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Impact of climate change and other factors on emerging arbovirus diseases

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Summary

While some sceptics remain unconvinced that global climate change is a reality, there is no doubt that during the past 50 years or so, patterns of emerging arbovirus diseases have changed significantly. Can this be attributed to climate change? Climate is a major factor in determining: (1) the geographic and temporal distribution of arthropods; (2) characteristics of arthropod life cycles; (3) dispersal patterns of associated arboviruses; (4) the evolution of arboviruses; and (5) the efficiency with which they are transmitted from arthropods to vertebrate hosts. Thus, under the influence of increasing temperatures and rainfall through warming of the oceans, and alteration of the natural cycles that stabilise climate, one is inevitably drawn to the conclusion that arboviruses will continue to emerge in new regions. For example, we cannot ignore the unexpected but successful establishment of chikungunya fever in northern Italy, the sudden appearance of West Nile virus in North America, the increasing frequency of Rift Valley fever epidemics in the Arabian Peninsula, and very recently, the emergence of Bluetongue virus in northern Europe. In this brief review we ask the question, are these diseases emerging because of climate change or do other factors play an equal or even more important role in their emergence?

Keywords

Climate change; Emerging diseases; Arboviruses; Chikungunya; Rift Valley fever; Bluetongue

1. Introduction

Undoubtedly, if the damage we have already done to the ozone layer and thus to our planet cannot be reversed, or at least if we cannot reduce harmful chemical emissions and prevent further damage, the emergence of either new or reemerging arthropod-borne virus (arbovirus) diseases in new areas of the world, such as southern and northern Europe, would be expected to continue to occur, perhaps with increasing frequency.

During the past decade, human and animal pathogenic arboviruses such as West Nile virus (WNV), Chikungunya virus (CHIKV), Rift Valley fever virus (RVFV) and Bluetongue virus

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(BTV) have emerged and caused epidemics in North America, Europe and the Arabian Peninsula. Their emergence may be attributable to the impact of climate change,[1,2] but a variety of other factors have in many cases been important contributory determinants of emerging epidemics.3 These include: local levels of socio-economic development; increasing human travel; commercial transportation; urbanization; deforestation; land reclamation; irrigation projects; human, animal and arthropod population density increase; and political and military activities that lead to mass human evacuation. However, local climatic fluctuations may have exerted a transient impact on particular arbovirus epidemics. In the four specific examples of emerging arbovirus diseases provided below, we briefly examine the potential effects of climate change and other factors that have contributed to the most widely reported cases of recent arbovirus emergence.

2. Chikungunya virus

CHIKV, a member of the genus *Alphavirus* in the family *Togaviridae*, was isolated from the serum of a febrile female patient suffering with joint pains.[4] The virus is responsible for major outbreaks of febrile arthralgia in humans,[5] but until the recent outbreaks of chikungunya fever on the islands in the Indian Ocean was not associated with fatal disease. For many years chikungunya fever has occurred in or near many of the forested regions of Africa, among simians and humans. Arthropod vectors include sylvatic *Aedes* spp. mosquitoes (particularly *Aedes furcifer-taylori*, *Ae. luteocephalus* and *Ae. dalzieli*) that feed on simian species in the African jungles and the nearby savannah regions. Neither the simians nor the vectors display clinical evidence of infection by the virus. Nevertheless, mosquitoes infected after taking a bloodmeal from infected monkeys amplify the virus, which, it has been suggested, may be transferred to the eggs, which are then deposited in the forests. It is believed that, in common with certain other arboviruses, CHIKV may survive for long periods of time in these eggs. If this is the case, then during rainy periods, these transovarially infected eggs would hatch and subsequently produce adults able immediately to transmit virus to susceptible primates.

As there are no field or laboratory data that can confirm this mechanism of long-term CHIKV survival, alternative hypotheses have been proposed. One suggestion is that the virus may survive in wildlife species through constant transmission cycles moving in epizootic waves.[6] Outbreaks in rural regions tend to be on a small scale and dependent upon sylvatic mosquito densities, which increase following periods of heavy rainfall.[7] Humans entering areas in which infected mosquitoes circulate may serve as incidental hosts for the mosquitoes and thus become infected. These humans may then provide a source of virus to infect peridomestic mosquitoes, which then become involved in the transmission cycle of the virus. In the case of urban-dwelling anthropophilic *Ae. aegypti* and/or *Ae. albopictus*, if either of these species becomes involved in the transmission cycle, a human epidemic may ensue in the urban community (Figure 1).

In general, human epidemics due to CHIKV in Africa occur at irregular intervals, varying widely from 3 to 20 years, usually coinciding with particularly rainy periods as described above. Conversely, some outbreaks in coastal East Africa in 2004 were associated with drought and inadequate socio-economic development. In these cases, it is believed that infrequent replenishment of water stores and breeding of mosquitoes in storage containers in close proximity to humans may have facilitated CHIKV transmission.[2] It seems reasonable to speculate that these coastal epidemics could have been the precursors to those that subsequently spread throughout the Indian Ocean islands. Previously, while African epidemics occasionally involved large numbers of urban/peri-urban-dwelling humans, they generally remained localised and rarely involved more than a few thousand individuals.

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In contrast to this typically sylvatic epidemiological picture of CHIKV in Africa, there have been many recent major outbreaks of chikungunya disease in the Indian Ocean, India, Malaysia and Sri Lanka.[8–10] The emergence of CHIKV as a human epidemic virus of major importance in the Indian Ocean surprised everyone, and it has taken a significant effort to understand the most important factors that contributed to its appearance and severity. Records show that the first of the recent outbreaks began in Kenya during June 2004. Subsequently, during January through March 2005 more than 5000 cases of chikungunya fever were reported on the Comoros islands and between March and June the epidemic started to be reported on Mayotte, Seychelles, La Réunion Island and Mauritius. By January 2006, it was also reported in Madagascar. All of these outbreaks are now known to have been caused by a single African strain of CHIKV transmitted to humans by *Ae*. *aegypti*.[8] As the epidemic intensity increased on the Indian Ocean islands, new outbreaks were reported in India, Thailand and subsequently Sri Lanka, although it is difficult to know precisely when the virus responsible for these particular outbreaks was introduced into these regions. By April 2006, it is estimated that up to one-third of the 777 000 population on La Réunion may have been infected with CHIKV. Undoubtedly, the figures for the neighbouring islands will have been at least proportionately similar, and while accurate figures for India, Madagascar, Sri Lanka and other parts of Asia are unknown, the virus has clearly spread very effectively in these countries.

It is of particular interest that the virus strain that has caused most of the epidemics in the Indian Ocean is believed to have originated in Central/East Africa, and it is widely assumed that this virus dispersed to the Comoros islands either via infected mosquitoes or humans. In support of this assumption is the recent phylogenetic evidence implying that the strain of CHIKV currently responsible for the outbreaks in India is closely related to the early La Réunion virus.[9] Thus at least 5 years before the Indian Ocean islands experienced their first major outbreak of chikungunya fever, a similar strain had dispersed from Africa to India. It therefore seems likely that the appearance of CHIKV in the Comoros islands in January 2005 represents a second wave of the virus out of Africa.[9] In contrast to the sylvatic nature of CHIKV in Africa and the recent outbreaks on islands in the Indian Ocean, which show seasonality, chikungunya fever in India and Southeast Asia is recognised as an urban disease, which may occur at most times of the year in the tropical zones. Thus, in Asia, a sylvatic virus cycle does not appear to be important for the maintenance of the virus. However, until very recently, in common with the typical human epidemics in Africa, CHIKV outbreaks in India were primarily associated with *Ae*. *aegypti*.

An interesting and scientifically important observation resulted directly from the study of CHIKV nucleotide sequences in La Réunion isolates collected in early 2005. These were compared with isolates made later in 2005. The early isolates closely resembled those from East Africa, but as the epidemic accelerated, later isolates showed significant sequence changes throughout the genome with one amino acid substitution: an alanine being substituted by a valine (A226V) in the E1 envelope glycoprotein. This particular amino acid substitution is interesting, as it appears to be found only in CHIKV isolated from *Ae*. *albopictus*. The situation is different in India. Phylogenetic analyses suggested that the CHIKV originating from East Africa, or Comoros, was introduced into India in 2006 and probably originated from an ancestor with an alanine at amino acid position 226 in the CHIKV envelope (E1) protein. However, in 2007, an infected traveller from India arrived in Italy, and within a few weeks, more than 200 indigenous cases of chikungunya fever had arisen. Surprisingly, this `Italian strain ITA07-RA1' (GenBank accession no. **EU244823**) had the A226V mutation in the E1 envelope glycoprotein. Thus, this mutation was either acquired in Italy, where *Ae*. *albopictus* is present or, more probably, was acquired in India, where both *Ae*. *aegypti* and *Ae*. *albopictus* are present). Seasonal synchronicity between the tropical Indian climate and the warm summer climate of northern Italy provided conditions

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suitable for mosquito breeding in both countries. This probably accounts for the successful establishment of the introduced CHIKV in northern Italy.[11]

These observations stimulated experiments to test whether or not the A226V substitution impacts on the ability of the virus to infect different vector species. *Aedes albopictus* trapped on La Réunion Island were tested for their sensitivity to infection by early and late isolates of CHIKV (A226 and A226V, respectively). Compared with the early isolate, the late isolate of CHIKV replicated and disseminated more efficiently in *Ae. albopictus*.[12] Using molecular methods and laboratory mosquito transmission studies it was conclusively demonstrated[13] that the single amino acid substitution of alanine for valine in the E1 glycoprotein directly influenced vector specificity by enhancing CHIKV replication and transmission efficiency in *Ae. albopictus*. These studies are consistent with the observation that the mutant virus caused an epidemic in northern Italy, a region lacking *Ae. aegypti*, but in which *Ae. albopictus* is known to circulate. Presumably, the A226V mutation must have been acquired independently from the identical mutation of the Indian Ocean isolates. Additional evidence supports the case for independent mutations. Chikungunya outbreaks were observed in Cameroon (2006) and Gabon (2007), where *Ae. albopictus* has displaced *Ae. aegypti*.[14,15] CHIKV strains from both outbreaks originate from the Central-African lineage (i.e. are distinct from the Indian/Indian Ocean isolates from the same period), but, in contrast to the original Central-African strains (transmitted by *Ae. aegypti*), both the Cameroon and Gabon isolates have the A226V mutation, implying an independent adaptive mutation in response to a similar requirement for transmission by *Ae. albopictus*. It is extremely rare for this phenomenon, known as `evolutionary convergence', to be observed in nature. These data therefore have important implications with respect to how viruses may establish a transmission cycle when introduced into a new area. Moreover, *Ae. albopictus* is now present in parts of southern Europe[8,16] and also North and South America.[17,18] Thus, evidence of the capacity for selection of this CHIKV adaptive mutational variant, presumably from a quasi-species population, increases the perceived risk that CHIKV might extend its range globally.

Aedes albopictus has effectively displaced *Ae. aegypti* on La Réunion Island. Such interspecific competition has been observed both in the wild and in an insectary,[19,20] but other factors, such as mosquito eradication programmes to reduce the risk of malaria, may also have contributed (Didier Fontenille, personal communication). These measures would probably be more effective against *Ae. aegypti* than *Ae. albopictus* due to the stronger urban preference of *Ae. aegypti*. Unlike *Ae. aegypti*, which is highly anthropophilic (preferentially feeds on humans), *Ae. albopictus* circulates much more widely in urban, peri-urban and rural areas and will feed upon a relatively broad range of vertebrate host species. Moreover, *Ae. albopictus* has adapted well to the activities of humans, such as the transportation, abandonment and storage of used car tyres (Figure 2) and transportation of plants, which provide small pools of water in which *Ae. albopictus* lay their eggs. However, appropriate climatic conditions such as warmth and humidity are also essential to enable efficient transmission and virus reproduction in the infected mosquitoes.

In summary, the success of CHIKV in invading the Comoros Islands and subsequently dispersing to Mauritius, La Réunion Island and other nearby islands, and also India and Malaysia, resulted from a combination of factors. Firstly, increasing human mobility and commercial transportation of scrap car tyres and other water-retaining objects such as plants, both into and out of Africa and also between and within the Islands, provided a mechanism for dispersal of *Ae. albopictus*. Secondly, adaptive mutation of CHIKV to *Ae. albopictus*, resulting in increased transmission and amplification in this successful mosquito species. Thirdly, the presence of an immunologically naïve human population, including tourists, providing a high number of susceptible individuals. Finally, the difficulties in rapidly

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implementing mosquito control measures and disseminating relevant information to local communities on the islands compounded the problems. It therefore seems reasonably safe to conclude that while climate change may have contributed to the epidemic outbreaks through a lack of socio-economic development, it is unlikely to have exerted a major influence on dispersal of the African virus to the Indian Ocean, India, Sri Lanka and Malaysia.

Currently, there are no vaccines or antivirals with which to control CHIKV epidemic outbreaks; thus, the only effective methods of avoiding infection are to reduce the number of potential breeding sites for *Ae. aegypti* and *Ae. albopictus* and to avoid exposure to infected mosquitoes.

3. Rift Valley fever virus

RVFV, which is primarily transmitted to animals and humans by *Aedes* spp. mosquitoes, may cause severe disease with high rates of abortion and fatal infections in livestock. RVFV is a member of the genus *Phlebovirus*, in the family *Bunyaviridae*. The virus was first identified in 1931 during an investigation into an epidemic on a farm in the Rift Valley of Kenya.[21] Humans that come into close contact with the blood, excreta and infected mosquitoes associated with clinically infected animals may also become infected. Most human cases are relatively mild, but some individuals develop much more severe symptoms that may present as ocular disease (0.5–2% of patients), meningoencephalitis (less than 1%), with residual neurological deficit and occasional fatalities, or haemorrhagic fever (less than 1%) with a case:fatality rate as high as 50%. Currently, a vaccine is available to immunise animals, but its use is usually confined to limitation exercises after an epidemic arises. Human vaccines have also been developed but to date they have been used mostly for occupational risk groups and military personnel. Clearly, unless vaccines are used on a very large scale in Africa, Rift Valley fever will continue to be a significant problem, particularly for livestock and humans associated with these animals.

A wide range of mosquito species, including *Aedes* (*Neomelaniconion* and *Stegomyia*), *Culex*, *Mansonia*, *Anopheles* and *Eretmapodites* are capable of transmitting the virus,[22] as is the sandfly *Phlebotomus duboscqi* (Diptera: Psychodidae).[23] While vector competence has not been determined for all of these species, most samples trapped during epizootics have tested positive for RVFV. Many other *Aedes* and *Culex* species have been implicated in disease transmission in different regions of Africa. RVFV has been shown experimentally to replicate in a wide variety of mammalian species, but there is considerable variation in the response to infections in the environment. Sheep, cattle, goats and camels are most frequently associated with significant epizootics, primarily because they usually outnumber other potential hosts in the regions where disease is observed. Mechanical transmission of the virus by *Culicoides* spp., and other insects such as the tsetse fly, none of which replicate the virus, has also been demonstrated.[24] This may be an important component of RVFV transmission and is largely attributable to the very high levels of virus found in the blood of sheep and cattle, combined with the phenomenon of interrupted feeding. During this process, the insect may feed on more than one host within a few minutes, thus mechanically carrying infectious virus from one animal to another without replication of the virus between the feeding periods.

The first recorded outbreak occurred in Kenya in imported sheep, with very large numbers of abortions and many deaths in newborn lambs and older animals. No symptomatic disease was observed in indigenous animals kept nearby. This implies that the virus had circulated relatively harmlessly for some time in Africa, among indigenous species, before its discovery in 1930. Subsequently, as animal trading with countries outside Africa increased, further outbreaks were reported in South Africa, sub-Saharan Africa and North Africa.

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On the basis of serological studies and epizootic reports, it is now known that RVFV is distributed widely in Africa, with only the arid regions of the Sahara desert and North West Africa apparently being devoid of this virus (Figure 3). Indeed, many outbreaks have occurred throughout the Ethiopian faunal region, but extension of the disease beyond this range occurred in Egypt, where a dramatic epizootic in late 1977 resulted in at least 600 human deaths and more than 60 000 severe clinical cases.[25] The total morbidity was thought to be measurable in hundreds of thousands, and the resources of the hospitals in the affected areas were severely strained by the numbers of cases presenting daily. The virus continued to disperse further afield, and in September 2000, Rift Valley fever cases were confirmed in Saudi Arabia and Yemen,[26,27] representing the first reported outbreak of the haemorrhagic disease outside Africa. This inevitably raises the question as to whether or not it is a sign of things to come, i.e., might RVFV subsequently disperse more widely into Asia and Europe? The virus continues to cause epidemics, and during the past 2 years several major outbreaks of haemorrhagic disease due to RVFV are known to have occurred in East Africa.

Disease outbreaks normally follow high rainfall, and are usually associated with floodwater plains or water-pans flooded for prolonged periods, and seasonally inundated wetlands known as *dambos*, which are widespread in Central and southern Africa (reviewed in Zuckerman et al.28). Major irrigation projects during the twentieth century have also contributed to outbreaks of RVFV; the resulting flooding on the African plains triggers the emergence of mosquitoes from the billions of eggs that are deposited by female adult mosquitoes. Furthermore, RVFV outbreaks in East Africa are closely associated with the heavy rainfall that occurs during the warm phase of the natural and relatively regular El Niño/Southern Oscillation (ENSO) phenomenon. There is usually little or no recognised virus activity during inter-epizootic periods (IEPs), which can vary between 1 and 40 or more years, depending on the local climate and ecology. RVFV characteristically causes rural and semi-rural, but not urban, epizootics among livestock, particularly breeds imported from outside Africa. Humans associated with these animals, either through their occupation (i.e. farmers, shepherds, abattoir workers, etc.), or through the sharing of common housing with the animals, are the most likely to be infected as the result of close contact with the blood, tissues and excreta of these infected animals or when they are inadvertently exposed to the bites of infected mosquitoes, which are attracted to the herded animals.

Climatic conditions are clearly an important driver of Rift Valley fever, because the primary vectors of virus transmission to animals and humans are *Aedes* spp. mosquitoes. Direct evidence that these mosquitoes can harbour the virus for long IEPs was obtained by artificial flooding of the *dambo* formations in an epizootic area in the Central Highlands of Kenya. Millions of *Ae. mcintoshi* larvae hatched and RVFV was isolated from the adult mosquitoes (including males), raised in the laboratory from the field-collected larvae. Thus, transovarial transmission of the virus provides a plausible explanation for the survival of the virus during the IEP and for its simultaneous emergence throughout epizootic areas, exhibiting similar environmental conditions. Indeed, River Valley fever cases have occurred in areas separated by a thousand kilometres or more, virtually at the same time. Remote sensing satellite imagery is now being used to study a variety of environmental parameters, such as cold cloud density and intensity of green vegetation, in order to evaluate their potential to predict the emergence patterns of mosquito vectors of RVFV.[29] As knowledge and understanding of the information gained from these remote sensing methods increases, it is hoped that they can assist in the implementation of more effective vaccination and vector control programmes before an epidemic and thus reduce the spread of RVFV.

In conclusion, climatic conditions have clearly been an important determinant of RVFV epidemiology in Africa and the Arabian Peninsula over a long period of time, and climate change could theoretically create conditions in southern/central European countries and the

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US that might enable introduced RVFV to become established in these regions. However, in addition to climate change, other factors, such as the movement of infected animals and/or competent mosquito vectors into non-RVFV regions, will determine whether or not the virus disperses beyond its current boundaries.

4. West Nile virus

WNV is a member of the genus *Flavivirus*, in the family *Flaviviridae*. The virus is antigenically and genetically closely related to other flaviviruses in the Japanese encephalitis virus serological complex,[30–32] many of which cause human encephalitic infections in tropical and subtropical regions worldwide. On the basis of serological studies, virus isolation, and PCR-sequencing using samples obtained from healthy birds, horses, mosquitoes and ticks, there is now compelling evidence that WNV circulates widely and relatively harmlessly in Africa, Europe and many parts of Asia and Australasia among birds, horses, a range of other animal species and humans.[33–36]

In the Old World, WNV is most frequently associated with ornithophilic *Culex* spp. mosquitoes, which amplify the virus and transmit it to resident and migratory birds, thus facilitating the observed wide geographic dispersal of WNV. Detailed phylogenetic analyses of WNV strains originally identified two major clades of WNV, defined as lineages I and II. The lineage II viruses were primarily isolated in sylvatic African environments and were rarely associated with human epidemic outbreaks, whereas the lineage I viruses were mostly obtained during outbreaks of West Nile fever/encephalitis in Africa, southern Europe, the Russian landmass, India or Australia.[37] Subsequently, several new isolates of WNV from mosquitoes and/or ticks in the Volga region of Russia[38] and in the Czech Republic[39] have shown greater genetic diversity, implying the possibility of further evolutionary divergence as these viruses have dispersed into more northerly climates.

The implications of the phylogenetic data, combined with the widespread serological evidence of WNV throughout Africa,[40,]41 are that this virus originated from ancestral African lineages less than 2000 years ago42 and was dispersed out of Africa via migratory birds.43,[44] This argument is supported by several independent studies. Firstly, in the UK, healthy resident and migratory birds and sentinel chickens were shown to possess neutralising antibodies and viral RNA specific for WNV and Usutu virus (USUV).[33,]35 Secondly, similar findings have been reported in many European and Asian countries, including Spain, France, Portugal, northern Italy, Poland and the Czech Republic.45–53

From a virological perspective, this is not surprising, as Ockelbo virus, a close relative of the African alphavirus, Sindbis virus, has been isolated from humans suffering with polyarthritis in Scandinavia.[54,55] It seems most likely that Ockelbo virus was introduced into Scandinavia by birds migrating from Africa. Moreover, as cited above, both WNV and USUV RNA sequences have been detected in mosquitoes collected in Portugal and Spain, i.e. regions of Europe directly beneath avian migratory flight paths to the UK and Scandinavia.

It is to be emphasised that the evidence of WNV, or indeed USUV and the alphavirus, Sindbis virus, circulating among birds and possibly humans in the UK does not necessarily imply that under the present climatic conditions these arboviruses are causing human epidemics. It is likely that the significant levels of immunity in avian species and indeed in humans (unpublished results), combined with the relatively low mosquito densities in the UK, provide a barrier to epidemics equivalent to those occasionally observed infrequently in central Europe, southern Russia, or the Mediterranean Basin. Recent evidence, based on sequencing and phylogenetic analysis, supports previous observations that both lineage II and lineage I viruses are carried long distances by migratory birds,36,56 supporting the

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belief that these viruses could circulate at low levels in many species in northern Europe. Climatic conditions in northern Europe are rarely suitable for the development of the high density populations of competent mosquitoes that would be required to ensure efficient transmission between arriving infected birds (carrying the virus from Africa) and UK residents. Nevertheless, the frequent introduction of strains of WNV from warmer geographic regions would at least in part explain why low-level immunity does appear to be present in different wildlife species.

In contrast to the UK, some regions of North America have a climate that is conducive to the development of high mosquito population densities. To a certain extent this explains why, during the late summer of 1999, the discovery of unusually high numbers of dead birds (particularly corvids) and cases of human encephalitis in New York residents heralded the first appearance of WNV in North America.[57] Subsequent studies using nucleotide sequencing of the virus showed it to be closely related genetically to a strain of WNV from Israel (Isr98). The first isolation of the virus was from birds at the Bronx Zoo, and it has therefore been suggested that it could have been inadvertently introduced via imported birds on an incoming flight to New York Kennedy Airport, from Israel or Egypt.34 The weather in New York during the spring and summer of 1999 had been particularly warm and humid, conditions that favour intensive mosquito breeding and efficient arbovirus transmission.58

During the period between the commencement of the outbreak of West Nile fever/ encephalitis and the onset of winter in 1999, when mosquito feeding activity stopped, hundreds of bird deaths were recorded in the metropolitan area of New York City, with 28 counties showing evidence of the presence of WNV in birds. Several cases of West Nile encephalitis were also identified in horses, and in total 69 human cases of meningoencephalitis were diagnosed, with seven fatalities. On the basis of seroepidemiological evidence and a survey of individuals in the epicentre it was estimated that thousands of asymptomatic or very mild viral infections occurred, with less than 1% resulting in severe neurological disease.[59]

The initial localised distribution of WNV in the New York area (Figure 4A) and the subsequent pattern of dispersal across North America (summarised in Figure 4) during the ensuing years was remarkable, although, perhaps in the light of our knowledge of WNV in the Old World, not so surprising. By the end of the year 2000, WNV had been detected in birds in 136 counties, predominantly in those that surrounded the original 28 positive counties from 1999; but in addition the virus had clearly begun to disperse southwards on the eastern side of the US (Figure 4B). Early in 2001, the virus was isolated in Florida and later in the year in the midwest and north to the Great Lakes (Figure 4C). Moreover, the first WNV-positive bird was identified in Ontario, Canada in August 2001. The virus continued to disperse westwards during 2002, and although the Rocky Mountains initially appeared to be a barrier to its dispersal, WNV was eventually isolated in birds in California during 2002 (Figure 4D). By the end of 2003, the virus had been identified in almost every mainland state of the US (Figure 4E) and was beginning to be identified in Mexico and the Caribbean. The virus has since been identified as far south as Argentina.

Following its introduction into North America, considerable resources were provided with which to study all aspects of the virus. It quickly became clear that WNV in North America had found a highly susceptible environment in which to amplify and disperse. In addition to avian species and humans, the virus has been shown to infect an extremely wide range of other mammals, and even reptilian species. Moreover, WNV has been isolated or demonstrated to be present in 62 different mosquito species (http://www.cdc.gov/ncidod/dvbid/westnile/mosquitoSpecies.htm [accessed July 2008]).[60] Also of major concern was the discovery that the virus can be transmitted to other humans

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via the blood and organs of apparently non-infected individuals.[61,62] There is also circumstantial evidence for transmission of the virus from mother to infant during breastfeeding.[63] Moreover, there is evidence based on laboratory investigations to suggest that WNV can be transmitted non-viraemically between infected and non-infected mosquitoes.[64] If this mechanism of virus transmission does occur in the wild, it effectively overcomes the barrier of host susceptibility and thus increases the likelihood/efficiency of virus dispersal.

Overall, phylogenetic evidence supports the concept that WNV has been introduced into North America and become established there only once. Nevertheless, several studies have concluded that although WNV remains a relatively homogeneous virus population, with the most divergent strains containing only a few nucleotide and/or amino acid substitutions, a single WNV genotype that differs from the introduced strain has arisen since 1999 and has become dominant, largely displacing previously circulating strains throughout North America.[65–70] Therefore, it appears to be undergoing a process of adaptation to local transmission cycles.[71]

Interestingly, because the virus was frequently isolated both from sick and healthy birds it was widely assumed that migratory birds were responsible for the observed dispersal patterns that appeared to follow the recognised bird migratory routes. However, for some time it proved difficult to produce direct evidence that infectious migratory birds (i.e. birds that develop viraemia) are responsible for the observed pattern of WNV dispersal. This has now been evaluated by experimentally infecting birds in migratory disposition. These birds display increased locomotor activity or restlessness, which can be recognised under captive conditions. The results of this investigation support the concept that migrating passerine birds are probably the dispersal vehicles for WNV.[72]

Another recent and interesting discovery as the result of the studies on WNV in North America also relates to migratory birds. It has been known for some time that in the more northerly parts of North America the peak incidence of WNV infections in humans occurs in the late summer and early autumn period of the year. Studies of the primary ornithophilic arthropod vectors of WNV in north east America, *Cx. pipiens*, and in California, *Cx. tarsalis*, suggest that these mosquito species shift their feeding preferences from birds to mammals in the late summer, when the birds become less numerous as they begin to migrate south.

This shift of feeding preference by *Cx. pipiens* may have a significant impact on WNV epidemiology in the northeast and north central parts of North America. A similar shift in feeding preference of *Cx. tarsalis* appears to have the same impact on WNV epidemic intensity in west and central North America. This can be explained as follows: the feeding preference for avian species in the early period of the summer intensifies epidemics of WNV infection among avian species, thus increasing the proportion of infected mosquitoes. The shift of feeding preference to mammals in the late summer then intensifies the epidemics in humans.[71] These observations, at least in part, could also explain why WNV appears to have been more virulent for birds and causes a higher number of human infections in the New World than in the Old World. Other possible contributory factors to the increased intensity of epidemics in North America include: (1) the lack of immunity in mammalian populations in North America before the introduction of WNV;[73] (2) the fact that *Cx. pipiens* in the New World is a hybrid between European *Cx. pipiens*, a bird-biting mosquito, and *Cx. molestus*, a human-biting mosquito;[74] and (3) the possibility that the strain of WNV introduced into North America is more virulent for American crows than for those circulating in the Old World.[75]

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Although environmental conditions, in terms of local temperature and rainfall, are clearly very important in determining whether or not WNV is efficiently transmitted between vertebrates and mosquitoes, climate change, in terms of progressive increases of average temperature and rainfall, has not played an obvious role in the epidemic outbreaks of WNV seen in North America. The most important factors have been the availability of competent vector species and the wide range and large numbers of susceptible species of migratory birds that have dispersed the virus throughout the Americas. Human activity, in the form of animal transportation, farming practices, blood transfusion, organ transplantation, leisure activities, sanitation infrastructure, etc., have also contributed to local outbreaks and possibly, through air transport, to the original introduction of the virus from Israel/Egypt into the Western Hemisphere.

Currently there are no vaccines or antivirals with which to prevent and control WNV encephalitis in humans, although it is possible that individuals immunised against Japanese encephalitis virus, tick-borne encephalitis virus and yellow fever virus would be protected against the severest forms of infection by WNV as the result of immune cross-reactivity.

5. Bluetongue virus

Although BTV has been the subject of intense molecular and structural studies, the epidemiology and geographic dispersal of BTV have also been a major subject of interest to virologists and entomologists, because this virus is pathogenic for a range of domestic and wild ruminants. Seasonal incursions of the virus from Africa into more temperate latitudes, sometimes accompanied by disease, have occurred under favourable climatic conditions, but the recent introduction of serotype BTV-8, and the establishment of a transmission cycle that has resulted in its spread into northern Europe including the UK (see below), is of significant economic importance. BTV is a member of the genus *Orbivirus* in the family *Reoviridae* but, unlike many other arboviruses, does not infect humans and therefore is not zoonotic. There are 24 recognised serotypes of the virus, which contain between 10 and 12 segments of double-stranded RNA. Until recently BTV was considered to be almost exclusively a disease of some European breeds of sheep that, for commercial purposes, have been distributed widely in Africa, Asia and Australasia. In cattle and goats, clinical disease has been considered rare, and much milder than in sheep.[76] However, recent observations suggest that cattle frequently show disease symptoms resulting from infection by the BTV-8 serotype that is currently circulating in northern Europe (see below). There is evidence that infected midges are carried on the wind for long distances,[77,78] and it has been postulated that the major epidemics of bluetongue, in regions where disease occurs only sporadically, result from wind-borne carriage of infected *Culicoides* from distant endemic areas.79 Competent midges may be infected when biting viraemic vertebrates. The probability of infection depends in part on the genotype of the midge, the strain of virus, the level of viraemia and environmental factors.[80] The extrinsic incubation period (the period between feeding on infected blood and the appearance of virus in the saliva of the arthropod vector) is 1–2 weeks. Contrary to the BTV strains referred to above, the recent appearance of BTV-8 in northern Europe, including the UK, has unexpectedly been accompanied by the appearance of overt disease and mortality in cattle. Moreover, as the result of currently unpublished evidence reported by Dr Oura on 20 March 2008,[81] it is now recognised that healthy infected animals may remain ELISA- and RT-PCR-positive for at least 4 months.82 This observation helps to explain how BTV-positive animals may be detected in mid-winter in the UK when midge transmission activity is presumed to be minimal.

Symptoms of BTV infection in sheep are variable but typically include fever. Facial oedema results in swelling and soreness of the lips and nose with mucopurulent discharge, which is exacerbated by champing to produce frothy saliva. The term `bluetongue' is derived from the

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cyanosis of the tongue that is observed in some cases. Erosion of the coronal band above the hooves and musculoskeletal damage cause pain and lameness, inducing the sheep to adopt a posture similar to that shown in Figure 5.

BTV circulates widely throughout tropical and subtropical regions, but until relatively recently the disease had been observed only infrequently in some areas of southern Europe. However, during the past decade, six strains of BTV are known to have spread across 12 European countries, and significantly the virus has gradually dispersed further north in central and western Europe. This dispersal has probably been driven by the northward expansion of the range of *Cu. imicola*, the main BTV vector, and by climate change, which has probably contributed to increased persistence during winter, consequently increasing the subsequent risk of transmission over larger geographical regions[83] and an extended period of time. To the north of the *Cu. imicola* range, other species (*Cu. obsoletus*, *Cu. pulicaris*, *Cu. chiopterus* and *Cu. dewulfi*) with distributions extending across central and northwestern Europe[84] were probably involved in the appearance of BTV-8 in Belgium, France, Luxembourg, Germany and the Netherlands in August 2006, and subsequently in the UK in September 2007.[85] This presence of multiple vectors of BTV-8 appears to apply to large parts of northern Europe and has almost certainly contributed to the dramatic spread of this arbovirus across this area. In addition to the impact of climate change on vector range expansion and the northerly establishment of BTV-8, the commercial transportation of asymptomatic infectious ruminants and the wind-borne dispersal of infected midges are believed to be highly significant contributory factors to the rapid dispersal of the virus. Understanding this sequence of events may aid predictions of the emergence of other vector-borne pathogens, such as the more devastating African horse sickness virus, another animal pathogen in the genus *Orbivirus* that may be transmitted by several of the same vectors as BTV.

Another important observation has appeared as the result of the incursion of BTV into northern Europe. Conventional opinion has previously considered it extremely unlikely that BTV could be transmitted vertically to newborn offspring. New evidence suggests that this virus may be transmitted across the bovine placenta to infect the fetus, causing an unusually high rate of malformed, stillborn and weak calves born on holdings with a known history of BTV infection.[86] At the time of writing, this observation has not been confirmed through systematic investigation. Nevertheless, whether or not this represents an acquired new characteristic of BTV-8 clearly needs close attention. Transplacental infection has only previously been associated with attenuated BTV vaccine viruses. In further support of these reports, the recent unpublished finding of imported heifers in Northern Ireland, leading to the suspicion that newborn calves infected *in utero* can act as virus reservoirs for the *Culicoides* vector, is another worrying development that needs immediate investigation.

Methods for controlling BTV include reducing exposure of the animals to the competent midges, the use of insecticides to dissuade the insects from biting the animals, and the use of vaccines. While the strategies of reducing exposure and using insect repellents might reduce the levels of BTV transmission, clearly these measures cannot be expected to eradicate BTV from northern Europe. Vaccination is associated with several practical difficulties. Firstly, there are 24 serotypes of BTV, and while there is some antigenic cross-reactivity between different serotypes, the preparation of a single live attenuated virus multivalent vaccine to protect against all 24 is impractical, partly because different serotypes may outcompete each other in the vaccine, partly because at the moment only BTV-8 is circulating in northwestern Europe and partly because of the costs and time involved in producing a multivalent vaccine. Moreover, the use of live attenuated vaccines presents a low but potential risk of reversion to virulence, or in some circumstances the possibility of reassortment of the RNA gene segments between different serotypes of BTV. However, for reasons beyond the

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control of the manufacturers, the production of a vaccine in time to prevent the reemergence of BTV-8 in northern Europe during 2008 is proving to be seriously problematic. It will be interesting to see whether or not BTV-8 is brought under control in the UK and northern Europe during 2008. Non-infectious vaccines based on engineered recombinant proteins are also under development, but in addition to the requirement for multiple dosing, these vaccines are likely to be expensive and therefore not favoured by farmers.

6. Conclusions

We have briefly described four different arbovirus diseases that have recently emerged outside their usual endemic range and discussed the question, can climate change explain these incursions? The answer is different for each of the four viruses. Firstly, as arthropods are a critical component of the transmission cycle, they are all inevitably dependent on specific climatic conditions for their epidemicity. Nevertheless, each virus has emerged and become established in new areas primarily as the result of: (1) human travel and/or invasion by foreign species (CHIKV); (2) climatic conditions and/or commercial transportation of animals (RVFV, BTV); (3) natural patterns of bird migration (WNV). In the case of CHIKV, a single mutation in the viral genome that facilitated adaptation to the mosquito species *Ae. albopictus* has played a major role in its emergence. We cited the transportation and mass storage of scrap car tyres and plants as primary methods by which this mosquito species has dispersed globally in the tropics and subtropics. If global climate change is taking place, and if it continues according to the predictions of some experts, *Ae. albopictus and Ae. aegypti* will disperse beyond their current geographic boundaries, and we could expect to see more cases of epidemic outbreaks typified by the incursion of CHIKV into northern Italy. One cannot ignore the possibility of outbreaks of other arboviral diseases for which these species are the primary vector, namely Dengue virus and Yellow fever virus. In the case of RVFV, climate has always been the major factor for the onset of new outbreaks, due to emerging competent mosquitoes in flooded areas. Human activities, including irrigation projects, the movement of herded animals and importation of animals to feed large numbers of humans, for example pilgrims to Mecca, have almost certainly contributed significantly to RVFV epidemics.

Climate change may play a greater role if the specific environmental conditions required for the development and maintenance of appropriate competent vector species become established in regions beyond the Arabian Peninsula. Epidemics of WNV encephalitis in Europe have always correlated with warm and humid summers; thus, once again climate is an important factor. However, the presence of large numbers of susceptible migratory birds, the availability of competent vectors and human commercial and leisure activities have been major factors in the emergence of WNV in Europe as a human epidemic virus. As this virus already circulates in northern Europe, via migratory birds, the induced low levels of immunity might be expected to reduce disease severity in northern Europe. The impact of climate change may be to move the disease further north by increasing virus transmission efficiency (increased vector population densities and vector—vertebrate encounters, and shorter extrinsic incubation period), but new vaccines and antivirals that are being developed may provide the means by which this virus can be controlled. Finally, BTV is a proven example of a virus that has moved into and become established in northern Europe, partly as the result of climate change. Nevertheless, the exportation of animals across Europe and other factors such as wind-borne midges have clearly contributed to the northerly dispersal of BTV.

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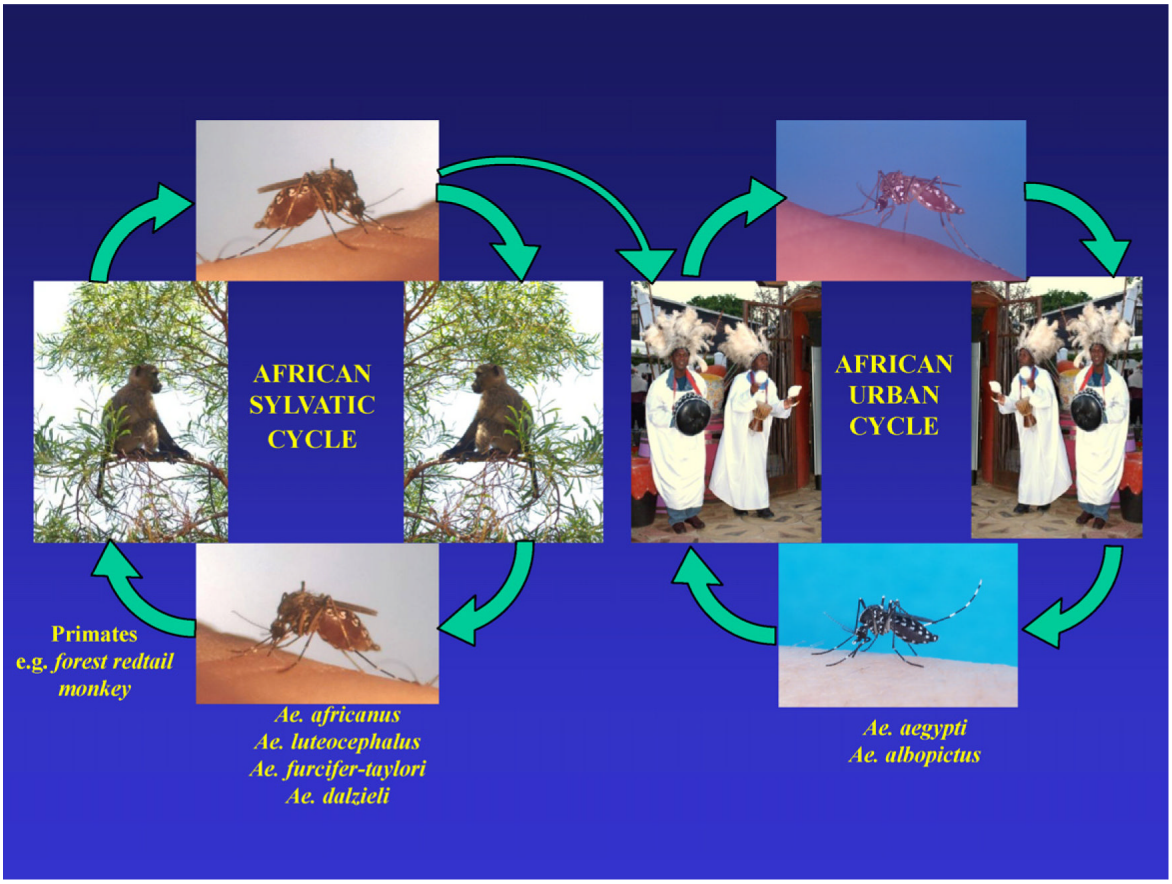

Figure 1.
Representation of chikungunya virus life cycle in Africa.

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Figure 2.
Pools of water in scrap tyres are breeding grounds for mosquito larvae.

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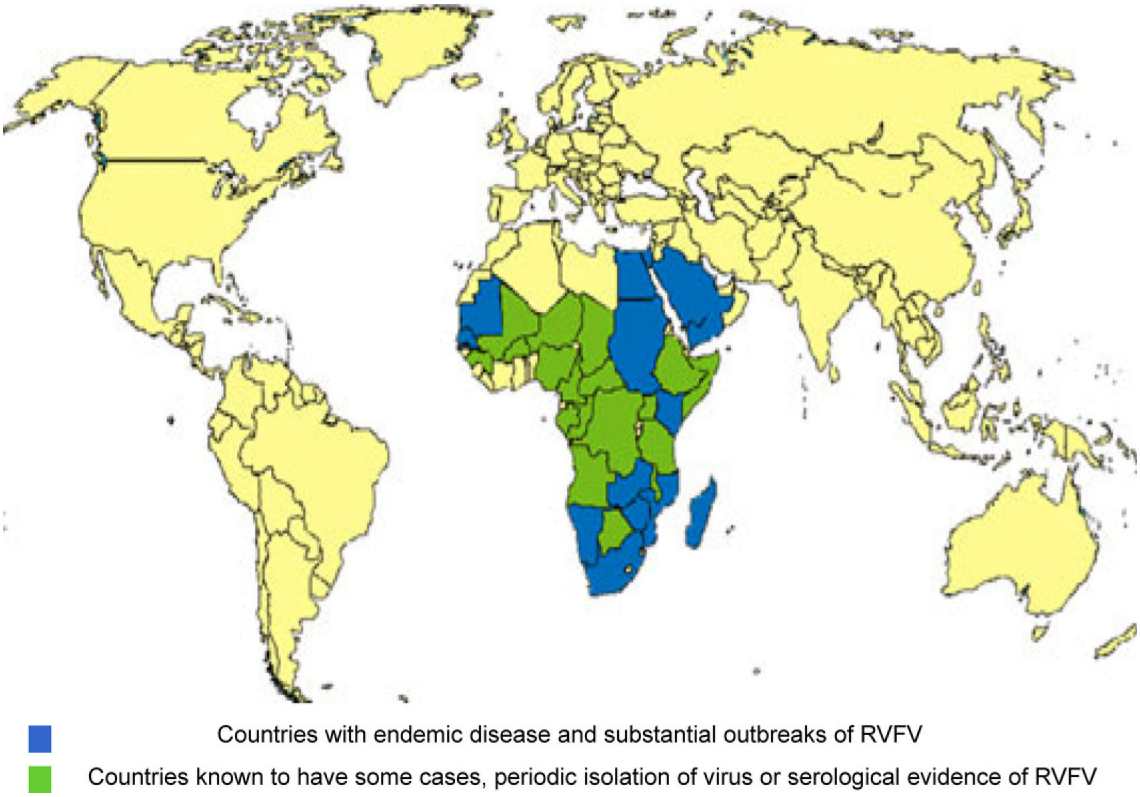

Figure 3.
Geographic distribution of Rift Valley fever virus (RVFV) (source: http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/rvfmap.htm).

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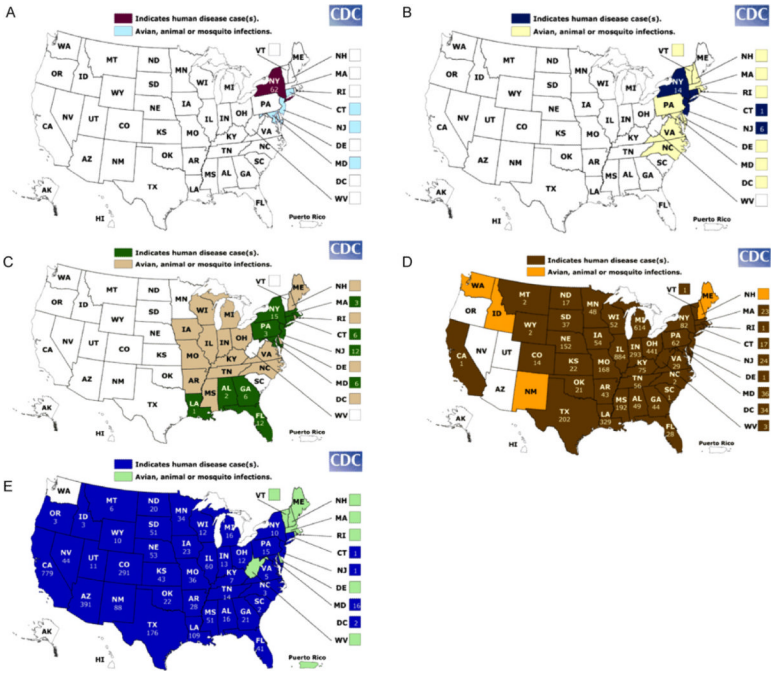

Figure 4.

Dispersal of West Nile virus in the USA during: (A) 1999; (B) 2000; (C) 2001; (D) 2002; (E) 2003 (source: http://www.cdc.gov/ncidod/dvbid/westnile/background.htm).

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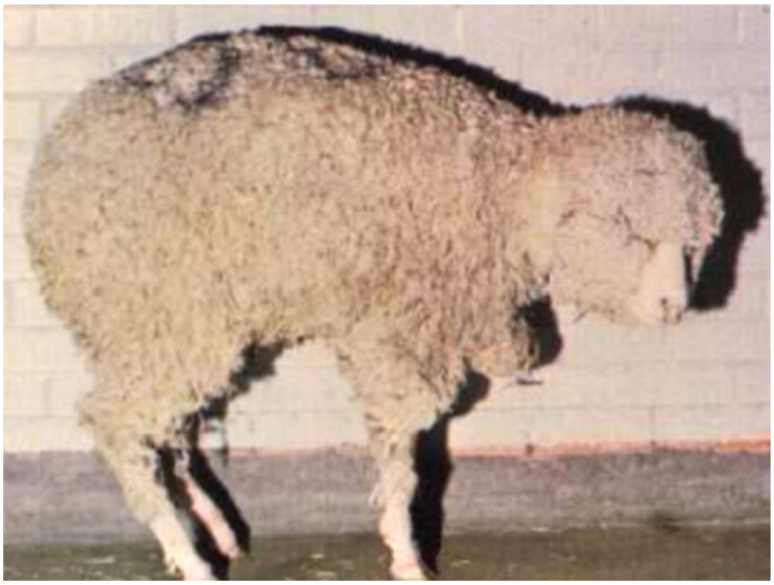

Figure 5.
Posture often observed in cases of bluetongue infection in sheep (source: http://129.186.78.52/DiseaseInfo/ppt/bluetongue.ppt#17).