zamberg  
c/o Dr Ella Mendelson  
Central Virology Laboratory  
Chaim Sheba Medical Center  
Tel-Hashomer 52621  
Israel  
ellamen@shebahealth.gov.il

Dr Sonja Zerjav  
Virological Laboratory  
Institute for Infectious Diseases  
Bulevar JNA 16, 11000 Belgrade  
Jugoslavija  
franc@www.yu

**WEDNESDAY 9 JANUARY 2002****1500 External and Internal Quality Control for the Detection of Influenza Virus Genome and Antigen****H. ZEICHHARDT<sup>1</sup>, H.-P. GRUNERT<sup>1</sup> & K.-O. HABERMEHL<sup>2</sup>****<sup>1</sup>Institute for Infectious Diseases Medicine, Free University of Berlin, Hindenburgdamm 27, 12203 Berlin, Germany; <sup>2</sup>Institute for Biotechnological Diagnostics, Potsdamer Chaussee 80, 14129 Berlin, Germany**

External Quality Assessment Schemes (EQASs) give evidence about test performance and interpretation of results in the laboratory as well as the robustness, sensitivity and specificity of commercial and in house tests. The EQASs are organized under the scientific responsibility of the German Association against Virus Diseases (DVG), the Society of Virology (GfV), the German Society for Hygiene and Microbiology (DGHM) and WHO in cooperation with INSTAND (Institute for Standardization and Control in Medical Laboratories, Duesseldorf, WHO Collaborating Centre for Quality Assurance in Laboratory Medicine). The introduction of EQASs in Germany, 17 cooperating countries and WHO (42 countries) with approx. 900 laboratories participating twice a year and more than 340,000 distributed samples since 1988 revealed new insights for industries, requirements for licensing by governmental institutions and for clinical application as well as evaluation. The experience from 503 EQASs for Germany, Europe and for international WHO control programs resulted in the establishment of a well characterized pool of samples for control material and national references.

Four EQASs for the detection of influenza virus genome and antigen have been performed since 2000 (February 2000 - April 2001: influenza A Beijing/262/95 (H1N1) and Sydney/5/97 (H3N2), influenza B Yamanashi/166/98); since November 2001: influenza A New Caledonia/20/99 (H1N1) and Moscow/10/99 (H3N2), influenza B Sichuan/379/99). The antigen tests for the individual detection of influenza virus A or B produced correct results in most cases, problems, however, became obvious for in house tests and commercial tests for the combined detection of influenza A and B. The majority of genome detection tests showed correct results. False negative results were frequently obtained with nested PCR.

**FRIDAY 11 JANUARY 2002****1445 Rapid Detection and Quantification of Pathogenic *Bunyaviridae* by a TaqMan-RT-PCR Approach**  
**M. WEIDMANN & F.T. HUFERT****Abt. Virologie, Institut für Medizinischen Mikrobiologie & Hygiene, Universität Freiburg, Hermann-Herder-Str. 11, 70104 Freiburg, email: weidmann@ukl.uni-freiburg.de**

The TaqMan-PCR technology offers the possibility of specific and highly sensitive one tube RT-PCR. There is no need for a second round nested PCR, which reduces the risk of carry over contamination. Including all sequences available in the EMBL-databank the concept of this PCR-system has been applied to devise a set of primers to detect and distinguish pathogenic *Bunyaviridae* of the genera *Bunyavirus*, *Hantavirus*, *Nairovirus* and *Phlebovirus*.

Amplicons for almost all pathogenic *Bunyaviruses*, *Phleboviruses* and eurasian *Hantaviruses* were successfully established with sensitivities of 100 to 10 copies. Adjusting the TaqMan-PCR chemistry to the Light-Cycler system, led to increased sensitivities for some of the RT-PCR assays. The assays were also run on the mobile Smart Cycler yielding similar results as obtained with the Light Cycler.

The Dobrava and Oropouche assays showed high specificities and sensitivities when tested on patient material.