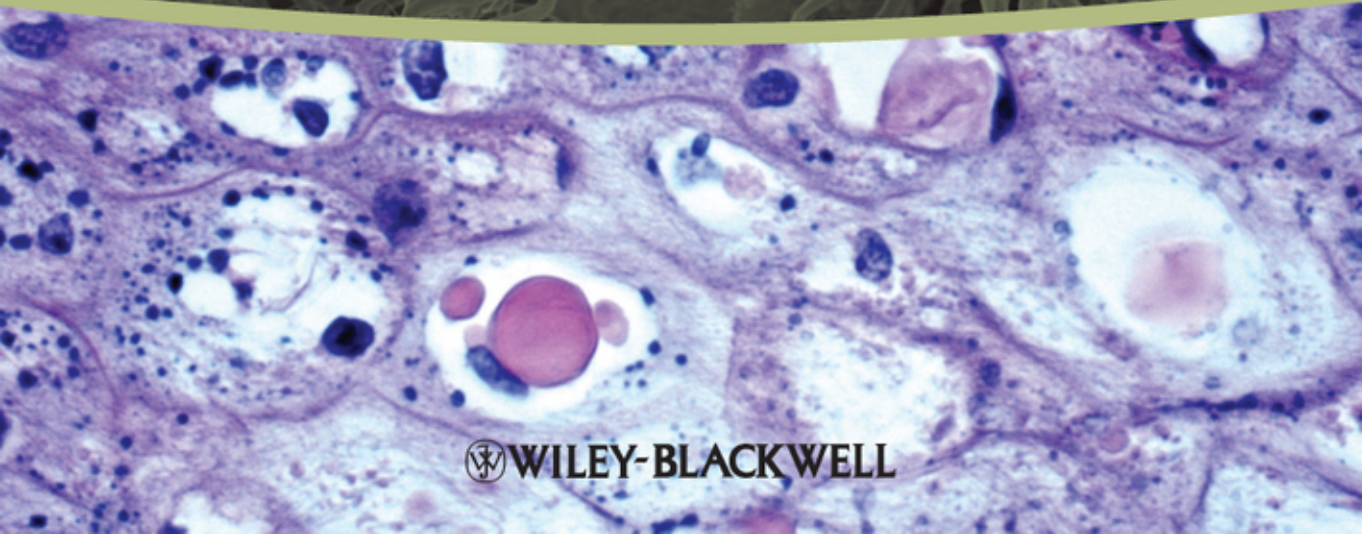
INFECTIOUS DISEASES OF WILD MAMMALS AND BIRDS IN EUROPE

Edited by
Dolores Gavier-Widén, J. Paul Duff & Anna Meredith



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Infectious Diseases of Wild Mammals and Birds in Europe

To my dear husband Frederik and my wonderful children,
Alexander, Verónica and Emelie.
Dolores Gavier-Widén

To Sam, Kitt and Anna, my family, and colleagues especially
in the AHVLA, Europe and America.
The intricacies of infection add to the wonder of our world.
J. Paul Duff

To friends and colleagues in the wildlife field,
and to my family for their patience and support.
Anna Meredith

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Edited by

Dolores Gavier-Widén
National Veterinary Institute (SVA) and
Swedish University of Agricultural Sciences, Uppsala, Sweden

J. Paul Duff
Animal Health and Veterinary Laboratories Agency,
(AHVLA) Diseases of Wildlife Scheme, Penrith, UK

Anna Meredith
Royal (Dick) School of Veterinary Studies, University of Edinburgh, Scotland, UK

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CONTENTS

NOTES ON CONTRIBUTORS

Marc Artois, DMV, PhD
Professor
VetAgro sup
Campus vétérinaire de Lyon
Marcy l'Etoile, France

Alex M. Barlow, Mr. BVSc, MSc (Aquatic Veterinary Studies), MRCVS
Animal Health and Veterinary Laboratories Agency
Diseases of Wildlife Scheme (AHVLA DoWS)
Great Britain Wildlife Disease Surveillance Partnership
Langford, Somerset, UK

Richard Birtles, BSc (Hons), PhD
Professor
School of Environment and Life Sciences
University of Salford
Greater Manchester, UK

Hervé Bourhy, DVM, PhD
Institut Pasteur
Unit Lyssavirus dynamics and host adaptation
National Reference Centre for Rabies
WHO Collaborating Centre for Reference and Research on Rabies
Paris, France

Debra Bourne, MA, VetMB, PhD, MRCVS
Wildlife Information Network
Twycross Zoo – East Midland Zoological Society
Atherstone, UK

Canio Buonavoglia, DVM
Professor
Department of Veterinary Public Health
Faculty of Veterinary Medicine of Bari
Valenzano (Bari), Italy

Claudia Cafarchia, D B. Sci., PhD
Department of Veterinary Public Health
University of Bari
Valenzano (Bari), Italy

Mark Chambers, Dr
TB Research Group
Department of Bacteriology
Animal Health and Veterinary Laboratories Agency
Weybridge, UK

Ruth Cromie, Dr
Wildfowl & Wetlands Trust (WWT)
Slimbridge, Gloucester, UK

Nicola Decaro
Associate Professor
Department of Veterinary Public Health
Faculty of Veterinary Medicine of Bari
Valenzano (Bari), Italy

Richard Delahay, Dr
The Food and Environment Research Agency
Woodchester Park
Nympsfield
Gloucester, UK

Kevin Eatwell, BVSc (hons) DZooMed (Reptilian), Dip ECZM (Herp), MRCVS
Exotic Animal and Wildlife Service
Royal (Dick) School of Veterinary Studies
Edinburgh, Scotland

Károly Erdélyi, DVM, PhD, Dip ECZM (Wildlife Population Health)
Department of Domestic Mammal and Wildlife Diseases
Veterinary Diagnostic Institute
Central Agriculture Office
Budapest, Hungary

Antonio Fasanella, Dr, PhD
Istituto Zooprofilattico Sperimentale of Puglia and Basilicata
Foggia, Italy

Ezio Ferroglio, DVM, PhD, Dipl. EVPC, Dipl. ECVPH
Professor
Università degli Studi di Torino
Dipartimento Produzioni Animali
Epidemiologia ed Ecologia
Grugliasco, Italy

Kai Frölich, Privatdozent, Dr, Dr
Tierpark Arche Warder
Warder, Germany

Alessandra Gaffuri, DVM
Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna
Department of Bergamo
Bergamo, Italy

Marco Giacometti, PhD, Dr Med Vet
Wildvet Projects
Stampa, Switzerland

E. Paul J. Gibbs, BVSc, PhD, FRCVS
Professor
College of Veterinary Medicine
University of Florida
Gainesville, Florida, USA

Jacques Godfroid, DVM, MSc
Professor
Section of Arctic Veterinary Medicine
Department of Food Safety and Infection Biology
Norwegian School of Veterinary Science
Tromsø, Norway

Carlos Gonçalo das Neves, DVM, PhD
Norwegian School of Veterinary Science
Department of Food Safety and Infection Biology
Section of Arctic Veterinary Medicine
Tromsø, Norway

Miklós Gyuranecz, DVM, PhD
Veterinary Medical Research Institute
Hungarian Academy of Sciences
Budapest, Hungary

Christian Gortázar, Dr
IREC National Wildlife Research Institute (CSIC-UCLM-JCCM)
Ciudad Real, Spain

Kjell Handeland, DVM, PhD
Department of Animal Health
Section of Wildlife Diseases
National Veterinary Institute
Oslo, Norway

Paul Heyman
Research Laboratory for Vector-Borne Diseases
Epidemiology and Biostatistics Department
Queen Astrid Military Hospital
Brussels, Belgium

J. Paul Holmes, Mr, BVSc, MSc (Wild Animal Health), MRCVS
GB Wildlife Disease Surveillance Partnership
Animal Health and Veterinary Laboratories Agency Wildlife Group
Diseases of Wildlife Scheme (AHVLA DoWS)
AHVLA Shrewsbury, UK

Désirée S. Jansson, DVM, PhD
Department of Animal Health and Antimicrobial Strategies
National Veterinary Institute & Department of Biomedical Sciences and Veterinary Public Health
Swedish University of Agricultural Sciences
Uppsala, Sweden

Erhard Franz Kaleta, Dr Med Vet, Dr Vet Med H.C.
Professor
Clinic for Birds, Reptiles, Amphibians and Fish
Faculty of Veterinary Medicine
Justus Liebig University
Giessen, Germany

Frank Koenen, Dr, DVM
CODA-CERVA
OD: Interaction and Surveillance
Belgium

Thijs Kuiken, DVM, PhD, DACVP
Professor of Comparative Pathology
Department of Virology
Erasmus MC and Artemis Research Institute for Wildlife Health in Europe
Rotterdam, The Netherlands

Annick Lindén, DVM, PhD
Professor
University of Liège
Liège, Belgium

Ignasi Marco, DVM, PhD
Servei d′ Ecopatologia de Fauna Salvatge (SEFaS) – Wildlife Diseases Research Group
Departament de Medicina i Cirurgia Animals
Facultat de Veterinària
Bellaterra. Spain

Philip Scott Mellor, OBE, DSc, BSc, MSc, PhD, FRES, FHEA
Professor
Institute for Animal Health
Pirbright Laboratory
Pirbright, Woking, UK

Carol U. Meteyer, DVM, Dipl ACVP
USGS National Wildlife Health Center
Madison, Wisconsin, USA

Javier Millán, DVM, PhD, Dip ECZM (Wildlife Population Health)
Servicio de Ecopatología de Fauna Salvaje (SEFaS) - Wildlife Diseases Research Group
Departamento de Medicina y Cirurgía Animales
Facultad de Veterinaria
Universidad Autónoma de Barcelona
Bellaterra. Spain

Volker Moennig, Dr
Professor
Institute of Virology
Department of Infectious Diseases
University of Veterinary Medicine
Hannover, Germany

Thomas Frank Müller, Dr Med Vet
Friedrich-Loeffler-Institut
Federal Research Institute for Animal Health
Wusterhausen, Germany

Hristo Najdenski, DVM, DSc
Professor
The Stephan Angeloff Institute of Microbiology
Bulgarian Academy of Sciences
Sofia, Bulgaria

Aleksija Neimanis, M.Sc., D.V.M., M.Vet.Sci., Dipl. ACVP
Department of Pathology and Wildlife Diseases
National Veterinary Institute
Uppsala, Sweden

Robin A.J. Nicholas, MSc, PhD, FRCPath
Mycoplasma Group, Animal Health and Veterinary Laboratories Agency (Weybridge)
Weybridge, UK

Albert D.M.E. Osterhaus, DVM, PhD
Professor
Department of Virology
Erasmus MC, and Artemis Research Institute for Wildlife Health in Europe
Rotterdam, The Netherlands

Hugh W. Reid, MBE, BVM & S, DipTVM, PhD, MRCVS
The Moredun Foundation
Pentlands Science Park
Bush Loan, Penicuik,
Midlothian, UK

Leslie Anne Reperant, DVM, PhD
Department of Ecology and Evolutionary Biology
Department of Virology
Erasmus Medical Centre
Rotterdam
The Netherlands

Marie-Pierre Ryser-Degiorgis, Dr Med Vet, Dip ECZM (Wild Pop Health)
Centre for Fish and Wildlife Health
Institute of Animal Pathology
Department of Infectious Diseases and Pathobiology
Vetsuisse Faculty
University of Bern
Bern, Switzerland

Jolianne Miriam Rijks, DVM, PhD
Dutch Wildlife Health Centre
Utrecht, The Netherlands

Francisco Ruiz-Fons, PhD
Instituto de Investigación en Recursos Cinegéticos IREC (CSIC-UCLM-JCCM)
Ciudad Real, Spain

Thomas Selhorst, Dr
Friedrich-Loeffler-Institut
Institut für Epidemiologie
Wusterhausen/Dosse, Gemany

Graham C. Smith, Dr
The Food and Environment Research Agency
York, UK

Stephanie Speck, DVM
Bundeswehr Institute of Microbiology
Department of Virology and Rickettsiology
Munich, Germany

Daniel Todd, BSc (Hons), PhD
Agri-Food & Biosciences Institute-Stormont
Belfast, UK

Turid Vikøren, DVM, PhD
Norwegian Veterinary Institute
Oslo, Norway

Herbert Weissenböck, DVM, DipECPHM
Associate Professor
Pathology and Forensic Veterinary Medicine
Department of Pathobiology
University of Veterinary Medicine
Vienna, Austria

Gudrun Wibbelt, Dr Med Vet
Leibniz Institute for Zoo and Wildlife Research
Wildlife Diseases – Pathology
Berlin, Germany

Frederik Widén, DVM, PhD
Assistant Professor
National Veterinary Institute (SVA) and Swedish University of Agricultural Sciences
Uppsala, Sweden

Bjørnar Ytrehus, DVM, Dr Med Vet
Norwegian Veterinary Institute
Oslo, Norway

PREFACE

The aim of this book is to provide a reference text on infectious diseases which affect free-living wild mammals and birds in Europe. This is a broad field and currently involves many scientific disciplines including ecology, biology, wildlife management, epidemiology, animal and human health, molecular biology, evolutionary biology, genetics, virology, bacteriology, pathology, and diagnostics. A wildlife disease literature in journals covering these diverse disciplines exists in Europe; however there was a pressing need to review this, and bring the essential information together in one text.

A volume of knowledge on wildlife disease has been produced in Europe over recent decades and research on wildlife diseases has significantly increased in the last 15 years, partly due to the growing concern about new and emerging pathogens and partly through projects financed by the EU and other international organisations. This interest has also concentrated on investigations into the risks to human health (the zoonotic risks from wildlife). Several recent discoveries in the field have been published together with the gathering of large amounts of supportive information. However, this information is frequently published as specialised articles, or it deals only with local situations or individual studies rather than in the continental context. It is now apparent that these diseases must be considered from the perspective of the European continent.

This book describes each significant wildlife infectious disease. The Europe-wide information has been extracted, condensed and written by specialists in each topic. The book presents high-quality, accurate, clear and up to date information on the important aspects of the infectious diseases of wildlife. This type of information is frequently sought-after, but not always easy to locate or assimilate.

We believe that this book is needed now because there are changing situations and increased awareness in Europe with respect to:

1. The emergence or re-emergence of new diseases from wild animal reservoirs, such as avian influenza, classical swine fever, rabies, tuberculosis and foot and mouth disease.
2. The zoonotic implications of wildlife, for example, in highly-pathogenic avian influenza, rabies, West Nile Virus, hantavirus infections and food borne zoonoses (tuberculosis, hepatitis E).
3. Changes in the environment that wildlife may be a sensitive indicator for, in particular climatic change and its effects on disease ecology, and vector popula-

tions (ticks, midges, mosquitoes) resulting in spread of disease to new areas within and into Europe, for example bluetongue, tick borne encephalitis, Usutu and West Nile viruses.

4. The involvement of wild animals in the infection of livestock and pets. As wild animals move freely and certain populations increase, then contact between wildlife and domesticated animals will increase. For example salmonellosis in domestic cats and classical swine fever from wild boar to pigs.
5. The public concern for the effects of disease on the health of wild animals, particularly if causing mass mortality, for example morbillivirus in seals and outbreaks of botulism in birds.
6. The opening of markets within Europe results in movements of animals and a higher risk of spreading disease between livestock and wildlife, for example foot and mouth disease, classical swine fever.
7. Limited control of wild populations, encroachment by man on wildlife habitat and decreased hunting is producing high density and urban populations of roe deer, red fox and wild boar. As a consequence, there is increased contact with domesticated animals and humans, which results in increased transmission of disease between species.
8. The importance of the sub-clinical reservoir role of wild animals and the need for surveillance methodologies in detecting these covert infections, for example in rabies and tuberculosis.
9. The potential for migrating wildlife to introduce new and exotic pathogens to Europe.
10. There is also recognition that those assessing diseased wild animals require background information and guidance as to treatment and control strategies.
11. Disease may threaten wild populations, endangered species, and ultimately biodiversity.

This book is original because it is the first text to describe in detail the infectious diseases of wild mammals and wild birds in Europe. Its key features are that –

- It presents information on aspects of each disease or group of pathogens to provide the reader with a clear background and also covers the distinctive nature of these diseases as they occur in Europe (pathogen strains, insect vectors, reservoir species, climate, etc).
- It concentrates on the Europe-wide situation, including geographical distribution of the diseases, European wildlife species and European regulations for the diagnosis and control of the diseases.
- It describes the latest advances in veterinary diagnostics including molecular technology. Wildlife vaccination and disease surveillance techniques are described.
- It provides practical information, for example listing the animal species in which the disease has been recorded; the samples required for diagnostic examination, the diagnostic methods and the EU community reference laboratories.
- It provides guidance on disease control measures.

Our aim is to provide useful information for scientists trying to understand the health of wildlife populations. The One World-One Health concept shows that this is essential in understanding global health systems. If biologists, ecologists, veterinarians, epidemiologists and wildlife rehabilitators find the text helpful then the aim will be achieved.

COVER IMAGE ACKNOWLEDGEMENTS

Top: A brown hare leveret belonging to a litter of four orphans was found opportunistically in the wild. Subsequently it was demonstrated that it had antibodies against *European brown hare syndrome virus*, indicating for the first time that passive transfer of immunity to this virus, probably through colostrum, occurs in hares. Photograph: Bengt Ekberg.

Middle: Scanning electron micrograph of cultured bacterial cells of the intestinal spirochaete '*Brachyspira suanatina*' isolated from a pig. This pig enteropathogen colonizes the intestines of free-living wild mallards and domestic pigs and may be experimentally transferred between the two species. Photograph: Désirée S. Jansson and Leif Ljung.

Bottom: Microphotograph showing intracytoplasmic eosinophilic (pink) inclusion bodies in degenerating skin cells of a musk ox calf with contagious ecthyma (orf) caused by parapoxvirus infection. Photograph: Turid Vikøren.

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The editors wish to express their sincere thanks to all the authors for their enthusiasm and commitment. The editors thank also the National Veterinary Institute of Sweden, the Animal Health and Veterinary Laboratories Agency and the Royal (Dick) School of Veterinary Studies for their support.

We acknowledge the inspiring gatherings of the Wildlife Disease Association and its section, the European Wildlife Disease Association, for working toward their shared mission 'to acquire, disseminate and apply knowledge of the health and diseases of wild animals in relation to their biology, conservation, and interactions with humans and domestic animals'. The solid scientific platform of these organisations and their welcoming atmosphere gave us the opportunity to learn about wildlife diseases, to keep our knowledge updated and to meet wildlife scientists, several of whom are contributors to this book.

We also acknowledge the OIE (the World Organisation for Animal Health), IUCN (The World Conservation Union), the European Association of Zoo and Wildlife Veterinarians and like-minded societies, which have contributed to the knowledge base of this book. Several of the chapters were reviewed anonymously and we thank those external reviewers.

SECTION

1

Viral Infections

CHAPTER

1

HERPESVIRUS INFECTIONS

FREDERIK WIDÉN, CARLOS G. DAS NEVES, FRANCISCO RUIZ-FONS, HUGH W. REID, THIJS KUIKEN, DOLORES GAVIER-WIDÉN AND ERHARD F. KALETA

INTRODUCTION

FREDERIK WIDÉN[1] AND CARLOS G. DAS NEVES[2]

[1]National Veterinary Institute (SVA) and Swedish University of Agricultural Science, Uppsala, Sweden
[2]Norwegian School of Veterinary Science, Department of Food Safety and Infection Biology, Section of Arctic Veterinary Medicine, Tromsø, Norway

Herpesvirales is a vast order of currently approximately 130 large enveloped DNA virus species divided into three families. Herpesviruses have been isolated from most species investigated, including mammals, birds, reptiles, insects, molluscs and amphibians; and several animal species have been found to be infected with several herpesvirus species. Herpesviruses are evolutionarily old viruses that have co-evolved with their hosts for more than 250 million years.

Morphologically, herpesviruses are distinct from all other viruses, with a linear, double-stranded DNA genome of 125–250 kbp contained within an icosadeltahedral capsid of 100 to 110 nm and containing 162 capsomers. This capsid is surrounded by an amorphous-looking, protein matrix, with variable thickness, called the tegument and then by a trilaminar envelope containing lipids and proteins, bringing the total size of the virion from 120 nm up to almost 300 nm. The presence of lipids in the envelope has practical implications, as it renders herpesviruses sensitive to detergents and lipid solvents. There are numerous spikes of glycoproteins protruding from the envelope. These spikes are more numerous and shorter than in other virus families. The variation in the size of the genome is to some extent attributed to the presence of internal and terminal repeats. Common to all herpesviruses is that they are complex and contain genes for a large number of enzymes necessary for their replication, that viral DNA synthesis and capsid formation takes place in the nucleus of the infected cell, and that infected cells are destroyed owing to the virus replication and release of virus progeny, together with the ability of herpesviruses to establish latent infections. During latency no virus progeny is produced and the genome remains in a circular form.

The order *Herpesvirales* can be divided into three families: the family *Herpesviridae* contains the viruses of mammals, birds and reptiles; the family *Alloherpesviridae* contains fish and frog viruses; and the family *Malacoherpesviridae* contains the bivalve virus. The family *Herpesviridae*, which includes approximately 79 known virus species so far, is further subdivided into three subfamilies: *Alphaherpesvirinae*, *Betaherpesvirinae* and *Gammaherpesvirinae*.

Alphaherpesviruses are characterized by a rather broad host range, short replication cycle, rapid destruction of

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infected cells and a rapid spread in the host. Furthermore, they have the ability to establish life-long latent infection in sensory ganglia, or sometimes in other ganglia. Alphaherpesviruses are known to cause several acute diseases of veterinary importance.

By contrast, betaherpesviruses, often called cytomegaloviruses, have a restricted host range, long replication cycle and a slow spread of infection, with latent or persistent infections possible in a range of tissues, e.g. lymphoreticular cells, secretory glands and kidneys. Infection usually results in significant enlargement of certain cell types, known as cytomegaly. Infections are often widely distributed in the host population and usually not clinically apparent, except when such a virus appears in a previously uninfected herd.

Gammaherpesviruses usually have a host range restricted to the host's family or order. Viruses of this subfamily have specificity for either B- or T-lymphocytes and may cause lymphoproliferative disease. Latency of gammaherpesviruses may be established in lymphoid tissue. Infections with viruses from this subfamily generally cause few clinical signs in the main host but may cause severe disease in other related species, as exemplified by malignant catarrhal fever.

The ability of herpesviruses to cause latent infections is of great epidemiological importance, as it is generally not possible to determine or confirm if an animal is latently infected owing to the almost complete absence of gene expression, viral replication or host immune response during latency. Thus, diagnostic assays usually do not detect latent infections. A latent infection can, however – under certain conditions such as in the presence of concurrent disease, stress, immunosuppression or hormonal changes – reactivate, resulting in a productive infection with excretion of viral particles, transmission and infection of susceptible animals.

HERPESVIRUS INFECTIONS IN WILD MAMMALS

CARLOS G. DAS NEVES

Norwegian School of Veterinary Science, Department of Food Safety and Infection Biology, Section of Arctic Veterinary Medicine, Tromsø, Norway

It is believed that most animal species can harbour at least one, if not more, endemic herpesviruses. With more than 5000 mammalian species and only around 200 herpesviruses identified so far, one can easily speculate on the many more yet to be found and added to the order *Herpesvirales*, already the biggest order of viruses in existence.

Phylogenetic studies show co-speciation between herpesviruses and their hosts, with divergences in viral taxonomy mimicking those of animal species. Whereas herpesviruses of mammals and birds have shared a common ancestor, divergence seems to have happened over 220 million years ago, with speciations within sublineages in the last 80 million years as mammalian radiation took place[1,2].

Although many herpesviruses are well adapted to their natural host, there are several that can cross the species barrier and infect other animals. This is the case for many herpesviruses that can circulate between wild animals and domestic animals (e.g. *Alcelaphine herpesvirus 1* and *2*). Some others can have zoonotic potential, such as herpesviruses from primates that infect and cause severe disease in humans (e.g. *Macacine herpesvirus 2*). Human-specific herpesviruses also have the potential to infect wild animals.

Table 1.1 summarizes some of the most important herpesviruses relevant to European wildlife.

AUJESZKY'S DISEASE, OR PSEUDORABIES

FRANCISCO RUIZ-FONS[1]

[1]*Instituto de Investigación en Recursos Cinegéticos IREC (CSIC-UCLM-JCCM), Ciudad Real, Spain*

Aujeszky's disease (AD), pseudorabies or 'mad itch' is a neurological/respiratory disorder that affects a wide range of animals, except humans and some primates. It is caused by porcine or suid herpesvirus type 1, also known as pseudorabies virus or Aujeszky's disease virus (ADV), which belongs to the family *Herpesviridae* in the genus *Varicellovirus*.

AETIOLOGY

ADV is a 150–180 nm virion composed of a 145 Kb linear double-stranded DNA genome within an enveloped

TABLE 1.1 Important mammalian herpesviruses for European wildlife. Viruses are presented according to their taxonomic distribution within the three subfamilies of the order *Herpesvirales*.

	Name	Acronym	Common name
Subfamily	***Alphaherpesvirinae***		
Genus	***Simplexvirus***		
Species in the genus	*Bovine herpesvirus 2*	BoHV2	Bovine mammilitis virus
	Human herpesvirus 1	HHV1	Herpes simplex virus type 1
	Macacine herpesvirus 1	McHV1	Herpes simian B-virus
Genus	***Varicellovirus***		
Species in the genus	*Bovine herpesvirus 1*	BoHV1	Infectious bovine rhinotracheitis virus
	Bubaline herpesvirus 1	BuHV1	Water buffalo herpesvirus*[a]
	Canid herpesvirus 1	CaHV1	Canine herpesvirus
	Caprine herpesvirus 1	CpHV1	Goat herpesvirus
	Cervid herpesvirus 1	CvHV1	Red deer herpesvirus
	Cervid herpesvirus 2	CvHV2	Reindeer herpesvirus
	Felid herpesvirus 1	FeHV1	Feline rhinotracheitis virus
	Phocid herpesvirus 1	PhoHV1	Harbour seal herpesvirus
	Suid herpesvirus 1	SuHV1	Pseudorabies virus
Unclassified in the subfamily	*n/a*	n/a	Bottlenose dolphin herpesvirus
	n/a	n/a	Tursiops truncatus alphaherpesvirus
Subfamily	***Betaherpesvirinae***		
Genus	***Cytomegalovirus***		
Species in the genus	*Macacine herpesvirus 3*	McHV3	Rhesus macaques cytomegalovirus*[b]
Unclassified in the subfamily	*Suid herpesvirus 2*	SuHV2	Porcine cytomegalovirus
	n/a	n/a	Bat betaherpesvirus
Subfamily	***Gammaherpesvirinae***		
Genus	***Lymphocryptovirus***		
	Human herpesvirus 4	HHV4	Epstein–Barr virus*[c]
Genus	***Macavirus***		
	Alcelaphine herpesvirus 1	AlHV1	Malignant catarrhal fever virus*[d]
	Alcelaphine herpesvirus 2	AlHV2	Hartebeest malignant catarrhal fever virus*[d]
	Caprine herpesvirus 2	CpHV2	Caprine herpesvirus 2
	Ovine herpesvirus 2	OvHV2	Sheep-associated malignant catarrhal fever virus
Genus	***Percavirus***		
	Mustelid herpesvirus 1	MusHV1	Badger herpesvirus
Unclassified in the genus	*Phocid herpesvirus 2*	PhoHV2	Phocid herpesvirus 2
Genus	***Rhadinovirus***		
Unclassified in the genus	*Leporid herpesvirus 2*	LeHV2	Herpesvirus cuniculi
Unclassified in the subfamily	*n/a*	n/a	Rupicapra rupicapra gammaherpesvirus 1
Unclassified in the family	*Erinaceid herpesvirus 1*	ErHV1	European hedgehog herpesvirus
	Sciurid herpesvirus 1	ScHV1	Ground squirrel cytomegalovirus
	Sciurid herpesvirus 2	ScHV2	Ground squirrel herpesvirus

n/a – not available

*[a] Most buffalos in Europe are semi-domesticated

*[b] Mostly only at zoos, only monkey wild population in Europe living in Gibraltar is free from McHV3

*[c] Shown experimentally to infect dog cells and also found in seroscreenings of canids

*[d] Present in Europe only in zoos but represent the type species in the genus

nucleocapsid. The 105–110 nm wide nucleocapsid is formed by different structural proteins and its envelope is a lipidic membrane composed of nine different enclosed glycoproteins used in the life cycle of the virus, immune modulation and pathogenicity.

EPIDEMIOLOGY

ADV is widely distributed in European wild boar populations (Figure 1.1)[3]. Some countries, where AD has not been identified in wild boar populations, have reported

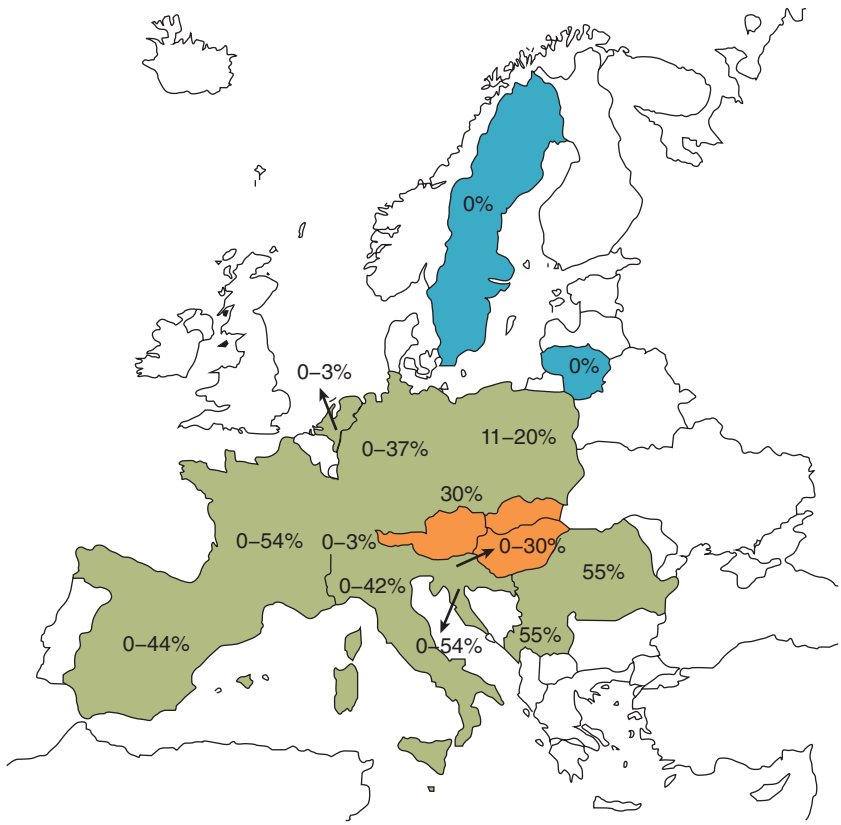

FIGURE 1.1 European countries where reports of ADV surveillance in wild boar populations have been published in the scientific literature[3] or reported in national wildlife surveillance programmes between 1987 and 2011. Countries shaded in green represent ADV-positive wild boar populations, whereas countries shaded in blue represent ADV-negative surveyed wild boar populations. Countries shaded in orange have reported pseudorabies outbreaks in hunting dogs associated with wild boar hunting, but where the status of wild boar populations is unknown. Seroprevalence/prevalence reported range of the within-country surveyed European wild boar populations are shown.

pseudorabies outbreaks in dogs used in boar hunting, i.e. Austria[4,5], Belgium[6], Hungary and Slovakia[7]. Several European countries where ADV has not been reported or where it was eradicated from domestic pigs have not assessed the status of ADV in their wild boar populations (e.g. Denmark, Norway, Finland or the UK). Thus, the current known distribution of ADV in European wild boar populations may not be accurate.

ADV is able to infect a wide range of mammals, including ungulates, carnivores, lagomorphs, rats and mice. Infection in mammals is usually fatal; however, in some species subclinical infection is possible[8]. In suids, the only natural host species for ADV, the infection may cause disease or be subclinical.

Many European wild boar populations have had laboratory assessments for the presence of ADV or anti-ADV antibodies (Figure 1.1); however, the basic understanding of ADV epidemiology in boar is poor. Pan-European serological studies on ADV in wild boar have shown that the probability of contact with the virus increases with age. ADV causes life-long latent infection in suids and naturally infected animals remain seropositive, and potentially infective, for life. A similar viral exposure risk occurs for males and females; however, sex-related differences, with higher exposure of females to ADV, is seen in some European and North African wild boar populations (9). This may be related to behavioural differences between the sexes. Intra-group transmission is higher in all-female groups of wild boar, whereas males tend to be solitary. The probability of wild boar acquiring ADV in endemic areas also seems to be dependent on population density and the extent to which the animals aggregate[10], both of which

are highly variable factors across Europe, and this gives rise to regional/local variations in prevalence. Additionally, wild boar population structure, female group size, management or predation may influence the rate of transmission of ADV within and between groups. This could be the reason for the similar viral infection risk of males and females observed in many wild boar populations in Europe. Movement of individuals between infected and susceptible wild boar groups or populations is likely to be important for virus spread.

ADV survival rate in the environment is low. Transmission by the aerosol route is also low in hot and dry weather conditions, which are unfavourable for the virus, but is enhanced if weather conditions are cool and wet.

The European wild boar is currently considered as a true ADV reservoir, because the virus can infect, replicate and be excreted in this species, which is sufficiently abundant to be a wild reservoir. Other mammalian species are dead-end hosts in which death occurs before viral excretion. In the USA, some experimentally infected raccoons (*Procyon lotor*) have been found to behave as short-term reservoirs of ADV when infected at low doses[8], which would suggest a transient reservoir role.

Currently the main routes of ADV transmission in the European wild boar are not known; however, they are suspected to be by direct contact between individuals. There is little information as to whether aerosol infection is an efficient transmission pathway between wild boar. The oronasal route is suspected to be the usual means of ADV transmission between European wild boar, but the precise importance of aerosol transmission even over short distances is not known.

Venereal transmission is considered of primary importance for ADV transmission in American feral pig populations[11], and it may be an important route in European wild boar as well. An increase in seroprevalence after the mating season was found in wild boar in Spain[9], which, apart from suggesting an increasing contact rate between individuals, may perhaps also reflect the occurrence of venereal transmission. Additionally, ingestion of infected meat via cannibalism is considered a possible route of transmission.

Wild boar females usually live in groups with their offspring and juvenile animals. This may give rise to closer contact within female groups, and oronasal transmission is thought to predominate in these groups. Wild boar males are usually solitary for most of the year except during the mating season, when they make contact with female groups. Venereal transmission could be linked with reactivation of latent infections due to mating stress. Behavioural patterns of wild boar depend to a large extent on the availability of food resources, and it is believed that these food-based behaviours may be an important influence in determining ADV prevalence. The threshold infective dose for ADV in wild boar may vary according to the virulence of the circulating strain and the immune status of the infected animal, as occurs in the domestic pig.

ADV is excreted in suids by nasal exudates, saliva, vaginal mucus, sperm, milk, faeces and occasionally urine. Different routes of infection by ADV are potentially possible because there is some, unquantified, survival of the virus in the environment, particularly in organic material, and some persistence in aerosols. Wild carnivores acquire infection after consumption of ADV-infected wild boar meat, as may happen to dogs that eat or bite infected wild boar during hunting. Direct contact with ADV-excreting boar or indirect contact with infected fomites or aerosols are assumed to be the main ways of infection for wild ungulates.

PATHOGENESIS, PATHOLOGY AND IMMUNITY

Following primary infection, viral replication of ADV takes place in the nasal or genital mucosa and in the tonsilar epithelium. Later, ADV invades the nervous system via the nerve endings present in the genital, oral and nasal mucosae and progresses by moving along the nerves into the central nervous system (CNS). At this stage of infection, ADV can be detected in oropharyngeal tonsils, nasal cavity, genital mucosa, sacral ganglia or trigeminal ganglia. At this stage the virulence of the ADV strain and the immune status of the host (in the case of true reservoirs) determine whether there is invasion of the CNS, or establishment of a latent infection in the trigeminal or sacral ganglia. Infection progresses rapidly into the CNS in dead-end hosts. The virus can be detected in association with blood cells after infection but peripheral blood mononuclear cells do not carry ADV in latent infections. The virus may also replicate in lung and pharyngeal respiratory epithelia and in endothelium.

Very little is known about natural disease development in wild boar, but recent natural AD cases in wild boar piglets in Germany[12] show similarities with domestic pigs. Clinical disease in the domestic pig ranges from fatal

nervous disease usually seen in piglets, respiratory problems in post-weaning pigs and respiratory and reproductive manifestations in adults. Encephalitis has been found in wild boar naturally infected with ADV[12,13] and in animals that have been experimentally infected with ADV of moderate virulence[14]. The pathological outcome of ADV infection depends on the virulence of the strain. It is hence probable that low-virulence strains present in European wild boar populations may cause no lesions in this species. The histopathological findings consist of non-suppurative meningoencephalitis and ganglioneuritis with neuronal degeneration, focal gliosis, perivascular mononuclear cuffing and lymphocytic inflammation. Intranuclear inclusion bodies may be observed in neurons of the CNS or in ganglionar neurons. The viral tropism for epithelial tissues in the respiratory tract leads to alveolar, bronchiolar and bronchial epithelial degeneration and mononuclear cell infiltration. Degeneration and necrosis, often with intranuclear inclusion bodies, may occur in the liver, spleen, kidneys, pancreas, adrenal gland, thymus, lymph nodes, tonsils and intestinal epithelium. Oedema and haemorrhages are frequently observed.

Disease in dead-end hosts progresses rapidly, usually with a fatal outcome within 24 to 72 hours following infection. The tropism of ADV for endothelial cells leads to extravasations and oedema in the lungs, nasal and oral cavities. ADV pathogenesis is broadly similar for different dead-end host species, except for mink, in which vasculopathy is predominant to neuropathy[15]. Gross and microscopic lesions of AD in dead-end hosts and domestic pigs reflect the neurotropic nature of this herpesvirus. Many of the affected dead-end hosts may show no gross lesions because of the rapidly fatal outcome of infection, or they may show skin lesions caused by self-trauma due to the intense pruritus (see the Clinical Signs section below). Fibrinoid vasculitis, with haemorrhages and myocardial necrosis, is inconsistently described but appears to be typical in farmed mink[16]. Cardiac alterations in dogs may cause sudden death due to arrhythmias. Lesions in abdominal organs have been also found in different species of North American carnivores such as bears, coyotes (*Canis latrans*) and a Florida panther (*Puma concolor coryi*).

ADV infection evokes both humoral and cell-mediated immune responses in suids, but the immune response is unable to completely clear infection, and reinfection and activation of latent infections may occur. The cellular immune response to ADV has been the subject of little research in wild boar. Outer envelope ADV glycoproteins stimulate the production of neutralising antibodies, particularly those directed against glycoproteins (g) C and D (gC and gD). During the early stages of infection, neutralizing antibodies block virus attachment and invasion of cells. Infection of wild boar with low-virulence ADV strains (those circulating in European wild boar populations) induces a long-lasting active humoral immunity, which can be passed on to the offspring and confer protection to boar piglets during the first 15 weeks of life[17].

A characteristic of herpesviruses is their ability to evade the host immune response by producing long-term latent infections in specific tissues. Subsequent immunosuppression in the host may allow the infection to reactivate with viral replication and then dissemination throughout the body. Virus can then be excreted in high titre and is able to infect other susceptible individuals. ADV mainly establishes latency in neuronal cells, such as the trigeminal or sacral nervous ganglia. Reactivation of latent infections does not usually lead to overt clinical disease. Reactivation of latent infections should be carefully considered when planning ADV eradication from domestic pigs. It should also be considered when studying ADV epidemiology in wild boar populations.

CLINICAL SIGNS

ADV strains circulating in some European wild boar populations are attenuated and as a result have low virulence. The majority of the wild boar infected with ADV show no clinical signs. Experimental infection of wild boar with virulent strains has resulted in fatal disease[14], similar to that following experimental infection in domestic pigs. Experimental infection of immune-compromised wild boar with ADV strains of wild boar origin has resulted in clinical disease[14]. An outbreak of AD was reported in European wild boar in Spain, where juveniles and adults showed nervous clinical signs and the mortality was 14%[13]. Two wild boar with signs of neurological disturbance have been diagnosed with AD in Germany[12]. These findings indicate that clinical disease cases in free-living boar in Europe may occur but are infrequently observed.

Mild clinical signs including mild pyrexia, sneezing, nasal discharge and conjunctivitis were observed in wild boar experimentally infected with an ADV isolate from wild boar origin[14]; however, following steroid-induced immunosuppression, when these animals were reinfected

using the same strain, they developed severe clinical disease with pneumonia and death.

In wild dead-end host species the clinical outcome of AD is usually fatal, resulting in death within a few days after infection. The first signs are appetite loss and diminished activity, but later the animal develops mild nervous signs. A sero-mucoid nasal discharge may appear, as well as respiratory distress and fever. The affected animals often develop pruritus, which may lead to self-mutilation. Later excitement and hyperaesthesia become greater and convulsions can occur before the animal collapses and dies. In some cases the clinical course is very short and death is rapid, with only minimal clinical signs observed.

DIAGNOSIS

Aujeszky's disease should be considered when neurological disease is seen in European wild mammals; however, some countries, such as the UK, are free of ADV. Detection of virus is by isolation in cell cultures or molecular detection of ADV genomic material in tissues. PCR testing utilizes the glycoprotein encoding genes, which are highly conserved between different ADV strains (gB/gD) and constitute the main target of polymerase chain reaction (PCR) tests.

Viral isolation and/or viral genome detection by PCR are used for the diagnosis of ADV infection in the European wild boar. The trigeminal ganglia (TG) are considered the best site to detect latent infections in domestic pigs. The attenuated nature of European wild boar ADV strains may lead to the establishment of latent infections in sacral ganglia after venereal transmission as has been recorded in feral pigs in North America. Hence, absence of ADV in TG does not exclude latent infection in European wild boar[18]. In preparation for PCR testing, both sets of ganglia require dissecting out and removal from dead animals.

Serological methods for detection of anti-ADV antibodies are of limited diagnostic use in non-suid species because of the rapid course of the infection. Viral neutralization tests, western blot and enzyme-linked immunosorbent assay (ELISA) may be useful techniques for the detection of antibodies against ADV in suids. The ELISA is a sensitive and specific test in the domestic pig. Owing to its low cost, high reproducibility and rapidity of use it is also a useful tool for epidemiological studies in European wild boar. However, 45% of European wild boar with viral ADV DNA did not have antibodies detectable with ELISA[18]. As a result of suspicions that the currently used ELISA may not detect all wild boar ADV antibodies, new serological tests may be necessary in particular to identify latently infected wild boar in Europe. Further research is required in Europe to ensure that diagnostic tests used for wild boar are reliable.

MANAGEMENT, CONTROL AND REGULATIONS

Management of ADV in wild boar populations first requires surveillance for the disease. Where presence of ADV is identified, management of the disease in free-living European wild boar is difficult because: i) ADV is widely distributed across European wild boar populations; ii) its prevalence is high in some wild boar populations and seems to be increasing, while the geographical range of ADV infected boar is also extending in some regions; iii) there is little relevant information on the efficacy of preventive management strategies such as vaccination, reduction of population densities (through targeted hunting) and avoiding supplementary feeding, which results in concentration of animals[19]. Risk assessment is particularly important when considering ADV control in wild boar. A limited amount of work has been done in Europe on the testing of an Aujeszky's disease vaccine for wild boar; however, currently no validated vaccine is available. There is no reporting regulation of ADV in wild boar in Europe. Aujeszky's disease is notifiable to the World Organisation for Animal Health (OIE).

PUBLIC HEALTH CONCERN

ADV is considered as a non-zoonotic pathogen, but mild pruritus may appear in humans when handling the virus in the laboratory[20].

SIGNIFICANCE AND IMPLICATIONS FOR ANIMAL HEALTH

Aujeszky's disease is common to both wild boar and domestic pigs, and it has been eradicated from the domestic pig in many European countries. Contact between wild boar and domestic pigs, especially in extensive production,

may lead to outbreaks in the domestic pig as a consequence of ADV circulating in wild boar populations.

The effect of ADV on the population dynamics of wild boar appears to be limited to reduced reproductive output and reduced survival of neonates, with little measurable effect in reducing the overall numbers of animals in boar populations. However, there is insufficient information on the disease in wild boar populations to properly assess the effects of ADV.

There are several reported incidents of Aujeszky's disease causing deaths in dogs used in boar hunting across Europe. Carnivores, including threatened species, that consume wild boar are at risk of acquiring ADV. Wolves are active predators of European wild boar and may be at a high risk of contracting Aujeszky's disease; however, there is little published evaluation of the effects of the disease on wild animals other than boar. The seroprevalence of ADV in wild boar has increased substantially in the remaining habitat for the IUCN critically endangered Iberian lynx (*Lynx pardinus*) in Spain, and the disease poses a risk to reintroduction programmes in these areas.

MALIGNANT CATARRHAL FEVER

HUGH W. REID

The Moredun Foundation, Pentlands Science Park, Bush Loan, Penicuik, Midlothian

Malignant catarrhal fever (MCF) is a generally fatal disease of artiodactyla, primarily affecting ruminants of the subfamily Bovinae and family Cervidae[21]. It is caused by closely related rhadino herpesviruses, which characteristically infect their natural host in the absence of any recognized clinical signs but which are capable of transmission to other species, causing a catastrophic immunological dysfunction and resulting in dramatic clinical and pathological disease[22].

AETIOLOGY

Worldwide, the principle cause of MCF is the rhadino herpesvirus, *Ovine herpesvirus 2* (OvHV2), which infects domestic sheep and may infect other species of the subfamily Caprinae, in the absence of recognised disease[23]. The other principle cause of MCF is *Alcelaphine herpesvirus 1* (AlHV1), which inapparently infects wildebeest (*Connochaetes* spp.). This form of the disease primarily affects cattle in Africa but has also affected other ruminant species in zoological collections elsewhere. In addition, *Caprine herpesvirus 2* (CpHV2) of domestic goats and the so-called virus of 'white-tailed deer' have also been implicated as causal agents in a few cases.

In the context of European wildlife, the only known potential causes of disease are OvHV2 and CpHV2, neither of which have been isolated in conventional culture systems. Infection with either agent can, however, be confirmed through PCR or detection of antibody that cross-reacts with the AlHV1 antigens.

These viruses, together with those of large African antelope *(Alcelaphinae* and *Hippotraginae)* form a complex of viruses referred to as the MCFV complex (Figure 1.2)[24].

EPIDEMIOLOGY

GEOGRAPHICAL DISTRIBUTION AND HOSTS

Initially MCF was described as a disease of domestic cattle in Europe, but a very similar disease of cattle was recognized in southern Africa shortly thereafter and subsequently has been reported in a variety of species worldwide[25]. Cattle of Asiatic origin (*Bos javanicus* and *Bos gaurus*), water buffalo (*Bubalus bubalis*), many species from the family Cervidae, excluding fallow deer (*Dama dama*), and North American bison (*Bison bison*) are particularly susceptible to infection.

Despite the normally dramatic fatal presentation of the disease and high incidences in deer and bison when managed as farm animals, there are relatively few reports of the disease affecting free-living animals[26–28]. In addition, as it is now recognized that OvHV2 can cause MCF in domestic pigs[29], it is probable that wild boar would also be susceptible, although no disease has been reported in Europe or elsewhere. It should also be noted that experimentally both AlHV1 and OvHV2 can be transmitted to laboratory rabbits, producing characteristic MCF[30]. It is therefore theoretically possible that wild rabbits could be affected, although no such cases have been reported.

Both sheep and goats appear to be able to act as natural hosts for OvHV2, whereas only goats have been identified in the case of CpHV2. In the natural host, infection appears to transmit efficiently with all, or most, adults

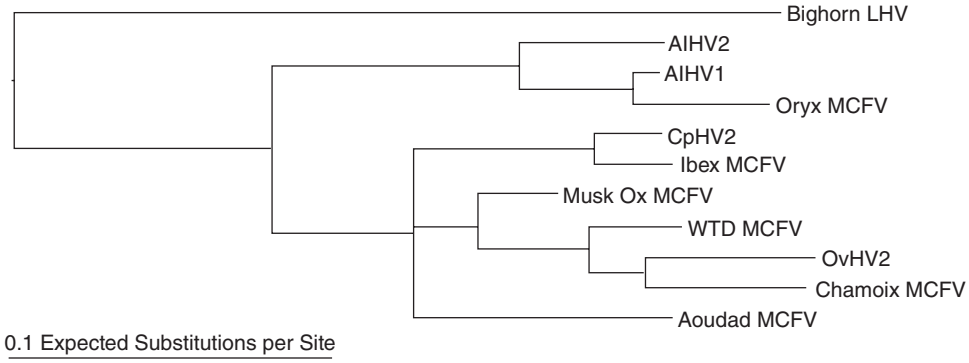

FIGURE 1.2 Phylogenetic analysis of MCF viruses was based on a 177 bp fragment of the DNA polymerase gene, for which the widest range of sequences were available. The DNA sequences were aligned using ClustalV, based on the translated amino acid sequences, and the phylogenetic analysis was done using TOPALi[24]. Model selection was used to define the appropriate parameters for analysis by Mr Bayes using codon position models. The sequence from the bighorn sheep lymphotropic herpesvirus was included as an outgroup. The analysis was performed by Dr George Russell, Moredun Research Institute. AlHV = alcelaphine herpesvirus; CpHV = caprine herpesvirus; LHV = lymphotropic herpesvirus; OvHV = ovine herpesvirus; WTD = white-tailed deer.

carrying latent infection. Transmission of OvHV2 in Europe would appear to be essentially perinatally among lambs, establishing a life-long latent infection, probably as with other herpesvirus infections, with periodic recrudescence and virus excretion[31]. All sheep and goats should thus be regarded as potential sources of infection. It is probable that native European species of sheep and goats and related species of the subfamily Caprinae are carriers of these, or similar, viruses, and evidence of infection with either virus is not normally associated with pathological changes.

In addition, the quantity of viral DNA detected in affected tissues is trivial, and there is no evidence of productive viral replication in any MCF-affected animals. It is concluded that MCF-susceptible species are not responsible for the spread of the virus, nor do they act as carriers. Disease in European wildlife has only been described in species of deer, although the susceptibility of North American bison to MCF suggests the potential susceptibility of European bison, while rare cases in domestic pigs does raise the possibility that wild boar could also be susceptible. The most convincing evidence of MCF in free-living wildlife is from a report from Norway in which disease was confirmed in moose (*Alces alces*), roe deer (*Capreolus capreolus*) and red deer (*Cervus elaphus*) over a 23-year period. Evidence of MCF in these animals on both histological and molecular virological grounds is compelling, and both OvHV2 and CpHV2 appear to have been involved. MCF in farmed deer is a relatively common disease, and in the early years of deer farming substantial outbreaks occurred both in the UK and in New Zealand. Disease in free-living animals has, however, never been reported in either country, despite the very substantial numbers of deer and sheep in both countries. It is noteworthy that, compared with the high incidence of MCF experienced in the first 10 years of deer farming in the UK, the disease is now sporadic and relatively uncommon. Spectacular outbreaks of MCF in farmed North American bison have also been reported in herds that have only recently been subjected to relatively intense management[32].

It is tempting to speculate that the susceptibility of certain species may therefore be related to exposure to management systems that have not been optimized in favour of animal welfare.

It is also noteworthy that reports of MCF of pigs have most frequently been associated with Scandinavia, although there are also reports of the condition from Germany, Switzerland and the USA. In these cases the causal virus has been OvHV2, and there is no evidence that a variant form of the virus with greater infectivity for pigs has been involved. In addition, the breeds of pigs affected in these outbreaks have been varied, which suggests that susceptibility is unlikely to be determined by breed. It is thus concluded that as-yet unidentified environmental factors result in pigs becoming apparently more susceptible to infection in Scandanavia. In the absence of any other explanation, such unidentified factors may be impacting similarly on free-living deer in Norway.

PATHOGENESIS, PATHOLOGY AND IMMUNITY

The most likely route of entry of the MCF viruses is the mucosa of the upper respiratory tract and the tonsils. The virus infects lymphocytes (CD8+ T cells); their role in the pathogenesis is unclear. Lymphoproliferation is likely to be the result of dysfunction of T-lymphocytes. Disturbed cytotoxic T-cell activity is probably involved in the development of vascular and epithelial lesions.

Gross pathological changes reflect the variable clinical signs and may involve most systems. MCF is characterized by erosions and ulcerations in the mucosae and in the skin, vasculitis and lymphoproliferation. Skin lesions are not infrequent in deer and may involve extensive alopecia, erosions and crusting dermatitis, primarily of the limbs and perineum. Bilateral corneal opacity and conjunctivitis are frequently present and catarrhal encrustation of the nares and oral cavity are often a feature, together with erosion of the epithelium. Lymph nodes are generally enlarged and oedematous, and may be haemorrhagic. Haemorrhage of the intestinal mucosa is frequently present and can affect the abomasum and most sections of the large and small intestine. Characteristic lesions of the urinary bladder include petechiae and ecchymosis and the kidney frequently has raised white nodules, which are the result of lymphocytic accumulations.

Presumptive diagnosis has relied on the detection of histological lesions characterized by epithelial degeneration, vasculitis, hyperplasia and necrosis of lymphoid organs and widespread accumulations of lymphoid cells in non-lymphoid organs. All epithelial surfaces may be affected and are characterized by erosion and ulceration with sub- and intra-epithelial lymphoid cell infiltration, which may be associated with vasculitis and haemorrhage.

Vasculitis affecting veins, arteries, arterioles and venules, but most typically medium-sized arterioles, is generally present and most pronounced in the brain (Figure 1.3). It is characterized by perivascular accumulation of lymphoid cells, and fibrinoid degeneration or necrotizing vasculitis, and there may be endothelial damage, which may lead to occlusion of vessels.

Lymph nodes characteristically are affected by lymphoblastoid cell expansion in the paracortex and degeneration of follicles, and oedema and inflammation are present in the perinodal tissue. Interstitial accumulation of lymphoid cells, particularly in the renal cortex and periportal areas of the liver, are commonly present and may be extensive. Non-suppurative meningoencephalitis with lymphocytic perivascular cuffing is frequently present in the brain. Histological lesions of the cornea are characterized by lymphoid cell infiltration originating in the limbus and progressing centrally, and vasculitis, hypopyon and iridocyclitis may also be present.

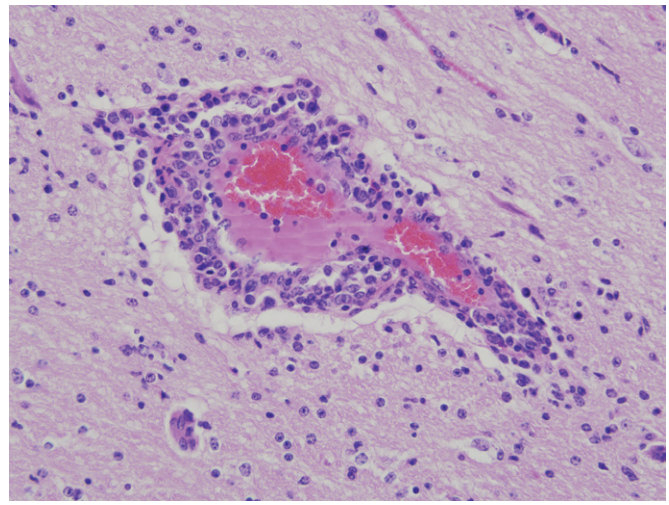

FIGURE 1.3 Histological section of farmed red deer brain with MCF, showing non-suppurative encephalitis. Note the characteristic accumulation of predominantly lymphoid inflammatory cells around the blood vessel (peri-vascular cuff) along with those free in the neuropil (gliosis, to the left of the blood vessel). Haematoxylin and eosin, original magnification ×100.

The serological response of MCF-affected animals may be undetectable or directed at only a few viral epitopes, implying that there is only limited virus antigen expressed in diseased animals[33]. The development of antibodies does not prevent a lethal outcome.

CLINICAL SIGNS

The clinical presentation of MCF is very variable and can involve most systems, ranging from peracute to chronic. In the peracute cases that have been observed in farmed deer, high fever, depression and profuse diarrhoea, which may be haemorrhagic, are the principle clinical signs. Generally, the course is more protracted and involves nasal and ocular discharges, which may be profuse and catarrhal, bilateral corneal opacity, enlarged lymph nodes, erosions in the oral cavity, erosion and/or hyperkeratosis of the skin and/or neurological signs involving blindness and behavioural changes. In chronic cases in deer, alopecia has also

been a feature. In the cases involving wild deer, they were thin, often recumbent and showed a variety of clinical signs, including diarrhoea, abnormal behaviour, incoordination, blindness and convulsions[26]. Thus in light of the variability of the clinical presentation of MCF, this disease should be considered in any unexplained condition observed in deer.

DIAGNOSIS

In suspected cases of MCF in wildlife, examination of tissues for evidence of characteristic histological lesions, especially in the brain, is the most appropriate method of achieving an initial presumptive diagnosis.

Of the viruses that have been associated with MCF, only AlHV-1 has been recovered in conventional tissue culture, although lymphoblastoid cell lines with limited productive virus replication have been propagated from animals affected with both AlHV1 or OvHV2 forms of the disease. Despite not being applicable as an aid to diagnosis, these lymphoblastoid cell lines have proved valuable in understanding the pathogenesis of disease and have provided a source of viral DNA. Such DNA has facilitated the sequencing of the genome of both viruses and permitted the selection of suitable PCR reactions for amplifying DNA sequences that detect either the MCF group of agents or are virus-specific[23]. Such PCR reactions are now the method of choice for reaching a definitive diagnosis of MCF and identifying potential carrier animals.

All serological tests rely on AlHV1 antigens, as none of the other viruses can be productively replicated in tissue culture to provide virus specific reagents. The only critical report employing immunoblotting indicated that the sera of sheep and cattle infected with OvHV2 reacted erratically with AlHV1 antigens compared with sera of wildebeest[33]. It is also known that serological tests for herpesviruses as a group can cross-react. Thus, despite a number of serological tests being available, caution in interpreting results when employing them with sera from novel species, which are almost certainly infected with their own specific herpesviruses, is essential. In addition, sera from free-living animals may be of variable quality, which has the potential to impact on the reliability of tests. The merit of surveys for evidence of infection with MCF viruses employing sera from free-living species of wild animals is thus questionable and the results should not be assumed to indicate evidence of the incidence of infection.

PUBLIC HEALTH CONCERN

There are no indications that MCF can infect humans.

MANAGEMENT AND CONTROL

Control of MCF is based on preventing contact between susceptible hosts and the natural carriers (sheep and goats).

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RUMINANT ALPHAHERPESVIRUS INFECTIONS

CARLOS G. DAS NEVES

Norwegian School of Veterinary Science, Department of Food Safety and Infection Biology, Section of Arctic Veterinary Medicine, Tromsø, Norway

The subfamily *Alphaherpesvirinae* includes several viruses that cause a range of diseases in members of the suborder Ruminantia. With the exception of *Bovine herpesvirus 2* in the genus *Simplexvirus*, a virus with little impact in European wildlife, all other relevant ruminant alphaherpesviruses are in the genus *Varicellovirus*, as shown in Table 1.2. Of these, *Bovine herpesvirus 1* (BoHV1) is by far the most studied, serving as model for this group of ruminant viruses.

BOVINE HERPESVIRUS 1

BoHV1 is the aetiological agent of infectious bovine rhinotracheitis (IBR), and infectious pustular vulvovaginitis (IPV) or infectious pustular balanoposthitis (IPB). BoHV1 causes significant economic losses for the cattle industry worldwide, for which programmes of eradication and/or control of the disease have long been in place.

Although there are several differences in genomic organization and sequences between the different ruminant alphaherpesviruses, mechanisms related to gene expression

TABLE 1.2 Ruminant alphaherpesviruses in the genus *Varicellovirus* (with permission from Das Neves, 2009[34]).

Virus	Natural host	Disease	Geographic distribution	Status in European wildlife
Bovine herpesvirus 1 BoHV1	Bovine (*Bos taurus*)	Bovine rhinotracheitis, pustular vulvovaginitis and balanoposthitis	Europe, America, Asia and Oceania	Suspected but virus never isolated
Bovine herpesvirus 5 BoHV5	Bovine (*Bos taurus*)	Bovine encephalitis	Europe, America, Oceania	Not described
Bubaline herpesvirus 1 BuHV1	Water buffalo (*Bubalus bubalis*)	No clinical disease	Europe, Australia	Not described
Caprine herpesvirus 1 CpHV1	Goat (*Capra aegagrus*)	Vulvovaginitis, abortion, neonatal systemic infection, conjunctivitis	Europe, America, Australia	Suspected but virus never isolated
Cervid herpesvirus 1 CvHV1	Red deer (*Cervus elaphus*)	Ocular syndrome	Europe	Virus isolated
Cervid herpesvirus 2 CvHV2	Reindeer (*Rangifer tarandus*)	Ocular syndrome, respiratory disease, mucosal lesions, abortion	Europe	Virus isolated
Elk herpesvirus 1 ElkHV1	Elk (*Cervus canadensis*)	No clinical disease	America	Not described

or viral replication and latency, as well as pathogenesis, have been shown to be common to all of them.

The BoHV1 genome consists of a double-stranded linear DNA sequence with 135 301 nucleotides, comprising 67 unique genes. Some of these genes encode envelope proteins commonly called glycoproteins. Of these, gB not only plays an essential role in virus attachment and entry, but is also highly immunogenic, representing a dominant viral antigen that can lead to a protective immune response.

Despite its worldwide spread in domestic cattle and being the target of intense study, BoHV1 has not been reported to naturally cause disease in wildlife. Wildlife species have been screened using serological kits for BoHV1 based on gB as antigen. These tests, however, do not enable discrimination between the various ruminant alphaherpesviruses, so it is not possible to rule out the possibility that many wildlife species may harbour herpesviruses closely related to BoHV1 rather than BoHV1 itself.

Seropositive results against BoHV1 have been described throughout Europe in ibex (*Capra ibex*), chamois (*Rupicapra rupicapra*), red deer (*Cervus elaphus*), roe deer (*Capreolus capreolus*), reindeer (*Rangifer tarandus*), fallow deer (*Dama dama*), mouflon (*Ovis musimon*), European bison (*Bison bonasus*) and water buffalo (*Bubalus bubalis*)[35].

Several studies have focused on BoHV1 infections of heterologous hosts. Goats can be infected with BoHV1, leading to high excretion titres and latency. Experimental reactivation has also been successful, but these studies focused on domestic goats and little is known about BoHV1 infections of wild goats, for example. BoHV1 infections of deer and reindeer lead to minimal or no excretion, and latency does not occur. Altogether, studies seem to demonstrate that although BoHV1 can infect some wild ruminants it cannot be maintained over time, and wildlife seem therefore not to be important reservoirs for this virus.

In primary infections, BoHV1 has potential ports of entry in the nasal cavity, oropharynx, eyes and genital tract. Replication normally takes place in the epithelial cells, and high titres of BoHV1 are excreted at those ports of entry within 4–5 days post-infection. Although, as for most ruminant alphaherpesviruses, viraemia is possible, it seems that BoHV1 shows little systemic spread and is often restricted to the local ports of entry in primary infections. Nonetheless, BoHV1 can spread by association with mononuclear blood cells and reach the digestive tract, ovaries and fetus, where it can lead to abortion.

A strong humoral and cell-mediated response develops within 5 days post-infection, with maximum antibody titres around days 10–12 days post-infection. Residual antibody titres can be detected for up to 2 to 3 years post-infection. Besides the viral lytic cycle, in which active replication takes place, BoHV1 can become latent when viruses migrate to the CNS ganglia (e.g. TG or sacral ganglia) and enter a dormant stage. Different stimuli such as transport stress, calving, and other concurrent infections may lead to reactivation of BoHV1, with the virus returning to the port of entry or spreading to other organs and replicating. Although reactivation can lead to re-excretion,