Emerging zoonoses: crossing the species barrier

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Summary
The ability of infectious disease agents to cross the species barrier has long been recognised for many zoonotic diseases. New viral zoonotic diseases, such as acquired immune deficiency syndrome (AIDS), caused by human immunodeficiency viruses 1 or 2, emerged in the 1980s and 1990s, and have become established in the human population. Influenza virus continues to find new ways to move from avian species into humans. The filoviruses and the newer paramyxoviruses, Hendra and Nipah, highlight the increasing proclivity of some animal viral agents to infect human populations with devastating results. A previously unknown transmissible spongiform encephalopathy, bovine spongiform encephalopathy, has emerged in cattle in Europe and spread to humans as well as other animal species. A novel toxicosis, caused by Pfiesteria spp. dinoflagellates, has become a secondary problem in some areas where large fish kills have occurred. The increasing proximity of human and animal populations has led to the emergence of, or increase in, bacterial zoonoses such as plague, leptospirosis and ehrlichiosis. The factors which influence the ability of each infectious agent to effectively cross the species barrier and infect new cells and populations are poorly understood. However, for all of these diseases, the underlying theme is the growth of the human population, the mobility of that population, and the efforts expended to keep that population nourished.

Keywords
Bacteria - Emerging diseases - Prions - Public health - Species barriers - Viruses - Zoonoses.

Introduction
As defined in the broadest sense, emerging zoonotic diseases are among the most important public health threats facing humanity. As the population of the world continues to expand in a logarithmic fashion, species are thrust into new environments, with all the attendant possibilities for exposure to, and dissemination of, novel infectious agents. Although zoonotic diseases have been known for millennia, a recent surge in new diseases and in new forms of existing zoonoses has occurred. This short review will concentrate on the emergence, since the 1980s, of several new zoonotic disease threats. The diseases concerned have recently achieved greater notoriety due to their ability to cross species barriers.

Influenza
In a review published in 1991, Cedric Mims remarked that many human diseases acquired from animals do not subsequently spread in the human population, but that influenza was an exception (20). Mims attributed this to the fact that the transmission of avian or animal influenza to man requires reassortment between the human and the avian or animal influenza viruses, such that the new virus contains a mixture of genes that includes genes derived from the human virus. Such events occurred in 1957, and again in 1968, when pandemic influenza viruses which derived one or more genes from avian influenza viruses swept through the human populations of the world (29). A new pandemic of this type is
expected to occur within the next few years. In the meantime, however, an outbreak of influenza which caused eighteen human cases, including six deaths, occurred in Hong Kong in 1997, and was unusual for two reasons, namely: the viral haemagglutinin was subtype H5, never previously seen in a human cases, including six deaths, occurred in Hong Kong in 1997, and was unusual for two reasons, namely: the viral haemagglutinin was subtype H5, never previously seen in a human influenza virus. Such an event could generate a virus with high human transmissibility, carrying a surface antigen (H5 or H9) which is completely novel to the world population, with severe respiratory infection were shown to result from infection with another avian influenza virus, this time of the haemagglutinin subtype H9 (33). As with the H5 virus, nucleotide sequence analysis showed that all eight gene segments of the virus were of avian origin.

These observations have led to increased influenza surveillance, especially in the People's Republic of China. How these avian viruses were able to infect and cause disease in humans is not known, but the viruses are of great concern in view of the potential for reassortment with a human influenza virus. Such an event could generate a virus with high human transmissibility, carrying a surface antigen (H5 or H9) which is completely novel to the world population, with potentially devastating consequences. Information on influenza is expanded by Alexander and Brown in this volume (1).

Human immunodeficiency viruses

Although the human immunodeficiency viruses, HIV-1 and HIV-2, have a seemingly narrow host range which is limited to humans, these viruses are now known to represent examples of species cross-over (18). The first evidence for this was obtained for HIV-2, when a close relationship between HIV-2 and a virus isolated from a sooty mangabey (Cercocebus atys) from West Africa, was demonstrated (16). The close relationship between humans and sooty mangabeys, and the clear origin of HIV-2 cases in a geographic region where sooty mangabeys are common, supported the idea that HIV-2 was derived from a species cross-over (26). More recently, all HIV-1 strains known to infect humans were shown to be closely related to a virus isolated from the chimpanzee subspecies Pan troglodytes troglodytes, supporting the notion that the spread of this chimpanzee retrovirus into humans was the origin of the major HIV pandemic that now affects some 35 million people world-wide (13).

Filoviruses

Marburg and Ebola haemorrhagic fevers are caused by filoviruses, so named because of the threadlike appearance of the viruses in the electron microscope. Four recognised species of Ebola virus (Sudan, Zaire, Reston and Côte d'Ivoire) and one species of Marburg virus comprise the filovirus genus. Given the high fatality rates seen in human infections, which range from 22% for Marburg virus to as high as 88% in some outbreaks of Ebola virus disease, the filoviruses are probably the most feared of known infectious agents. The viruses contain a negative-strand ribonucleic acid (RNA) genome, and have now been fairly well characterised in terms of molecular properties, which place them in the order Mononegavirales along with paramyxoviruses and rhabdoviruses. Both viruses clearly cause zoonotic infections, with many human cases resulting from contact with infected monkeys. This occurred in 1968, when Marburg virus disease was first discovered in laboratory workers preparing primary monkey kidney cell cultures. However, since the disease is usually fatal in monkeys, these animals are not considered to be the true natural reservoir of infection, and the origin of these infections remains unknown (12).

Re-emergence of Ebola virus infections has occurred several times in the past ten years. In 1989, a new species of Ebola virus appeared in captive monkeys in Reston, Virginia, United States of America (USA). This virus species, known as Ebola Reston virus, originated in a non-human primate exporting facility in the Philippines, and is the only filovirus that has not yet been associated with disease in humans, although infections have been recorded. In 1996, the virus reappeared in a non-human primate facility in Texas, USA, again due to importation of infected monkeys from the Philippines. Another new species of Ebola virus appeared in the Côte d'Ivoire in 1994; this species caused a single non-fatal human case.

The highly virulent Zaire strain of Ebola virus, first recognised in 1976, re-emerged in 1995 in Kikwit, Zaire, with devastating consequences (315 cases, of which 77% were fatal), and again in Gabon in 1996. Molecular characterisation has shown these viruses to be virtually unchanged genetically from the original 1976 strain (25). Similarly, an outbreak of Marburg virus infection, in the Democratic Republic of the Congo in 1999, yielded a virus that closely resembled previous Marburg viruses, the most recent known case of which had occurred in Kenya in 1987.

Despite extensive searches, filoviruses have not yet been detected in any species which might constitute the natural reservoir. Viruses causing all known human disease have originated in Africa, whereas Ebola Reston virus has emerged only from the Philippines. Much needs to be learned before the origins of these emerging zoonotic diseases can be understood.
Hendra and Nipah viruses

In 1994, a horse trainer in the Hendra suburb of Brisbane, Queensland, Australia, died of severe respiratory disease caused by a previously unknown paramyxovirus which had infected twenty horses in his stable, killing thirteen of them. A stable worker was also infected and became severely ill, but survived. The virus was initially named equine morbillivirus (23), but was subsequently renamed Hendra virus. In another episode, a farmer became infected in August 1994 while performing a necropsy on two horses; the farmer suffered a mild febrile infection, and recovered, but died a year later of fatal encephalitis. One of the horses was found to be infected with Hendra virus. A search for the reservoir of Hendra virus showed that it was a frequent infection of the *Pteropus* species (commonly known as fruit bats or flying foxes), as evidenced by the presence of antibodies in 20% to 30% of all four known *Pteropus* species in Australia (34). Serological evidence for Hendra virus infection was sought in thousands of horses in Australia and elsewhere, but none was found. A third case in equines occurred in January 1999, in Cairns, also in Queensland, Australia.

Beginning in October 1998, an epidemic of severe febrile encephalitis with up to 40% fatality occurred in peninsular Malaysia in people who had close contact with pigs. Disease was also seen in pigs on farms associated with human cases, though the fatality rate in pigs was less than 5%, and most pigs exhibited respiratory rather than encephalitic symptoms. Overall, more than 100 people died in Malaysia, and one death was reported among the thirteen cases that occurred in Singapore, the latter associated with an abattoir processing pigs from Malaysia. The epidemic of human disease in Malaysia was stemmed by the slaughter of more than a million pigs on infected farms. A previously unknown paramyxovirus, which has been named Nipah virus, was isolated from a patient who lived in Sungai Nipah, in the Negeri Sembilan district of Malaysia. This virus proved to be the cause of both the encephalitis outbreak in humans and the respiratory disease in pigs. The virus was first identified because cross-reaction occurred with antisera against Hendra virus. However, subsequent molecular characterisation showed that the two viruses, which are now considered to represent a hitherto unknown genus within the family Paramyxoviridae, differed by some 30% at the nucleotide sequence level across the genome.

An unusual feature of both these viruses is the ability to infect and cause severe disease in a wide range of species. For example, Nipah virus infection causes fatalities in cats and dogs, in addition to pigs and humans. The reservoir of natural infection for both viruses appears to be fruit bats, though a significant amount of additional research will be required to understand the natural history and origin of these unusual virus infections. Although some evidence exists, in the case of Nipah virus, to suggest that infection was occurring in pig farms as early as 1997, it is remarkable that such a virulent infection was previously unknown. There is an urgent need to understand the nature of the emergence of the virus in the pig and human populations. Disease associated with both of these viruses is described in greater detail elsewhere in this volume (21, 31).

Bovine spongiform encephalopathy

A new fatal neurological disease of cattle was first recognised in the United Kingdom (UK) in 1986, with cases retrospectively identified from April 1985 (30). The disease was characterised by a long latent period of two to five years, followed by clinical manifestations of unsteady gait, nervousness, kicking, myoclonus, hyperaesthesia, loss of weight and reduced milk yield. The infection became popularly known as 'mad cow disease' because of the behaviour of cattle in the late stages of the disease. Much is now known about the causative agent, which is a prion, although the precise origin (whether bovine or sheep) remains unknown. A change in the production process for meat and bone meal, used as a feed supplement for young cattle, was responsible for amplifying the agent, leading to over 170,000 cases in cattle. Cessation of this feeding process led to a halt in the appearance of new cases within a few years.

From the outset, recognition of this new disease raised suspicions among the public of a risk to human health (9), but technical experts declared that the risk was extremely small (17). However, the potential of the bovine spongiform encephalopathy agent for crossing the species barrier became apparent early in the 1990s, as cats and various zoo animals succumbed to fatal neurological infection after eating beef or bovine products prepared from affected cattle. Definitive evidence of human infection and disease was published in 1996 (32), and since then over fifty cases have been described, principally in young people under thirty years of age. A detailed description of the human disease is given by Zeidler and Ironside in this volume (35). Currently, the mode by which these infections are contracted remains unknown. Although transmission is widely suspected to be through consumption of infected beef, epidemiological links between the human cases are lacking. Measures have been introduced in the UK which should reduce the risks associated with beef consumption, but uncertainty remains. Although only three human cases have occurred outside the UK (two in France and one in the Republic of Ireland), the risks of contracting the disease in other countries of Europe where bovine cases have been reported, are unknown.
Plague

Plague, caused by *Yersinia pestis*, is a disease of great historical impact that continues to emerge and re-emerge as a zoonotic disease. Transmitted by fleas, the bacterium is maintained in rodent reservoir species. Recent urban outbreaks of plague, seen within the last decade in India and Madagascar, are attributed to infection of *Rattus rattus*, thus having an epidemiology similar to that classically described for urban plague (8). In the south-western USA, sylvatic plague is an increasing public health problem, largely because of the transfer of the infectious agents from cats and dogs to humans. The increase is attributed to a variety of factors, all of which involve encroachment on infected habitat. In addition, in the last three years, *El Niño* effects have led to increased rainfall, greater food supply, and a higher density of rodents (22). Cats and dogs which have contact with infected rodent populations serve as a bridge for human infection. The majority of cats infected with *Y. pestis* present with buboes and draining abscesses, usually cervical and often bilateral. Approximately 10% of feline cases have the pneumonic form of the disease (10). Infection of dogs is less frequent and also less specific, with signs including lethargy, pyrexia, and possibly abscesses or purulent dermatitis in the cervical region (24). Cats may be at greater risk because of their proclivity for hunting rodents. Humans become infected by contact of infective material with a break in the skin (e.g. flea bite, draining abscess on cutaneous abrasion, bite or scratch from an infected animal), or through pneumonic aerosols. The number of domestic animals infected with plague has escalated dramatically in recent years, with a corresponding increase in human cases.

Ehrlichiosis

Human ehrlichiosis in the USA has emerged as a serious concern and is represented in a variety of syndromes. *Ehrlichia chaffeensis*, first described in 1991, causes an acute febrile illness with central nervous system manifestations or rashes seen frequently. As *E. chaffeensis* forms colonies (morulae) in monocytes, the disease is referred to as human monocytic ehrlichiosis. Humans contract *E. chaffeensis* infection from the bite of a tick vector, *Amblyomma americanum*, and the reservoir host is suspected to be white-tailed deer (*Odocoileus virginianus*). This disease is seen mostly in the south-central and south-eastern regions of the USA. A second syndrome, human granulocytic ehrlichiosis, was first described in the upper Midwest of the USA (3). Clinical similarities to human monocytic ehrlichiosis exist, but morulae are typically found in neutrophils. The agent of human granulocytic ehrlichiosis has not been identified definitively, but is known to infect a variety of wild and domestic animals, including dogs.

Leptospirosis

Leptospirosis, a well-known disease of many animal populations, is caused by a variety of serovars of the spirochaete *Leptospira interrogans* (15). Leptospirosis as a zoonotic disease in humans occurs as an accidental infection. The leptospires have an ability to penetrate intact mucous membranes and only a few organisms are required to establish an infection. Given the fact that leptospires are shed in urine of affected animals, human infection is associated with periods of high rainfall, poor drainage, and a high density of carrier and susceptible animals. The clinical syndrome in humans includes fever, headache, myalgia, abdominal pain and variable degrees of icterus. High-risk groups have traditionally been workers on livestock farms and in slaughterhouses, but recent examples emphasise the role of leptospirosis as an emerging zoonotic pathogen, from species other than livestock. In October 1995, a large epidemic in Nicaragua, with high morbidity and mortality, was attributed to leptospirosis secondary to regional flooding. Contamination of ground water by dogs infected with leptospires was incriminated as the source. This outbreak was unusual in that many cases presented with pulmonary haemorrhage, not previously considered to be a characteristic feature of leptospirosis (28). In the summer of 1998, an outbreak of acute febrile illness was recorded in approximately ninety athletes participating in a triathlon in the upper Midwest of the USA. Leptospirosis was diagnosed, with the common risk factor being swimming in a contaminated lake (7). The lake in question was bordered by both livestock-producing areas and wildlife refuges, so the
animal source could not be determined. The occasional occurrence of leptospirosis as a result of contact with fresh water is not unusual. However, what made this outbreak noteworthy was the large number of people affected simultaneously. Lastly, increasing reports of leptospirosis diagnosed in emergency rooms in urban settings have been made, with the source of infection thought to be rodents (4). Consequently, leptospirosis, acknowledged for many years as a zoonotic disease, appears to be gaining momentum in its emergence as a greater public health threat, with multiple source species involved.

Pfiesteria

In 1992, a newly described dinoflagellate, *Pfiesteria piscicida*, was shown to be the cause of massive fish mortality in estuaries along the eastern seaboard of the USA (6). *Pfiesteria piscicida* and *Pfiesteria*-like species, now known to be the aetiological agents of these outbreaks, are unusual dinoflagellates. The organisms have a large variety of life forms and one of these, the toxic zoospore, emits toxins in response to the presence of fish excrement and secretions. Thus, as fish accumulate in large numbers, toxins are produced. These toxins serve to strip away the skin of the fish, leaving eroded areas on which the dinoflagellates feed. Clinical signs in the fish include 'punched out' areas in the skin and erratic behaviour. As the fish die, the zoospores are transformed into non-toxic amoebic forms which then feed on dying and dead fish. One of the explanations given for the emergence of *Pfiesteria*-caused disease is the increase in fish populations, secondary to nitrification of run-off water due to agricultural practices, specifically poultry-related by-products. Laboratory workers became aware of the possible adverse effects of *Pfiesteria* on human health when scientists working with these organisms experienced various health problems, including disorientation, shortness of breath, and headaches. In the summer of 1997, many commercial fishermen, as well as recreational boaters and swimmers on the Pocomoke river, reported distinct signs of illness, concurrent with several episodes of extensive fish mortality in the area. Symptoms were burning skin lesions, fatigue, headache, diarrhoea and cognitive deficits (primarily problems with short-term memory and the learning of new tasks). The latter were measured quantitatively by neuropsychological testing, and a positive association was observed between deficits and exposure to contaminated water. Within three to six months after cessation of exposure, normal cognitive function returned (14, 19). Unfortunately, the toxin of *Pfiesteria* has not yet been identified and therefore definitive diagnosis of the syndrome in humans remains problematic. The route of exposure is presumed to be cutaneous; no reports exist of food-borne illness associated with *Pfiesteria* activity.

Conclusion

The global human population now exceeds six billion. The activities of that population, including mobility, impact on the environment, and inter-relatedness with all of the animal species sharing the planet, ensure that disease agents will continue to have the opportunity to cross species barriers and create disease. Prevention of initial occurrences can be problematic, as shown by the examples discussed, including HIV, Ebola virus, Nipah virus and *Pfiesteria*. Early recognition and prompt implementation of control measures can be critical in limiting damage and spread of these zoonoses. This approach requires an increased level of awareness and sufficient expenditures on public health and basic biomedical research.
dévastateurs. Une encéphalopathie spongiforme transmissible, inconnue auparavant, l'encéphalopathie spongiforme bovine, est apparue chez les bovins en Europe pour s'étendre ensuite à l'homme ainsi qu'à d'autres espèces animales. Une nouvelle toxicose due à des dinoflagellés du genre *Pfiesteria* spp. est apparue dans certaines régions comme conséquence secondaire d'une mortalité massive des poissons. Les contacts de plus en plus étroits entre les populations humaines et animales ont abouti à l'apparition ou à l'augmentation de zoonoses bactériennes telles que la peste, la leptoïse et l'ehrlichiose. Les mécanismes par lesquels chacun de ces agents infectieux franchit la barrière d'espèce et infecte de nouvelles cellules et populations sont encore mal connus. Cependant, dans tous les cas, la problématique sous-jacente est la croissance démographique, la mobilité de la population humaine et les efforts nécessaires pour nourrir cette population.

**Mots-clés**
Bactéries - Barrières d'espèce - Maladies émergentes - Prions - Santé publique - Virus - Zoonoses.

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**Zoonosis emergentes: la ruptura de la barrera interespecífica**

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**Resumen**
Hace mucho tiempo que se conoce la capacidad de numerosos agentes de enfermedades zoonóticas de franquear la barrera interespecífica. Tras surgir en las décadas de 1980 y 1990, nuevas enfermedades zoonóticas de carácter vírico, como el síndrome de inmunodeficiencia adquirida (SIDA), provocado por los virus de inmunodeficiencia humana 1 o 2, se han establecido en el seno de la población humana. El virus de la influenza sigue hallando nuevas formas de pasar de especies avícolas a la especie humana. Los filovirus, al igual que los paramyxovirus Hendra y Nipah, de aparición más reciente, ponen de manifiesto la creciente proclividad de algunos virus animales a infectar poblaciones humanas, con consecuencias devastadoras. La encefalopatía espongiforme bovina, una encefalopatía espongiforme transmisible desconocida hasta hace poco tiempo, empezó afectando al ganado europeo y se ha extendido ahora al hombre y otras especies animales. En ciertas zonas donde se han producido grandes matanzas de peces ha aparecido, como efecto secundario, una nueva toxicosis provocada por dinoflagelados del género *Pfiesteria*. La interacción cada vez más estrecha entre poblaciones animales y humanas ha acentuado asimismo la aparición o el incremento de zoonosis bacterianas como la peste, la leptoïsis o la ehrlichiose. Poco se sabe hasta ahora de los factores que influyen en la capacidad de un agente infeccioso para atravesar eficazmente la barrera interespecífica e infectar nuevas células y poblaciones. Sin embargo, el gran tema que subyace a todas estas enfermedades es el crecimiento demográfico que está experimentando la población humana, sumado a la gran movilidad de esta población y a los grandes esfuerzos requeridos para alimentarla.

**Palabras clave**
References


