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Viral Pathogens of Domestic Animals and Their Impact on Biology, Medicine and Agriculture

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Abbreviations

AHS	African horse sickness
AHSV	African horse sickness virus
AIDS	acquired immunodeficiency syndrome
ASF	African swine fever
BCG	Bacille Calmette–Guérin
BSE	Bovine spongiform encephalopathy
BTV	bluetongue virus
CMLV	camelpox virus
CSF	Classical swine fever
CSFV	classical swine fever virus
ELISA	enzyme-linked immunosorbent assay
enJSRV	endogenous JSRV-related retroviruses
F	fusion glycoprotein
FAO	Food and Agriculture Organization
FMD	foot-and-mouth disease
FMDV	foot-and-mouth disease virus
GREP	Global Rinderpest Eradication Program
GTPV	goatpox virus
HA	hemagglutinin
HIV	human immunodeficiency virus
HN	hemagglutinin-neuraminidase
HTLV	human T cell leukemia virus
JSRV	jaagsiekte sheep retrovirus
loNDV	low virulence NDV
MVV	Maedi-visna virus
NA	neuraminidase
NDV	Newcastle disease viruses
OIE	Office International des Epizooties
OPA	ovine pulmonary adenocarcinoma
RSV	Rous sarcoma virus
RT-PCR	reverse transcriptase-polymerase chain reaction
SA	sialic acids
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-Coronavirus
SPV	sheeppox virus
TB	tuberculosis
TSE	transmissible spongiform encephalopathy
VARV	variola virus
vCJD	variant Creutzfeldt–Jakob disease
vNDV	virulent NDV

Defining Statement

This article will furnish a historical perspective on how studies of animal diseases have made a major contribution to the current understanding of pathogen biology. In addition, the main features of some of the most important viral diseases of farm animals will be described.

Introduction

Approximately 10 000 years ago in an area of East Asia known as the 'fertile crescent', man began to breed animal species that are today known as domestic animals. Suddenly, the efforts and time that man had spent in hunting and gathering food were no longer necessary as domestic animals provided a continuous source of food supply. The process of domestication spread across Asia, Europe, and North Africa during the Neolithic 'agricultural revolution'. This was a significant breakthrough in human history and played a fundamental role in the development of most modern societies. Today, domestic animals represent one of the major sources of proteins for a significant portion of the world's population.

Animal husbandry practices have changed since the Neolithic and vary in different geographical areas.

However, in general, domestic animal species are raised in relatively small (and usually confined) spaces at a higher density than their feral counterparts. This is particularly true today in the industrialized countries where modern intensive farming brings, in some cases, thousands of animals together in the same location. Thus, domestication has given plenty of opportunities to pathogens, such as bacteria and viruses, to emerge and establish themselves in new populations. Moreover, national and international trade of farm animals amplifies the spread of infectious diseases.

Thus, infectious diseases are today one of the major threats to animal husbandry and can cause considerable damage at local, regional, or even at the international level. For example, the production of calves in a cattle farm can be seriously affected by virus- or bacteria-induced abortions. In some cases, however, the economy of a whole country can be threatened by animal pathogens that have a direct effect on the production efficiency, but also have various indirect effects on the international trade of animals and animal-derived products. For example, the estimated direct cost to agriculture and the food industry of the 2001 foot-and-mouth disease (FMD) outbreak in Great Britain was around £3 billion (British pounds; approximately US$6 billion), but the indirect costs to other businesses such as tourism were estimated to be another £3 billion.

Diseases of domestic animals not only affect animal production and animal trade but can, in some cases, be transmitted and cause diseases in humans (zoonoses). The H5N1 subtype of avian influenza is an example of a zoonosis with documented fatal outcomes that constitutes a serious pandemic threat. Bovine spongiform encephalopathy (BSE), a prion disease that primarily affects cattle, can be transmitted to humans by the ingestion of contaminated food. Economic losses due to the BSE outbreak in the United Kingdom in the 1990s were also estimated in millions of pounds. Zoonoses are not restricted to only production animals: human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), is the result of cross-species transmissions between African primates and humans. Of course, there are many more examples of pathogens that have jumped the species barrier from animals to humans and these will be discussed in detail in the articles dedicated to zoonoses and emerging diseases.

This article will first describe how studies on pathogens (focusing mainly on viruses) of veterinary importance influenced major discoveries in biology and comparative medicine. The second part of this article will summarize some of the major viral diseases that affect farm animals.

Historical Perspectives

Probably one of the earliest hypotheses concerning microbes as agents of disease was described by Varro (first century BC), who introduced the concept of 'invisible animals' carried by the air into the body and causing diseases. Girolamo Fracastoro in 1546 wrote a paper suggesting that diseases were caused by 'seminaria contagiosa', entities that could be transmitted by direct or indirect contact. In the seventeenth century, the invention of the microscope allowed for the first time to see 'wee animalcules' that we know now to be bacteria, algae, and protozoa. However, the invention of the microscope reinforced the prevalent idea at the time that microorganisms generate spontaneously in the air (miasma). It was in the nineteenth century that Louis Pasteur convinced the scientific community that the growth of such microorganisms is not due to spontaneous generation, although this point had been suggested previously by others.

The 'germ theory' of diseases was slowly accepted after the work of physicians such as Agostino Bassi, John Snow, and Jakob Henle. Finally, Robert Koch proved that anthrax was caused by the bacterium *Bacillus anthracis* and established criteria (his now famous Koch's postulates) that helped to causally associate specific microorganisms to specific diseases.

With the advent of solid media and Petri dishes, a wave of previously unknown bacteria (and their associated diseases) was discovered and bacteriology was established as probably the first exact medical science. Soon afterward it was clear that not all diseases were caused by bacteria and the existence of a new class of submicroscopic microorganisms appeared in the scientific arena. In 1898 Friedrich Loeffler and Paul Frosch, two former students of Robert Koch, first demonstrated that an animal disease could be caused by 'ultrafilterable agents'. Working on FMD, Loeffler and Frost collected fluid from vesicular lesions of affected animals and filtered it through bacteria-proof filter candles, hoping that the infectious agent would be retained in the filter. To their surprise, calves inoculated with the filtrate developed FMD lesions. Subsequent studies allowed them to rule out the possibility of a bacterial etiology, and thus foot-and-mouth disease virus (FMDV) became the first virus of vertebrates to be discovered (tobacco mosaic virus of plants had been discovered by Ivanovski in 1892). These landmark studies were published between 1897 and 1898. It should be noted that at the end of the nineteenth century, FMD was causing a large number of outbreaks in Germany and the magnitude of the problem was such that in 1893 the Prussian Ministry of Agriculture offered a prize of 3000 reichmarks for the person who could identify the cause of the disease. After 2 years of fruitless efforts by a number of different applicants, a research commission was established to systematically investigate FMD. About 55 000 reichmarks were invested in this venture and soon paid off with the results obtained by Loeffler and Frosch. Because of the highly contagious nature of the disease, in 1909 Loeffler had to move to an island in the Baltic Sea, Insel Reims, in order to continue studying FMD. Thus, despite the recent FMD incidents

in the United Kingdom, the awareness of biosecurity against devastating animal diseases was already well developed a century ago.

Studies on Animal Diseases and Their Contribution to Medicine and Pathogen Biology

Studies on diseases of farm animals have led to a variety of scientific milestones and biological paradigm shifts (Figure 1). Cattle plague (or rinderpest) is a disease that devastated livestock for hundreds of years in Europe until the nineteenth century. In the previous century, the consequences of cattle plague were so serious that Pope Clement XI instructed his physician, Giovanni Maria Lancisi, to develop measures to control the disease. Lancisi's recommendations included the destruction of all ill and suspect animals followed by their burial in lime. The first veterinary school was opened in Lyon specifically to teach Lancisi's principles. Today, we apply sanitary measures remarkably similar to those devised by Lancisi to avoid the spread of transmissible diseases: quarantine, animal movement restrictions, and culling of affected animals. The effectiveness of these measures is illustrated by the fact that rinderpest was eliminated from Europe prior to the discovery of its causative agent. Thus, Lancisi is correctly recognized as the first hygienist in history.

Rinderpest is also associated with other scientific landmarks. For example, it was to diagnose the fever associated with rinderpest that the thermometer was used first in a clinical setting. The concept of 'maternal immunity' was introduced during the rinderpest epidemic of 1768 by a Dutch farmer called Geert Reinders, who noticed that the offspring of animals that had survived the natural disease were protected from further infections.

The creation of the World Animal Health Organization (also known as Office International des Epizooties, OIE) is linked to the history of rinderpest. In 1920, the disease was reintroduced in mainland Europe, following the transit of an infected zebu herd on its way from India to Brazil through the port of Antwerp, Belgium. The extension of the outbreak in Belgium and the memories of the massive cattle death caused by rinderpest in the nineteenth century urged France to convene an 'International Conference for the Study of Epizootics'. The result of the conference was the creation of the OIE with headquarters in Paris.

Some historical diseases are indirectly linked to domestic animals, although only directly affecting humans. Smallpox has been one of the greatest scourges of humankind. The origins of variola virus (VARV), the

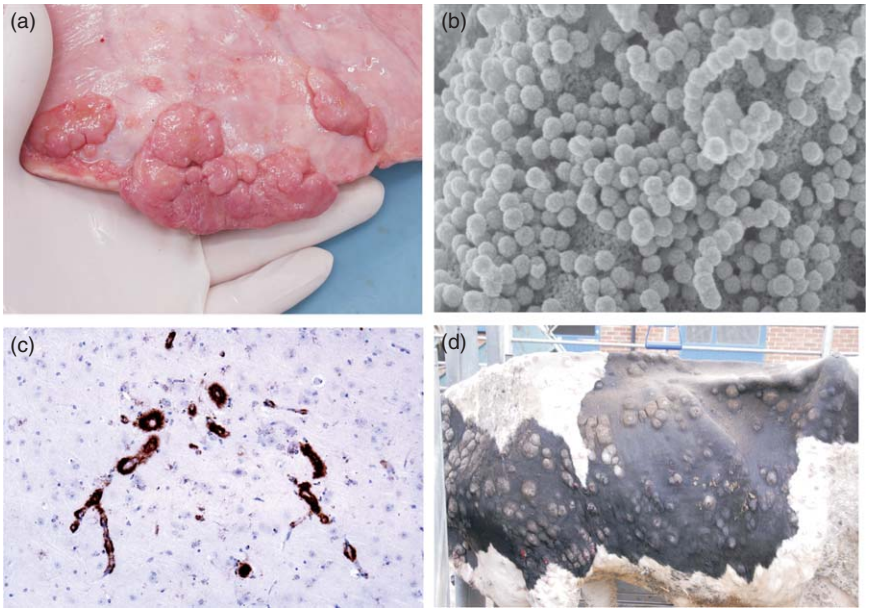

Figure 1 Infectious diseases of farm animals and their impact on comparative medicine. Studies on bacterial and viral diseases of domestic animals have been instrumental in understanding a variety of fundamental aspects of pathogen biology. (a) Lesions in the lungs of a cow induced by *Mycobacterium tuberculosis*. (b) Scanning electron microscopy image of Rous sarcoma virus (RSV) particles budding from the surface of chicken embryo fibroblasts. (c) Disease-associated prion protein (PrP) vascular amyloid in the cerebellar cortex of a sheep affected by scrapie as revealed by immunohistochemistry. (d) Cattle affected by bovine papillomatosis displaying the typical cutaneous lesions. Panels (a) and (d) were kindly provided by Hal Thompson and Richard Irvine. Panel (b) was provided by Marc Johnson while panel (c) was provided by Lorenzo Gonzalez. Panels B and C are reproduced with permission and were previously published in *PLoS Pathogens* 2007, 3: e12.

etiologic agent of smallpox, are uncertain but it is speculated that VARV derives from an ancestral poxvirus that affected animals during the early agricultural settlements in Asia or Africa. Interestingly, the closest relative of VARV is camelpox virus (CMLV). Despite its long history of terrifying lethality, smallpox is the first (and so far only) viral disease that has been globally eradicated, thanks to a very effective vaccine campaign. The basis of this achievement can be traced back to the end of the eighteenth century when Edward Jenner (1749–1823) laid the foundations of modern vaccinology. In Jenner's time, it was a popular belief that cowpox protected against smallpox, since dairymaids were immune to the disease. A physician himself, Jenner combined folk knowledge, comparative medicine (cowpox lesions in cattle were similar to those in people affected by smallpox), and hypothesis-driven research to carry out one of the most significant experiments in microbiology: he inoculated a number of people with material from cowpox lesions and further challenged them by variolation (a procedure that consisted in blowing dried smallpox scabs into the nose of an individual). Variolated individuals usually contracted a mild form of the disease, but the group treated by Jenner did not show any reaction, demonstrating that cowpox infection was protective against smallpox. This procedure marked the beginning of a new era in medicine. Despite initial resistance to Jenner's methods, vaccination as a strategy to prevent smallpox and later other infectious diseases was rapidly accepted. Pasteur developed the first attenuated vaccine against a disease of chickens (chicken cholera caused by *Pasteurella multocida*) and also produced vaccines against two lethal zoonoses: anthrax and rabies. Linked to the success of the smallpox vaccination was the development of a vaccine against tuberculosis. Bovine tuberculosis (**Figure 1(a)**) was first recognized in 1854 and Robert Koch subsequently determined that *Mycobacterium bovis*, the cause of bovine tuberculosis, could be differentiated from *Mycobacterium tuberculosis*, the cause of human tuberculosis. This led to the speculation that a successful vaccine for human tuberculosis (TB) could be generated by employing the same strategy that was successful for smallpox. However, early attempts at using freshly isolated *M. bovis* strains were unsuccessful as these were as virulent as *M. tuberculosis*. The veterinary influence in producing an effective vaccine against TB was evident in the work of Camille Guérin, a veterinarian, and Albert Calmette, a physician, who together produced the *M. bovis* BCG (Bacille Calmette–Guérin) vaccine strain. This was a highly passaged strain with negligible virulence, which took over 13 years to develop and was finally ready for use in 1921. To this day, over 200 years after Jenner's pioneer studies, vaccination constitutes our best tool to fight infectious diseases of both domestic animals and man.

FMDV and rinderpest virus were the first of a rapidly growing list of causative agents of major infectious diseases of domestic animals that at the beginning of the twentieth century led to the establishment of the discipline of animal virology. A few examples of other animal viruses discovered in those early days are those associated with African horse sickness (AHS), rabbit myxomatosis, fowl plague (avian influenza), and avian leukosis.

Interestingly, studies on chicken viruses in the early twentieth century led to landmark discoveries that eventually unveiled the genetic nature of cancer. In those pioneer studies, tumors were transmitted to animals by means of cell-free filtrates. Vilhelm Ellerman and Olaf Bang discovered that a virus caused erythroleukemia in chickens (1908), while Peyton Rous showed that sarcomas in chickens also had a viral etiology (1911). At the time, unfortunately, those studies did not receive the credit they deserved, as leukemias were not regarded as cancer and chickens were not considered a relevant animal model for the study of human diseases. In the 1950s Howard Temin and Harry Rubin developed an assay (focus assay) to quantify Rous sarcoma virus (RSV, the virus discovered by Rous) in tissue culture (**Figure 1(b)**). This assay revolutionized the study of RSV because it demonstrated the link between the biological activity of a single infectious viral particle and a single cell. Later, RSV was found to contain a cell-derived gene ('oncogene') that was sufficient to induce cell transformation. This was a major discovery as it highlighted that the DNA of the cells held the 'secret' of cancer. Thus, the genetic origin of cancer was discovered by studying chicken viruses. The RSV oncogene, *v-src*, was both the first oncogene and the first tyrosine kinase to be discovered and this had enormous repercussions, contributing to the foundation of entire disciplines such as signal transduction.

There are many other examples where studies on animal viruses led to true biological paradigm shifts. Björn Sigurdsson, an Icelandic physician, coined the term 'slow diseases' after studying a group of diseases of sheep that affected the Icelandic flocks in the 1930s–40s. In 1933 Iceland introduced a small number of rams from Germany to improve their genetic stock. Despite observing quarantine measures, the imported rams introduced at least three different diseases onto the island: ovine pulmonary adenocarcinoma (OPA), paratuberculosis, and Maedi-visna. Another disease of sheep, scrapie, was also included in this group of diseases although it was probably imported to the island before 1933. The geographical and epidemiological circumstances of the outbreaks allowed Sigurdsson to develop the concept that an infectious agent can cause disease after a very long incubation period that can last from several months to years (slow diseases). This concept has had enormous influence on the study and control of infectious diseases.

Maedi-visna was subsequently shown to be caused by a retrovirus, Maedi-visna virus (MVV). MVV was chosen as the prototype of the *Lentivirus* genus, a group of phylogenetically related viruses including other viruses of domestic animals, such as equine infectious anemia virus. The name lentivirus derives from Latin (*lenti* = *slow*), which underlines the biological property of these viruses. Studies on animal lentiviruses have been instrumental in understanding the biology of HIV, the causative agent of the AIDS epidemic.

Another 'slow' disease of sheep described by Sigurdsson in Iceland was scrapie (**Figure 1(c)**). Scrapie is a disease of the central nervous system characterized histologically by vacuolar degeneration of the neurons. Scrapie was the first disease to be recognized as a transmissible spongiform encephalopathy (TSE). This group of diseases, named after the typical 'spongious' appearance of the neurons of affected animals, includes human Kuru, TSE of mink, and chronic wasting disease of deer represented a fascinating biological enigma that led to the postulation of the prion theory. Stanley Prusiner hypothesized that an infectious protein, devoid of nucleic acid, was the cause of TSEs and was awarded the Nobel Prize in 1997 for his studies. In humans, Kuru was initially described by Carleton Gajdusek and Vincent Zigas, who were working in Papua Guinea with the Fore tribe. Gajdusek was the first to link the occurrence of the disease with the cannibalistic rituals of the tribe, in particular with the consumption of the brains of affected people. Although scrapie had been known for a long time before the first description of Kuru, the initial connection between these two diseases was made by a veterinarian, William Hadlow, who recognized that the lesions observed in neurons of individuals affected by Kuru were strikingly similar to those of sheep affected by scrapie.

Another TSE, BSE (mad cow disease), spread in the United Kingdom in the 1990s. Unlike scrapie, BSE proved to be zoonotic, causing in human patients a variant of the already known Creutzfeldt–Jakob disease (vCJD). The early studies performed on scrapie served as a platform to better understand BSE when the epidemic that took place in the 1990s spread across the United Kingdom.

OPA is another of the slow diseases of sheep. Its causative agent, jaagsiekte sheep retrovirus (JSRV), displays unique characteristics: it is the only known retrovirus (and the only oncogenic virus in general) to possess a structural protein (the viral envelope) acting as a dominant oncoprotein. Furthermore, the sheep genome contains 27 copies of endogenous JSRV-related retroviruses (enJSRVs). enJSRVs are remnants of past retroviral infections that integrated into the germ line of virtually all animal species, including humans. Studies on enJSRVs have unveiled basic evolutionary roles of endogenous retroviruses in the evolution of mammals. enJSRVs have been shown to be instrumental for the reproductive biology of sheep by playing a critical role in placentation and conceptus development. Human endogenous retroviruses have been hypothesized to play similar roles in human placentation.

Studies on animal viruses have also stimulated the search for related, previously uncharacterized human viruses. The presence of many oncogenic retroviruses in animals, including domestic animals, has sparked the search for human oncogenic retroviruses, which culminated with the isolation of human T cell leukemia virus (HTLV).

Rotaviruses were associated with diarrhea in calves and lambs long before they were identified in humans. Today we know that rotaviruses are the main cause of diarrhea in children from developing countries. Studies performed in ruminants showed the importance of local immunity and colostrum antibodies in the resistance against diseases caused by this virus family and proved invaluable for preventing human rotavirus infection.

In some cases, the existing knowledge of veterinary pathogens has provided the scientific framework that helped to understand human diseases of obscure origin. For example, the first emerging human epidemic of this century, severe acute respiratory syndrome (SARS), originated in China in November 2002 and rapidly spread throughout the world, causing 811 reported deaths by July of the following year. The etiological agent of SARS is SARS-Coronavirus (SARS-CoV). Several coronaviruses are major pathogens of mammals and birds and the data generated on these viruses proved invaluable in adopting measures that helped to contain the SARS outbreak.

Papillomaviruses are another interesting example of animal viruses that inspired important advances for the treatment and prevention of human viruses. The identification of human papillomaviruses as causative agents of cervical and cutaneous cancers has been largely aided by previous studies on other members of this viral family in other species such as dogs, rabbits, and cattle (**Figure 1(d)**). Indeed, the recently developed vaccine against human papillomavirus is based on vaccinology studies conducted with animal papillomaviruses.

It is estimated that 70% of human pathogens are zoonotic in origin. Thus studies on animal viruses also have a direct impact on public health. One of the best examples to illustrate the relationship between animal pathogens and public health is influenza, a viral disease that caused the death of over 20 million people in the last century. Wild aquatic birds are considered the primary hosts of influenza virus A, the causative agent of flu. Influenza virus usually replicates in the intestinal tract of these birds, causes no disease, and is transmitted by fecal contamination of water. Occasionally, such viruses establish stable lineages in land-based birds and a limited number of mammalian species including swine, horses, dogs, and humans. The H5N1 subtype of avian flu currently poses a pandemic threat: it has caused large outbreaks of the disease among bird populations in

Southeast Asia, and the number of human cases reached almost 400 at the beginning of 2008.

In conclusion, studies on animal pathogens have played a vital role in the development and maintenance of animal health with obvious consequences for the progress of agriculture in industrialized and developing countries. Veterinary microbiology had a major impact in the development of comparative medicine and public health and, in some cases, resulted in paradigm shifts in entire biomedical disciplines.

Major Viral Diseases of Farm Animals

This section will cover the fundamental aspects of the most significant viral diseases of farm animals. It is not possible to cover this subject exhaustively in a single article. Therefore, examples of the most significant viral diseases of farm animals based on the list of notifiable diseases of the OIE will be described. These are diseases (**Table 1**) that when present in the territory of the 172 member states have to be notified to the OIE. The overarching criterion for the inclusion of a disease in the list of notifiable diseases is the potential for international spread, the likelihood of its spread within naïve populations, its potential to cause significant mortality or exhibit significant morbidity within a country (or a zone), and its zoonotic implications. Emerging diseases caused by a newly recognized pathogen or a known pathogen behaving differently are also rapidly assessed for their zoonotic potential and spread in naïve populations in order to be included in the OIE list of notifiable diseases.

Foot-and-Mouth Disease

FMD is probably one of the most feared diseases of farm animals. FMD is a highly contagious disease that affects all cloven-hoofed livestock such as cattle, pigs,

Table 1 Notifiable diseases of farm animals

Domestic species affected	*Disease name*	*Causative agent*
Multiple	Aujeszky's disease	Pseudorabies virus
	Bluetongue	Bluetongue virus
	Brucellosis	*Brucella* spp.
	Foot-and-mouth disease	Foot-and-mouth disease virus (serotypes A, O, C, SAT1, SAT2, SAT3, Asia1)
	Japanese encephalitis	Japanese encephalitis virus
	Paratuberculosis	*Mycobacterium avium* subsp. *paratuberculosis*
	Q fever	*Coxiella burnetii*
	Rabies	Rabies virus
	Rift Valley fever	Rift Valley fever virus
	Rinderpest	Rinderpest virus
	Tularemia	*Francisella tularensis*
	Vesicular stomatitis	Vesicular stomatitis virus
	West Nile fever	West Nile fever virus
Cattle	Bovine genital campylobacteriosis	*Campylobacter fetus* subsp. *venerealis*
	Bovine spongiform encephalopathy	BSE prion
	Bovine tuberculosis	*Mycobacterium bovis*
	Bovine viral diarrhea	Bovine viral diarrhea virus
	Contagious bovine pleuropneumonia	*Mycoplasma mycoides* subsp. *mycoides*
	Enzootic bovine leukosis	Bovine leukemia virus
	Hemorrhagic septicemia	*Pasteurella multocida*
	Infectious bovine rhinotracheitis/infectious pustular vulvovaginitis	*Bovine herpesvirus 1*
	Lumpky skin disease	Lumpky skin disease virus
Sheep and goats	Caprine arthritis and encephalitis	Caprine arthritis and encephalitis virus
	Contagious agalactia	*M. mycoides* subsp. m*ycoides,* *M. mycoides* subsp. *capra*, *Mycoplasma capricolum* subsp. *capricolum*
	Contagious caprine pleuropneumonia	*Mycoplasma capricolum* subsp. *capripneumonie*
	Enzootic abortion of ewes (ovine chlamydiosis)	*Chlamydophila abortus*
	Peste des petits ruminants	*Peste-des-petits-ruminants virus*
	Salmonellosis	*Salmonella spp.*
	Scrapie	Scrapie prion
	Sheeppox and goatpox	Sheeppox and goatpox viruses

(*Continued*)

Table 1 (Continued)

Domestic species affected	*Disease name*	*Causative agent*
Equine	African horse sickness	African horse sickness virus
	Contagious equine metritis	*Taylorella equigenitalis*
	Equine encephalomyelitis (eastern)	Eastern equine encephalomyelitis virus
	Equine encephalomyelitis (western)	Western equine encephalomyelitis virus
	Equine infectious anemia	Equine infectious anemia virus
	Equine influenza	Equine influenza virus
	Equine rhinopneumonitis	*Equine herpesvirus 4*
	Equine viral arteritis	*Equine arteritis virus*
	Glanders	*Burkholderia mallei*
	Venezuelan equine encephalomyelitis	Venezuelan equine encephalomyelitis virus
Swine	African swine fever	African swine fever virus
	Classical swine fever	Classical swine fever virus
	Nipah virus encephalitis	Nipah virus
	Porcine reproductive and respiratory syndrome	Porcine reproductive and respiratory syndrome virus
	Swine vesicular disease	Swine vesicular disease virus
	Transmissible gastroenteritis	Transmissible gastroenteritis virus of swine
Avian	Avian chlamydiosis	*Chlamydophila psittaci*
	Avian infectious bronchitis	Avian infectious bronchitis virus
	Avian infectious laryngotracheitis	Infectious laryngotracheitis virus
	Duck hepatitis	Duck hepatitis virus
	Fowl cholera	*Pasteurella multocida*
	Fowl typhoid	*Salmonella enterica* subsp. *enterica* serovar Gallinarum (*S. Gallinarum*)
	Avian influenza	High and low pathogenic avian influenza viruses
	Infectious bursal disease (Gumboro disease)	Infectious bursal disease virus
	Marek's disease	Marek's disease virus
	Newcastle disease	Newcastle disease virus
	Pullorum disease	*Salmonella pullorum*
	Turkey rhinotracheitis	Avian metapneumovirus

sheep, goats, and domestic buffalos. It also affects more than 70 species of wild ruminants, including deer. The highly contagious nature of FMD and the ability to induce serious disease in all the major production animal species underpins the extremely serious economic damage inflicted by this disease.

The causative agent of FMD is FMDV, a member of the Picornaviridae family, genus *Aphthovirus*. FMD virions are rounded, nonenveloped, and have a diameter of about 25 nm. The genome of FMDV consists of a single-stranded RNA molecule of positive polarity with an approximate size of 8.5 kb. Virions are extremely resistant in the environment.

There are currently seven different recognized serotypes of FMDV: O, A, C, ASIA1, SAT1, SAT2, and SAT3. In turn, each serotype possesses a variety of antigenically distinct strains. Because there is no cross-immunity among different serotypes, animals that recover from infection with a specific serotype are susceptible to the other six. Signs of the disease include fever, vesicles on the feet, mouth, and udder of lactating animals. FMD can produce high mortality in young animals, particularly in dairy cattle and pigs. In contrast, the appearance of the disease can be relatively mild in adult sheep and goats, making its diagnosis difficult in these species. Particular attention has to be paid during clinical diagnosis of FMD in swine, since pigs are susceptible to other vesicular diseases with similar signs (swine vesicular disease, vesicular exanthema of swine, and vesicular stomatitis).

Diagnosis and control measures have proven difficult because of the existence of the previously described seven different serotypes. In addition, FMDV, like other RNA viruses, displays a high mutation rate due to the lack of proofreading activity of the viral polymerase (approximately 10^{-3}–10^{-5} per nucleotide site per genome replication). Immunological pressure and high mutation rates result in the emergence of antigenic variants with mutations in the capsid-coding region. This antigenic plasticity makes the design of effective measures to control the disease extremely difficult.

As mentioned above, FMD affects a broad range of species. However, pathogenesis studies have been mainly carried out in swine and cattle. The severity of lesions is dependent on many factors, such as infecting dose, viral

strain, host species, age, and individual susceptibility. The main route of transmission in cattle is via aerosol through the respiratory tract, although infection can also occur through abrasions either on the skin or on the mucosal membranes. Infected animals develop viremia and the virus is excreted in urine, feces, semen, and milk (particularly in dairy cattle). Clinical signs usually take place shortly after infection (between 2 and 14 days depending on the dose and infection route) and include hyperthermia and vesicular lesions in various areas such as feet and tongue. Aerosol infection is less common in pigs than in cattle, although swine shed much more virus through aerosol than sheep and cattle. As with the latter, the length of the incubation period depends on the dose and inoculation route. Lesions in swine most commonly affect feet and when observed in the tongue they are usually small. Moreover, young piglets can die of heart failure as a result of viral replication in myocardial cells.

Sheep are fully susceptible to FMD. They also develop viremia and foot-and-mouth lesions, although clinical signs in this species can be difficult to detect. Moreover, a proportion of infected animals fail to develop clinical signs. This is why sheep played an important role during the outbreak of 2001 in the United Kingdom, spreading the disease before it was clinically detected.

Infected or vaccinated animals rapidly develop a humoral response. High levels of neutralizing antibodies directed toward the external structural proteins protect against reinfection in a serotype-specific fashion, or, in the case of vaccination, against infection. After the acute phase of FMD, cattle, sheep, and goats may remain persistently infected for a variable period of time without displaying any signs of disease. A similar scenario can take place in vaccinated animals after infection. These animals are regarded as 'carriers' and it is thought that they may play a significant role in an outbreak situation because infectious virus can be easily detected in pharyngeal scrapings despite the presence of high levels of neutralizing antibodies. A carrier is, by conventional definition, an animal from which live virus can be isolated after 28 days post infection. The length of the carrier state period is variable: African buffalos and cattle can carry the virus for up to 5 and 3 years, respectively. The carrier state has been also described in sheep (up to 9 months) and goats (up to 4 months), but not in pigs.

Diagnosis of FMD in a country that is free of the disease relies on viral identification and isolation. There is a need for accurate and fast diagnostic tests for FMDV, which should be able to identify persistently infected animals and discriminate between infected and vaccinated ones.

With regard to control, new vaccines are required and are currently being developed and tested. Accurate epidemiological models are also needed in order to determine effective control policies that should be applied within the broad range of scenarios that can develop during an outbreak of FMD.

Influenza

Influenza viruses are respiratory pathogens that affect humans and a broad range of animals, including birds, pigs, horses, dogs, cats, and marine mammals such as whales and seals. They cause major losses to poultry, pig, turkey, and the horse racing industry and constitute a serious concern to public health, as evident from the current threat posed by the H5N1 subtype of avian influenza. Migratory birds represent the main reservoir of influenza viruses, with over 105 wild bird species from which virus has been isolated.

Influenza viruses are members of the Orthomyxoviridae family. The main characteristics of this virus family will be covered specifically in the article on influenza. Orthomyxoviruses have a single-stranded, negative-sense, and segmented RNA genome. The segmented genome allows the reassortment of gene segments among the members of the same genera with potentially disastrous outcomes. The pandemics that took place in 1957 and 1968 were caused by the reassortant viruses containing gene segments of avian origin within a human background.

Three viral proteins decorate the envelope: neuraminidase (NA), hemagglutinin (HA), and the M2 protein. The antigenic properties of HA and NA define different subtypes of influenza A. At present there are 16 HA and 9 NA subtypes. Immunological pressure exerted by neutralizing antibodies results in the selection of mutants that can no longer be neutralized by antibodies to the parental strain, in a process known as antigenic drift. More dramatic antigenic changes can result from the introduction of new HA or NA variants (usually by reassortment), in a process regarded as antigenic shift. These newly introduced variants, if immunologically distinct from previously circulating strains, can lead to higher infection rates or even to pandemics.

During the initial stages of viral replication, the HA protein binds to neuraminic acids (sialic acids) located on the cell surface. This binding is a major determinant for the broad host range of influenza A viruses. Avian and human viruses display differential binding preferences: while the former exhibits high affinity to sialic acids (SA) with an α2,3 linkage the latter preferentially binds to SA with an α2,6 linkage. Consistent with this, the epithelium of the human airways mostly consists of α2,6Gal sugar moieties, and ducks have mainly α2,3Gal in the gut epithelium. Because pigs possess both types of receptors, it is thought that they provide a mixing vessel for reassortment between human, avian, and swine viruses. Moreover, it is thought that the replication of avian viruses in land-based poultry results in the

emergence of influenza A viruses with altered receptor specificity that are able to replicate in humans with the concomitant risk of pandemic variants.

In pigs and horses, influenza infection displays high morbidity with an incubation period of 24–72 h. Clinical features of the disease include high temperature, inappetence, and depression, although signs of respiratory distress are dominant. In agreement with this, histological lesions are mainly observed in the respiratory tract (**Figure 2**). While in pigs recovery takes approximately 6 or 7 days, horses usually make a full recovery after 2 or 3 weeks. In both species the disease is highly contagious and usually affects several establishments at the same time. The international movement of horses constitutes an extra risk for spreading the disease.

In birds, disease presentation depends upon the viral strain involved. Only viruses of subtype H7 and H5 may become highly pathogenic after being introduced into poultry. Highly pathogenic influenza viruses exhibit high mortality rates, but animals that survive the infection display cessation of egg laying, respiratory signs, diarrhea, and edema of the head, neck, and face. If birds are affected by strains of lower pathogenicity, there is still a considerable reduction on egg production and weight gain, as well as respiratory disease. In avian species, viral replication takes place both in the intestinal and in the respiratory tract, and systemic replication is common when virulent strains are involved. As mentioned before, aquatic migratory birds are the main natural reservoir of the virus. Because these birds can remain healthy upon infection,

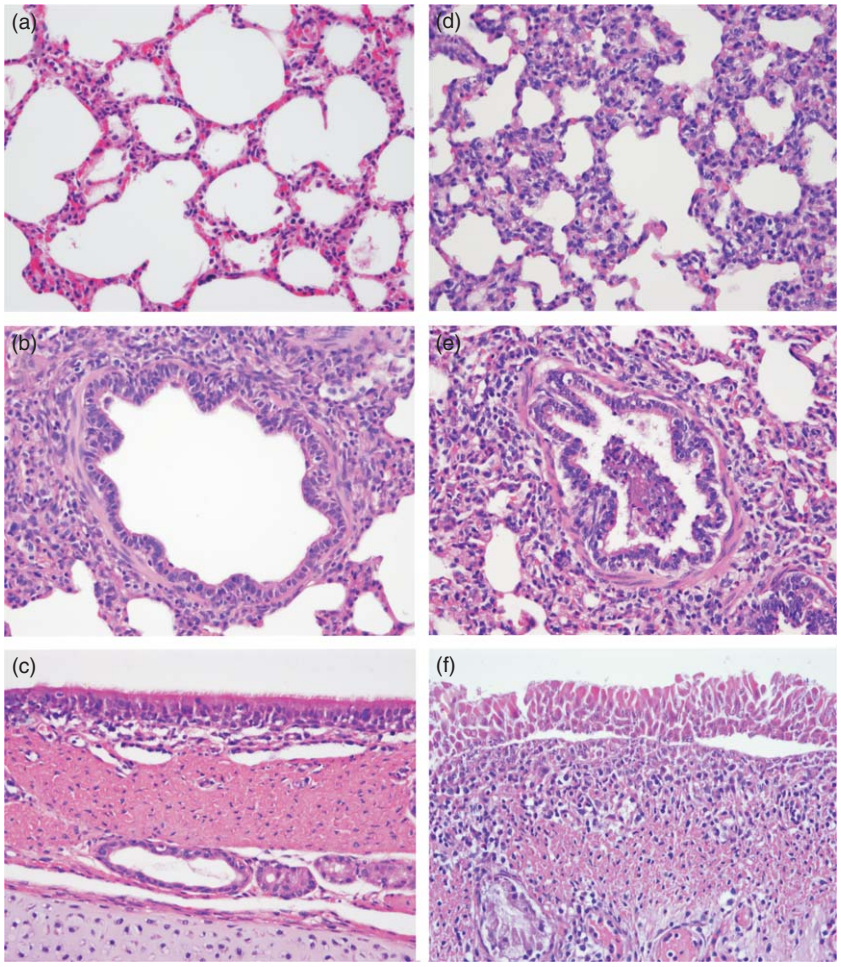

Figure 2 Lesions induced by swine influenza virus in the respiratory tract of pigs. Histological sections of the respiratory tract of a healthy control pig (a–c) and of a pig affected by swine influenza (d–f). Sections shown are at the level of the alveoli (a, d), bronchioli (b, e), and trachea (c, f). Sections from the healthy control pig display the normal histological architecture of alveoli (a), bronchioli (b), and trachea (c). Sections from the affected pig display a diffuse infiltration of round mononuclear cells in the alveoli and bronchioli (d, e). Lumen of the airways in the bronchioli is filled with desquamated cells, cells debris, and few neutrophils (e). In the tracheal mucosa (f) the epithelium is necrotic and epithelial cells are separated and detaching from the basal lamina. The underlying lamina propria is edematous and contains infiltrating inflammatory round cells and neutrophils. Images kindly provided by Marcelo de las Heras and Pablo Murcia.

they are able to carry and distribute the virus between different countries – and even continents – during migrations. Through contact in surface waters, the fecal–oral route may account for the efficient transmission of influenza viruses since infected aquatic birds excrete virus with feces, which in turn can remain infectious for up to 4 days in lake water.

In dogs, canine influenza was identified in 2004 in United States after an outbreak that affected racing greyhounds in Florida. Phylogenetic studies showed that canine influenza is the result of interspecies transmission of a complete equine influenza virus to the dog. Different subtypes of influenza viruses have also been isolated from marine mammals such as seals and whales, with severe outbreaks of the disease affecting the former species.

Influenza viruses are under constant surveillance at the global level, with the World Health Organization (WHO) coordinating a number of influenza centers where epidemiological, antigenic, and genetic information is generated and assessed.

Rinderpest

Rinderpest or cattle plague is a significant viral disease of cattle. Its agricultural, and social, importance has been already described in the historical perspectives section of this article. Rinderpest virus belongs to the Paramyxoviridae family, subfamily Paramyxovirinae, and genus *Morbillivirus*. Viral particles are enveloped with a viral genome consisting of a single-stranded, nonsegmented RNA of negative polarity, and an approximate size of 15.8 kb. Susceptible domestic animals include cattle, sheep, goats, and water buffalos. Various wild life species such as wildebeest, antelope, deer, hippopotamus, eland, kudu, and giraffe are also natural hosts of the disease.

Typically, clinical signs appear after 3–5 days of infection, with morbidity and mortality rates up to 100% in susceptible populations (in African indigenous breeds mortality is lower, around 50%). The clinical form of the disease can be divided in three phases. In the prodromal phase, hyperthermia develops rapidly and it is followed by the mucosal phase, in which ocular and nasal mucopurulent secretions are accompanied by anorexia and depression. The final phase of the disease is characterized by severe hemorrhagic diarrhea and prostration, followed by dehydration and death (affected animals usually die 6–12 days after symptoms appear). Infection is initiated in the upper respiratory tract, usually through nasal entry, and is followed by initial replication in the tonsils and local lymph nodes. The virus then spreads to other lymphatic tissues through blood and lymph. After this stage, rinderpest is readily detected in all the above-mentioned organs and also in the lungs and digestive tract. Replication of the virus in the nasal mucosa causes necrosis and erosions that are consistent with the clinical signs observed in the mucosal phase of the disease. Destruction of lymphoid organs due to viral multiplication results in severe immunodeficiency and subsequent opportunistic infections. The bloody diarrhea observed in the last stages of rinderpest is caused by replication of the virus in the gut mucosa.

Infected animals transmit the disease by direct contact via aerosol droplets derived from secretions from the nose, conjunctiva, and throat. Virus is also shed in feces, urine, and milk. Indirect transmission is unlikely due to the thermolability of the virus.

It is currently thought that rinderpest may have been globally eradicated although this has not been formally accredited by the OIE as yet. This enormous achievement began in 1993 with the establishment of the Global Rinderpest Eradication Program (GREP), sponsored by the Food and Agriculture Organization (FAO) with collaboration from UNICEF and various government agencies. This program combined massive vaccination in Asia and Africa (rinderpest had been previously eradicated from Europe and was never established in the Americas) with molecular and seroepidemiological studies. Currently, vaccination has been stopped and serosurveillance studies suggest that this once dreaded disease may no longer be present. Rinderpest eradication, if achieved, would probably represent the most important accomplishment in the history of veterinary medicine.

Classical Swine Fever

Classical swine fever (CSF; also known as hog cholera) is a contagious disease of swine and wild boar. CSF is probably the most important transmissible disease of pigs and it is caused by classical swine fever virus (CSFV), a member of the Flaviviridae family within the *Pestivirus* genus. Virions are enveloped with an approximate diameter of 40–60 nm and a positive, single-stranded RNA genome approximately 12.5 kb in length.

CSFV induces a disease of variable severity depending on breed and age of the infected animals, virulence of the virus, and other ill-defined factors. Typical signs of the classical form of CSF appear after an incubation period of 2–4 days and include anorexia, hyperthermia, and depression, followed by pneumonia caused by opportunistic infections, vomiting, and diarrhea or constipation. Neurological signs such as paralysis, circling, tremors, and in some cases convulsions can also be observed. Generally, the disease affects only a few animals during the initial period of an outbreak, but after around 10 days morbidity can reach up to 100% of the herd. Mortality rates can also reach 100% in a susceptible herd. Chronic forms of CSF have also been described, with a longer incubation period where clinical signs are intermittent and death can occur weeks or months after initial infection. *In utero* infection is

common in sows and usually results in abortion, mummification of the fetus, or stillbirth. Piglets may be persistently infected and die within weeks or months after birth.

Viral entry commonly takes place via ingestion and is followed by viral replication in the epithelial crypts of the tonsils as well as in granulocytic cells and monocytes. A second round of viral multiplication takes place in lymphoid organs, endothelial cells, and bone marrow, causing leukopenia, severe immunosuppression, and hemorrhages due to endothelial damage. Characteristic gross lesions include submucosal and subserosal petechial hemorrhages and congestion. Infarction in the spleen is typical and almost pathognomonic of CSF. In chronic cases, the most common lesion observed is atrophy of the thymus and germinal centers in the lymph nodes and spleen. Diagnosis of CSF requires laboratory confirmation, being the traditional method, viral isolation, and the observation of viral antigens in frozen tissue sections of affected organs.

Hog cholera is transmitted directly from pig to pig, and indirectly via pig products (fresh, frozen, and cured pig meat) and fomites. Transmission by semen from an infected boar stud was important during the outbreak of CSF that took place in the Netherlands in 1997–98.

CSF is endemic in Asia, Central America, and some parts of South America. The epidemiological situation in most of Africa is uncertain, while North America and Australasia have been free of the disease for a long time. Western Europe has made significant progress toward eradication, although intermittent reintroductions of CSF have occurred. In Central and Eastern Europe the disease is still present, although some countries have followed the nonvaccination model imposed by the European Union. The presence of large populations of wild boar in certain regions of Europe makes eradication of CSF extremely unlikely. In countries where the disease is prevalent, control measures include prophylactic vaccination with attenuated vaccines. In the European Union, vaccination is banned and control measures in an outbreak situation include destruction of affected and in-contact animals and restriction on animal movements.

African Swine Fever

African swine fever (ASF) is one of the major diseases of pigs. The etiological agent is African swine fever virus (ASFV), the sole member of the Asfarviridae family. ASFV is a large enveloped DNA virus with a genome of approximately 190 kb. ASFV is so far the only DNA arbovirus described. ASFV displays icosahedral symmetry with an approximate diameter of 200 nm. ASFV possesses two distinct lipid membranes: an external one, obtained from the cellular membrane during budding, and an internal one that surrounds the inner core of the particle and is likely derived from the endoplasmic reticulum of the infected cell. Depending on environmental factors, ASF displays two distinct epidemiological patterns: a sylvatic and a domestic cycle. The former takes place in southern and eastern Africa and consists of the infections of wild pigs and soft ticks. Infection is likely to occur in the burrows used by these animals. It is estimated that up to 25% of the soft tick population in southern and eastern Africa is infected with ASFV. Ticks become infected after a blood meal on an infected wild pig. Infected ticks can transmit virus to other ticks and to their offspring, as well as to wild pigs at each blood meal. This cycle can take place multiple times along the lifespan of a tick as they can live for several years. In warthogs, seroepidemiological studies have shown that ASF is widely distributed. However, because adult warthogs are rarely viremic, it is thought that the young are the ones from which ticks become infected. Therefore, it is assumed that ASFV is maintained within a cycle that involves young warthogs and soft ticks.

The domestic cycle involves the infection of domestic swine, which can result from the bite of infected ticks or from feeding animals with infected meat. If ASFV is introduced in a previously free region, infected animals constitute the major source of virus for susceptible pigs, although indigenous soft ticks can act as viral reservoirs. Direct contact, aerosol, and mechanical spread by people and fomites account for the high transmissibility of ASF. Feeding scraps of raw meat from infected animals has been associated with the international spread of ASF.

Depending on contributing viral and host factors, ASF presentation in domestic pigs ranges from a highly lethal to a subclinical form. ASFV shows a marked tropism for cells that belong to the monocyte/macrophage lineage, where virulence is linked with the ability of the virus to replicate and cause cytopathology in these cells.

Wild pigs infected with ASFV show no signs of the disease, with low viremia titers. However, viremia in bushpigs can take place for longer periods of time than in warthogs. In domestic swine, the incubation period ranges from 5 to 15 days, and the clinical features of ASF include fever (41–42 °C for about 4 days), diarrhea, inappetence, incoordination, prostration, coma, and death. Vomiting, nasal and conjunctival discharge, dyspnea, and anal and nasal hemorrhages can also be observed in some animals. Abortion is common in affected sows. In regions where the disease is exotic, mortality rates often reach 100% with an average survival time between 2 and 9 days. In endemic areas, ASF cases can be predominantly subclinical and persistent. Pathological findings are typically observed in the lymphatic and vascular systems and include widespread hemorrhages in spleen, lymph nodes, kidneys, and the gastrointestinal and respiratory tracts (**Figure 3**). Leukopenia, thrombocytopenia, B and T cell lymphopenia, together with apoptosis of mononuclear cells and

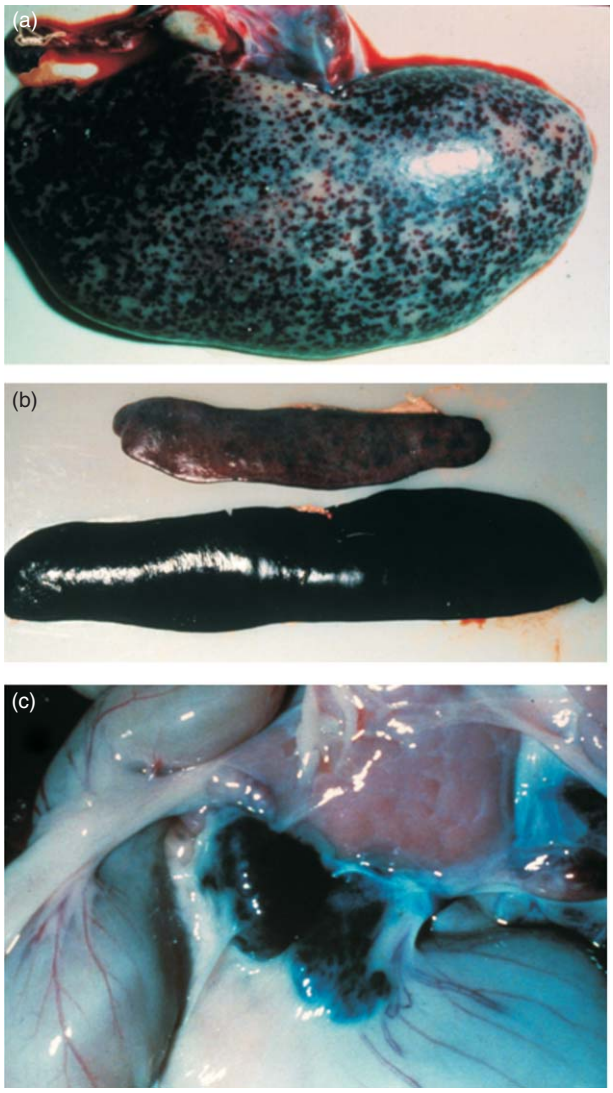

Figure 3 Gross pathology in African swine fever (ASF). Pathological lesions in ASF are typically observed in the lymphatic and vascular systems including widespread hemorrhages in kidneys (a), spleen (b), and lymph nodes (c). Note in panel (b) the size difference from the spleen collected from a pig with ASF (bottom) as opposed to the one collected from a healthy control. Images kindly provided by Daniel L Rock.

lymphocytes, is also common. Death probably occurs as a result of extensive necrosis in conjunction with hemostatic and hemodynamic changes. In subacute forms of the disease, hemorrhages are not as prominent as in acute cases and typical symptoms include loss of condition, swelling of the joints, as well as respiratory and cardiac signs. In chronic cases lesions include cutaneous ulcers, pericarditis, pneumonia, arthritis, and pleuritis. Animals that survive the infection develop protective immunity. Because ASF clinical signs are similar to other swine diseases, in particular to CSF, laboratory diagnosis is essential. Viral isolation and antigen detection can be readily done on samples from spleen, visceral lymph nodes, and blood.

Different factors make prevention and control of ASF difficult: the lack of an efficient vaccine; the ability of ASFV to transmit in fresh meat; the presence of soft ticks that can act as biological vectors in some regions of the world; the possibility of persistent infection in a fraction of infected pigs; and the existence of a sylvatic cycle in sub-Saharan Africa. Countries that are free of the disease maintain such status by banning the importation of pigs or pig-derived products from endemic countries. Introduction of ASF in an uninfected country requires rapid and effective measures of control, such as slaughter of affected and in-contact animals, control of swine movement within and across affected regions, prohibition of feeding with waste food, and fumigation of infested facilities if soft ticks are prevalent in the affected area. Currently, there is no available vaccine. Measures to control the disease include quarantine and slaughter of affected animals.

Sheeppox and Goatpox

Sheeppox and goatpox are probably the most significant pox diseases of domestic ruminants. They are caused by sheeppox virus (SPV) and goatpox virus (GTPV), respectively. Both diseases are endemic in southwestern Asia, India, and northern and central Africa. SPV and GTPV are members of the Poxviridae family (subfamily Chordopoxviridae, genus *Capripoxvirus*). SPV and GTPV particles are enveloped and oval with an approximate size of $200 \times 300 \times 270$ nm. The genomes of SPV and GTPV are approximately 150 kb and they are 96% identical. Both SPV and GTPV are very similar to lumpy skin disease virus, the other member of the *Capripoxvirus* genus.

Although SPV and GTPV are considered to be host-specific, it has been suggested that some strains may affect both sheep and goats. Morbidity and mortality rates range from 1 to 10% of the animals, although during an outbreak of sheeppox over 75% of the flock can be affected and lethality can reach up to 100% in young animals, as they are the most susceptible group. In countries where the disease is enzootic, indigenous breeds seem to be more resistant to the infection than exotic ones. The presence of sheeppox and goatpox in a region affects animal trading, and hence their economical importance. After an incubation period of 4–8 days, infected animals show a variety of clinical signs that include high body temperature, nasal discharge, hypersensitivity, and arched back. Appearance of typical pox lesions (**Figure 4**) such as macules and papules takes place a couple of days after the onset of the initial signs and can cover the entire body. Notably, nodular lesions in a variety of organs such as abomasum, trachea, and lungs are common. In the skin,

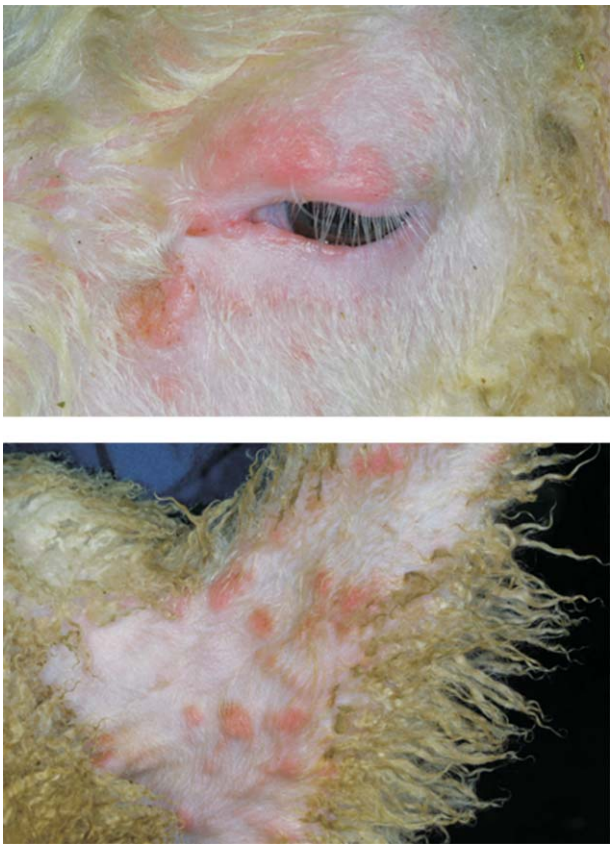

Figure 4 Sheeppox. Typical pox lesions in sheep affected by sheeppox. Images kindly provided by Gustavo Delhon and Daniel L Rock.

SPV infection results in marked changes in the epidermis, hypodermis, and dermis. Both diseases are clinically comparable; they are serologically indistinguishable from one another and highly contagious. Transmission occurs by direct contact between infected and susceptible animals. Transmission via aerosol, insect vectors, and contaminated objects is also suspected. Virus is present in milk and nasal secretions, and it can also be recovered from lung, skin, liver, and lymph nodes. In endemic countries, live attenuated and inactivated vaccines are commonly used.

Bluetongue

Two orbiviruses within the family of the Reoviridae are the causative agents of two similar infectious, noncontagious, insect-borne diseases of sheep and horses: bluetongue of sheep and AHS.

Bluetongue is caused by bluetongue virus (BTV), a member of the genus *Orbivirus* within the family of the Reoviridae. BTV, like other reoviruses, has a double-stranded RNA genome formed by ten segments. The virion is formed by a two-layered icosahedral capsid with no envelope and an approximate diameter of 70 nm. There are 24 serotypes of BTV.

All ruminants are susceptible to BTV infection but sheep are, by far, the most affected domestic species, followed by goats and white-tail deer in the United States. Infection in cattle is in general subclinical, but it has a considerable epidemiological significance for the maintenance of BTV in an endemic area. In sheep, susceptibility to bluetongue varies among different breeds. In general, breeds from tropical countries in Africa and Asia do not display severe clinical signs upon infection.

BTV is transmitted by an insect vector, the biting midge of the *Culicoides* spp. *Culicoides imicola* is one of the most important vectors for BTV. *C. imicola* had been traditionally confined to Africa and Southeast Asia but now, due to climate change, it is present in the whole of southern Europe and has been found even in Switzerland. *Culicoides obsoletus* (and closely related species) and *Culicoides pulicaris* can also act as vectors for BTV, the former possibly being the most common midge in central and northern Europe. Transmission of BTV is therefore limited to those areas and times of the year that allow vector activity.

Bluetongue is present in most tropical and subtropical regions of the world and lately several incursions have been recorded in southern Europe and subsequently in Central and even northern Europe. The geographical diffusion of BTV follows the distribution of susceptible *Culicoides* spp. Cattle have an important epidemiological role of amplifying disease spread as they do not succumb to infection and viremia in this species tends to be twice as long as in sheep. In addition, midges prefer biting large mammals like cattle and horses than sheep.

Bluetongue in sheep can show variable clinical signs ranging from subclinical disease to an acute clinical pattern leading to death in 70–80% of infected animals. The disease is initially characterized by fever and hyperemia of mouth and nasal mucosa leading to excess salivation and nasal discharge. In acute cases, the hyperemia becomes more pronounced and the tongue may become cyanosed, hence the name bluetongue, although a relative minority of animals will show these clinical signs. Necrotic lesions can develop on gums and tongue approximately a week after the initial onset of clinical signs and lesions on the feet can also occur at this time. There is a marked loss of condition, and death can occur up to 1 month after infection. Infection of pregnant ewes can lead to abortion. Most of the clinical signs can be reconciled with damage of the endothelium of small blood vessels.

Sheep surviving bluetongue are protected against subsequent BTV infections by acquired immunity that is fully protective against homologous serotypes. Several diagnostic tests are available for bluetongue diagnosis including enzyme-linked immunosorbent assays (ELISAs), serum

neutralization, and PCRs. Control of bluetongue can be achieved by vaccination.

African Horse Sickness

AHS is an infectious, noncontagious, insect-borne disease of horses. AHS is probably one of the most deadly viral infections of horses. AHS is caused by an orbivirus, the African horse sickness virus (AHSV), a member of the family of Reoviridae (like BTV). AHSV, like BTV, is an arbovirus transmitted by species of the *Culicoides* biting midge. AHS is endemic in tropical and sub-Saharan Africa with occasional excursions in other areas in India, Pakistan, North Africa, and the Arabian Peninsula. In the second half of the 1980s outbreaks of AHS occurred in Spain, Portugal, and Morocco.

AHSV naturally infects zebras, which are considered a natural reservoir for the virus as they rarely exhibit clinical signs of infection. The lack of zebras outside Africa is believed to be one of the main reasons because AHS did not establish itself outside this continent. In horses, AHSV infection induces lesions in the circulatory and respiratory system, resulting in hemorrhages and effusions. The disease is classified into four forms of different severity: the horse sickness fever, the subacute (or cardiac) form, the cardio-pulmonary form, and the peracute (or pulmonary) form. Susceptible horses most often display the cardio-pulmonary or the peracute form of AHS with a very high mortality rate, while donkeys usually display the milder clinical forms of the disease. Histopathological and clinical signs are the result of an increased permeability of the capillary walls and vasculitis of both small and medium-sized blood vessels. Diagnosis of AHS is traditionally based on virus isolation and virus neutralization for serotyping. Reverse transcriptase-polymerase chain reaction (RT-PCR) assays are also available for rapid diagnosis. Control measures in endemic areas include vaccination with attenuated AHSV strains.

Newcastle Disease

One of the most significant viral diseases of avian species is Newcastle disease. It is caused by a group of single-stranded, nonsegmented, negative-sense RNA viruses known as Newcastle disease viruses (NDV). NDV belong to the family Paramyxoviridae, genus *Avulavirus*, and possess a genome of approximate 15.2 kb. Originally, NDV were classified in three different strains according to their virulence: lentogenic, mesogenic, and velogenic. Today, mesogenic and velogenic strains are referred to as virulent NDV (vNDV), while lentogenic strains are regarded as low virulence NDV (loNDV).

The clinical presentation of Newcastle disease ranges from subclinical to highly lethal (**Figure 5**), depending on both host and viral factors. Velogens are the most virulent

Figure 5 Newcastle disease. Virulent Newcastle disease virus (vNDV) strains can kill almost 100% of the infected chickens. Image kindly provided by Daniel Jack King.

of NDVs; they may produce widespread hemorrhagic lesions in the gastrointestinal tract (viscerotropic strains), but can also cause neurologic signs (neurotropic strains). In contrast, infection with lentogenic viruses results in subclinical infections or at most a mild respiratory presentation. Mesogenic NDV exhibits an intermediate phenotype, with moderate respiratory disease and occasionally neurological signs. Although clinical signs depend on the age and the immune status of infected animals, symptoms such as dyspnea, clonic muscular gasping, and cyanosis of comb and wattles are suggestive of the disease and usually appear after an incubation period of around 5 days. Other signs include weakness, loss of appetite, and somnolence. When the nervous system is involved, typical symptoms include paralysis of wings or legs (or both), ataxia, torticollis, clonic spasms, and abnormal movements of the head. Signs of infection by viscerotropic NDV are foamy mucus in the pharynx, crop dilatation, and diarrhea. Egg production is immediately affected and eggs from infected animals exhibit a decrease in the quality of albumen together with loss or depigmentation of the shell. Given the relatively nonspecific clinical signs and the epidemiological importance of NDV, viral isolation (usually from brains, spleen, or lungs) and serological assays are required for diagnosis.

Initial replication of the virus takes place in the epithelium of the upper respiratory and intestinal tracts, followed by a viremic stage that allows viral spread into the bone marrow and spleen. Colonization of these organs results in secondary viremia and further infection of lungs, intestine, and central nervous system, where lesions develop and cause the aforementioned clinical signs. Virulence of NDV depends on the cleavability of the hemagglutinin–neuraminidase (HN) and fusion glycoprotein (F), similarly to influenza A viruses. Avirulent strains exhibit minimal basic residues at the cleavage sites, and hence only proteases present in the respiratory

or intestinal tract can cleave them. The presence of multiple basic residues at the cleavage sites allows cleavage by ubiquitous proteases and increases the ability to develop a systemic infection. NDV is highly contagious and transmission routes include direct and indirect contact, while transovarian transmission can occur with lentogenic strains, resulting in the hatching of infected chicks.

In many countries vNDV are exotic while lentogenic strains are endemic among wild birds and domestic poultry. Control measures include vaccination with either live vaccine composed of lentogenic viral strains or inactivated virus. Because the presence of vNDV within a country imposes trade restrictions, Newcastle disease is a viral disease with significant economic importance: the outbreak that took place in California between 2002 and 2003 resulted in the culling of more than three million birds and an estimated cost of eradication of approximately US$200 million.

Conclusion

Over the years, studies on veterinary pathogens have been instrumental in understanding the biology of viruses and bacteria. Research on pathogens of farm animals underpinned entire new disciplines and inspired the discovery of new human pathogens. Despite the progress achieved in science and technology in the last two centuries, viral and bacterial diseases of domestic animal species have still a considerable impact on animal health and agriculture, and affect the economy of both industrialized and developing countries. Changes in the environment and climate can alter the interaction between different animal species and between animals and man. These changes can in turn favor the emergence of new pathogens or the reemergence of old ones. Thus, it is critical that resources be devoted to research and surveillance of veterinary pathogens in order to preserve and improve both animal and human health.

See also: Influenza; Plant Pathogens and Disease: Newly Emerging Diseases; Zoonoses

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Relevant Website

http://www.oie.int (World Organization for Animal Health)