Reservoirs and Vectors of Emerging Viruses

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ABSTRACT

Wildlife, especially mammals and birds, are hosts to an enormous number of viruses, most of which we have absolutely no knowledge about even though we know these viruses circulate readily in their specific niches. More often than not, these viruses are silent or asymptomatic in their natural hosts. In some instances, they can infect other species, and in rare cases, this cross-species transmission might lead to human infection. There are also instances where we know the reservoir hosts of zoonotic viruses that can and do infect humans. Studies of these animal hosts, the reservoirs of the viruses, provide us with the knowledge of the types of virus circulating in wildlife species, their incidence, pathogenicity for their host, and in some instances, the potential for transmission to other hosts. This paper describes examples of some of the viruses that have been detected in wildlife, and the reservoir hosts from which they have been detected. It also briefly explores the spread of arthropod-borne viruses and their diseases through the movement and establishment of vectors in new habitats.

Highlights Panel:

- Wildlife, especially mammals, are reservoirs for an enormous diversity of viruses
- Bats and rodents are reservoirs for many viruses causing human and animal diseases
- Knowledge of viruses and their reservoirs may help predict future pandemic viruses
- Anthropogenic factors assist the spread of novel viruses from reservoirs to humans
- Arthropod vectors moving into new habitats may help the spread of arboviral diseases

INTRODUCTION

It is now 10 years since the world was faced with the first severe and readily transmissible new disease to emerge in the 21st century, Severe Acute Respiratory Syndrome (SARS). SARS was a disease that threatened to become a global pandemic as the virus spread rapidly along major air routes, but which was contained within 4 months of its first alert due to unprecedented international cooperation and collaboration [1]. One of the legacies of the outbreak has been a greater awareness of zoonotic diseases and of the need to better understand how and from where novel zoonoses emerge , and the factors which pertain to cross-species transmission. These are crucial to early detection of potential future threats [2].

The concept, definitions and concerns associated with disease emergence were encapsulated in two Institute of Medicine reports, which defined the major issues and described the major causes and mechanisms leading to infectious disease emergence, as well as discussing possible strategies for recognising and counteracting the threats [3,4]. The association of disease emergence with anthropogenic activities is well established, especially the effects of land changes and modifications including extraction industries, rapid movement of people, globalisation of trade, human encroachment on natural environments, and climate change [5-10]. More than 60% of emerging diseases are zoonoses, the majority of which arise from a wildlife source [8]. As more information has been generated about the underlying drivers or causes of emergence, there has been an expectation that it might eventually be possible to predict or forecast the emergence of novel pathogens [11,12,13], but until now, there has been little apparent success in predicting where and when a novel pathogen might arise, nor the spill-over events which might precede emergence. Nevertheless, there has been an unprecedented search for novel pathogens over the past decade, especially in at the human-animal interface in wildlife and domestic species, fuelled in part by SARS and by post-SARS concerns raised by H5N1 highly pathogenic avian influenza and H1N1(2009) pandemic influenza, and supported by the development of new technologies for detection and identification such as high throughput sequencing technologies and by the initiation of new pathogen discovery programs such as the PREDICT program funded by USAID [13]. During the decade, many new viruses have been described from wildlife belonging to a range of virus families, including Coronaviridae, Bunyaviridae, Astroviridae, Rhabdoviridae, Flaviviridae, Filoviridae, Paramyxoviridae, Adenoviridae, and Reoviridae. Most of the wildlife reservoir hosts of known viral pathogens and many novel viruses can be found in the mammalian Orders Rodentia, Chiroptera, Primates, Carnivora, as well as in birds. It is not possible to explore all of these wildlife reservoirs and

hosts of novel viruses, but rather this short review will concentrate on a few specific examples chosen because they represent recent reports of diversity or geographic spread.

WILDLIFE RESERVOIRS

Prior to the emergence of SARS, there had been a growing awareness of the importance of bats as reservoirs or hosts of novel diseases [14,15]. This is not unexpected given that they constitute 20% of known mammalian species, have unique and diverse lifestyles including the ability to fly, they often have gregarious social structures achieving incredible abundance and densities, some cave-dwelling bats reaching up to 500 individuals per square foot, and they have long life spans. Importantly they also frequently live in very close proximity to humans, often interact closely with livestock and other domestic animals that are potential intermediate hosts for human pathogens, and with habitat loss due to land changes, are therefore very much at the wildlife-human interface [16]. Bats are grouped into two suborders, Megachiroptera and Microchiroptera; the former comprises a single family, Pteropididae, containing 42 genera and 166 species of fruit bats and flying foxes which do not use echolocation; and the latter comprises 18 families of 135 genera and 917 species, most of which use echolocation. Thus bats provide a rich and diverse source of potential reservoirs. Prior to SARS, Pteropid fruit bats had been found to be the reservoirs of a number of novel viruses able to infect humans, including two new paramyxoviruses, Hendra [17,18] and Nipah [19,20] viruses which together formed a new genus, Henipaviruses, within the Paramyxoviridae, as well as two rubulaviruses, Tioman [21] and Menangle [22] and a new lyssavirus, Australian bat lyssavirus [23]. This latter virus, which is closely related to classical rabies virus, was also found in at least one species of insectivorous bat [24,25], but has not crossed into terrestrial wildlife or domestic animal hosts. Thus, it is clear that RNA viruses associated with Old World fruit bats pose zoonotic disease threats of high public health significance. Insectivorous bats have also been strong candidates as potential reservoirs, as demonstrated by their role as reservoirs of rabies and rabies-like Lyssaviruses in Europe, Africa and elsewhere in the Old World, and in the Americas. It was therefore not surprising that bats were the major initial target in the search for the natural reservoirs of SARS coronavirus (SARS-CoV).

The search for reservoirs of SARS and other novel coronaviruses in bats

In the decade since SARS, there has been a plethora of new viruses reported from bats. Only a few of these new viruses were cultured; some of the other viruses had their genomes fully sequenced using RT-PCR . Most of the more recent viruses have been detected using new high-throughput sequencing technologies which have revolutionised the ability to detect genomic fragments both in

terms of their exquisite sensitivity and speed, but also in a greatly reduced cost [26]. A problem of the technology is that only partial genomes are usually detected and identified and and although this can provide insights into virus evolution and phylogeny, it does nothing to assist in understanding virus ecologies nor in predicting which, if any, may be potential pathogens.

Studies conducted on animals sampled from live animal markets in Guangdong, China, during and immediately after the SARS pandemic indicated that masked palm civets (*Paguma larvata*) and two other species had been infected by SARS-CoV (27), but no evidence of infection was detected in wild or farmed civets [28-30] indicating they were probably spill-over hosts rather than natural hosts of the virus. The finding of SARS-CoV-like viruses in Chinese horseshoe bats from the from the genus Rhinolophus [31-34], however, clearly suggested that bats could be a potential reservoir of SARS-CoV, and possibly even the natural hosts for all presently known coronavirus lineages [35]. A large number of studies have since demonstrated further SARS-CoV-like viruses and an astonishing diversity of other coronaviruses belonging to alpha- and beta-coronavirus genera in the subfamily Coronavirinae occurring widely in bat species in most parts of the world including Africa [36-38], Europe [39-43], the Americas [44-49] and Asia [50-52].Interestingly, an analysis of viruses isolated from bats in Mexico showed that host species was a strong selective driver in coronavirus evolution, and that a single species of bat can maintain multiple coronaviruses. Furthermore, phylogenetic association of CoVs with host species/genus was particularly evident in allopatric populations separated by significant geographical distances[49]. A similar diversity of coronaviruses has also been found in birds, comprising the gamma-coronaviruses [53], and a new genus, the delta-coronaviruses recently described with viruses from birds and pigs [54].

The extraordinary diversity uncovered in these viruses over the past few years is largely due to the high frequency of recombination in coronaviruses [55] and the high rate of mutation found generally in RNA viruses, but aided by their worldwide dispersal and spread in flying hosts, bats and birds. The importance of understanding the diversity of these viruses was exemplified by the recent isolation of a novel coronavirus from a fatal human infection in Saudi Arabia, with further cases in Qatar and Jordan. The virus was isolated from the sputum of a fatal case of acute pneumonia with renal failure and with a clinical presentation that closely resembled that of SARS [56]. Phylogenetic analysis showed the novel coronavirus to be related to two bat coronaviruses, *Tylonycteris* bat coronavirus HKU4 and *Pipistrellus* bat coronavirus HKU5 [56,57], and is the sixth coronavirus known to infect humans. The new virus is able to replicate in bat cell cultures representing four major chiropteran families from both suborders, as well as in cell cultures from pigs and humans, indicating that it may use a receptor conserved between bats, pigs and humans

and suggesting a low barrier against cross-host transmission [58]. The emergence of this novel coronavirus clearly demonstrates the importance of uncovering and understanding the wildlife reservoirs and their potential for human infection.

Bats as reservoirs of Filoviruses.

The natural reservoir of Filoviruses (Ebola and Marburg viruses) was the subject of considerable conjecture for over 30 years [59]. The first indication that bats might be involved came from some experimental infection studies; it was found that some species of fruit and insectivorous bats supported virus replication and circulation of high titres of virus without necessarily falling ill [60]. Asymptomatic infection with Zaire Ebola virus was subsequently found in three species of fruit bat in Gabon and the Republic of the Congo [61,62]. Fruit bats were later believed to be the source of an Ebola outbreak in 2007 in the Democratic Republic of the Congo (DRC), supporting the contention that they are the natural reservoir hosts [63]. About the same time, Marburg virus was also detected in fruit bats in Gabon; this was particularly interesting as the virus had not been known to be present in Gabon, and thus extended the known range of the virus [64]. That bats were the reservoirs of Marburg virus was most clearly demonstrated by studies carried out near a mine in the DRC where there was an ongoing and protracted Marburg outbreak over two years in 1998-2000. Marburg viral genomic sequences were detected in various tissues collected from 12 bats comprising two species of insectivorous bats, *Rhinolophus eloquens* and *Miniopterus inflatus*, and from *Rousettus aegyptiacus* fruit bats, which shared the same mine/cave habitat [65]. Although no infectious virus could be isolated from the bats, 12 genetic variants were detected, six of which were also found in human isolates circulating during the outbreak, providing strong circumstantial that the bats were the source of the outbreak. An additional bat variant was similar to an earlier human isolate from Zimbabwe in 1975 [65]. Subsequent serological investigations confirmed that Zaire Ebola and Marburg viruses in Gabon were co-circulating in bats, with evidence of Ebola virus in six species and Marburg in two species, and the highest seroprevalence to both viruses was found in *Rousettus aegyptiacus* [66]. Seropositive fruit bats for Ebola virus were also reported from Ghana [67], and it is probable that Ebola and Marburg viruses will be found anywhere over the range of their bat hosts.

In Asia, serological evidence has suggested that *Rousettus amplexicaudatus* fruit bats may be the reservoir of Reston Ebola virus in the Philippines [68], and *Rousettus leschenaultia* for Reston Ebola and Zaire Ebola viruses, or to unknown but closely related Ebola strains, in China [69] and

Bangladesh [70]. There was also an indication that two insectivorous bat species, *Pipistrellus pipistrellus and Myotis* species, may also contribute to reservoirs of Ebola virus in China [69].

A genetically distinct Ebola-like filovirus has recently been described in Europe from dead Schreiber's bats (*Miniopterus schreibersii*), and has provisionally been named Lloviu virus [71]. It will be interesting to see whether this virus is more widespread in Europe, or in other parts of the world as this bat species is found extensively from Europe through Asia to Australia.

Bats as reservoirs of other virus families – some additional examples.

Fruit bats and insectivorous bats have been shown to harbour a wide range of novel viruses belonging to a number of different virus families. Recent studies have described the detection of **paramyxoviruses** in insectivorous bats in Europe [70] and south-west Indian Ocean [73], and in fruit bats in China [74], Indonesia [75], Australia [76] and Africa [77-79]. Major discoveries from these investigations include evidence of an origin of Hendra- and Nipah viruses in Africa, new Henipaviruses from Australia and Indonesia, identification of a bat virus conspecific with the human mumps virus, detection of close relatives of respiratory syncytial virus, mouse pneumonia- and canine distemper virus in bats. Novel fusogenic **reoviruses** have recently been described from human patients with acute respiratory disease in Malaysia [80,81,82] and in Hong Kong from a patient returning from Bali [83], for which there is strong circumstantial evidence to indicate an origin in fruit bats [84]. These reoviruses comprise a new species, *Pteropine orthoreovirus*, together with a number of orthoreoviruses from fruit bats in Malaysia, Australia and China [84,85]. Novel **Hantaviruses** have also been described in insectivorous bats over the past few years in Africa in Sierre Leone [86] and Côte d'Ivoire [87], and in Brazil [88], but the relance of these viruses to Hantavirus phylogeny remains to be determined.

Rodents as reservoirs of zoonotic pathogens

Rodents are important reservoirs of viral pathogens]89], especially for Arenaviruses [90,91] and Hantaviruses [92]. The Arenaviruses are a diverse group of viruses, some of which are capable of causing a wide range of human illness ranging from encephalitis to severe haemorrhagic fever throughout the New and Old World, whereas others have not been associated with disease. The Old World arenaviruses are associated with Eurasian rodents in the family Muridae, whereas New World arenaviruses are associated with American rodents in the subfamily Sigmodontinae, and each tightly associated with a specific host. Tacaribe virus is the only exception, having been isolated from a fruit-eating bat. The major pathogens are lymphocytic choriomeningitis virus (LCMV), which occurs

in many parts of the World in house mice; Lassa virus in West Africa; Lujo virus in South Africa; and various South American haemorrhagic fever (HF) viruses including Junin (Argentinian HF), Muchupo (Bolivian HF), Guanarito (Venezuelan HF), Sabia (Brazilian HF), and Chapare (the cause of an outbreak of HF in Bolivia). Several new Arenaviruses have been reported over the past 5 years either from human infections (including Lujo [93, 94] and Chapare [95]) or from rodents [96-101]. There is a continuing need to maintain a surveillance of these and related viruses because with the great large number of different Arenavirus host reservoirs, the great genetic diversity among virus species, and the ability of the viruses to adapt to rapidly changing environments, there is concern that a new virus potentially pathogenic for humans could arise [102]. Indeed this happened recently with Lujo virus, which led to several subsequent nosocomial infections [93,94].

The Hantaviruses are the etiological agents of haemorrhagic fever with renal syndrome (HFRS) in the Old World [92, 103] and hantavirus (cardio)pulmonary syndrome (HPS) in the New World [92,103-106]. The reservoir hosts of Hantaviruses are rodents and insectivores. The viruses cause asymptomatic persistent infections in their reservoir hosts with prolonged virus shedding in excretia, and although they have a strong history of co-divergence with their hosts, recent evidence suggests that this association may be due to a more recent history of preferential host switching and local adaptation (107). Approximately 150,000 to 200,000 cases of HFRS occur each year, with most of the cases occurring in the developing countries, and with a case fatality rate from <1% to 12% depending on the virus strain, whereas the annual number of cases of HPS in the New World is about 200, but with a 40% fatality rate. The reported cases of hantaviral infection is increasing in many countries and new hantavirus strains have been increasingly identified worldwide , which constitutes a public health problem of increasing global concern [105,108]. Hantaviruses are largely infections of rural communities, except for HFRS due to Seoul virus which is rat-borne and usually urban. Thus factors which predispose to an increased incidence of Hantavirus infection are habitat disturbance and ecological changes, climatic changes, and occupational exposure by outdoor workers. As with Arenaviruses, the Hantaviruses exhibit considerable diversity [109], and new potentially pathogenic strains could arise, indicating a need for ongoing surveillance.

VECTORS AND VECTOR-BORNE DISEASES

A vector can be defined as an organism that transmits a pathogen or disease-causing organism from a reservoir to a host. In the context of this review, vectors are restricted to arthropods, and particularly mosquitoes, ticks, sand flies and *Culicoides* or biting midges, as transmitters of pathogenic threats to humans or livestock. The role of mosquitoes in pathogen emergence is largely

one of major geographic spread due to incursions of mosquitoes into new habitats. There are a number of major mosquito species that have jumped continents over the past three decades [eg. 110], but there is little doubt that the most important ongoing threats come from extensive tropical urbanization and the colonization of this expanding habitat by *Aedes (Stegomyia) aegypti* [111], and the global expansion in the geographic distribution of *Aedes (Stegomyia) albopictus* [112]. The latter has expanded to establish in at least 26 new countries in Africa, Europe and the Americas from its original home in tropical forests of south-eastern Asia. Thus there is a significantly increased risk of transmission of arthropod-borne (arbo)viral diseases, especially dengue and chikungunya [110,113-115].

The dengue viruses are the most important human arboviral pathogens, with an estimated 50–100 million annual cases of dengue fever (DF) and tens-of-thousands of cases of the more severe and sometimes fatal dengue hemorrhagic fever/shock syndrome (DHF/DSS syndromes). The geographical areas in which dengue transmission occurs have expanded in recent years, and all four dengue virus serotypes are now circulating widely in Asia, Africa and the Americas [116]. Thus dengue is an ongoing global threat, and it will undoubtedly continue to spread as vectors become established in additional habitats. Chikungunya virus has also began an unprecedented global expansion, causing a series of epidemics probably involving 5–10 million people, and putting hundreds of millions at risk [117]. The most extensive was the Indian Ocean lineage (IOL)which evolved in Kenya in 2004, spread to the Indian Ocean islands, and the then to India and South-East Asia where major urban epidemics ensued [117,118]. The spread of the IOL was accompanied by a mutation in the envelope protein gene, A226V, which allowed the virus to utilise *A. albopictus* as a new vector. The mutation had the effect of increasing its infectivity for this new vector by ca. 100-fold [117]. Thus the epidemics were largely due to viruses with the A226V and transmitted by *A. albopictus* mosquitoes, which enabled the virus to spread in viraemic travellers to areas where the mosquito had established in new habitats.

The expansion of *A. albopictus* into Europe has already had major implications with the 2007 outbreak of chikungunya in northern Italy [119,120] with about 160 laboratory confirmed cases, and autotochthonous transmission in France in 2010 [121122]. In addition, autochthonous cases of dengue have been reported from France [122,123] and Croatia [124].

The cases represent the tip of the iceberg. With the increased incidence of diseases, as well as increased international travel, and global warming, the spread of vectors and, following closely

behind, exotic diseases are a very real global threat. Ongoing surveillance will be crucial as we try to manage these diseases in the future.

Arthropod-borne diseases also pose threats to livestock industries. In Europe, Bluetongue virus poses an ever increasing threat [111], and new viruses are emerging as witnessed recently by the appearance of Schmallenberg virus. Bluetongue virus (BTV) is in the genus Orbivirus (family Reoviridae) and currently consists of currently 25 viruses clustered within 10 distinct lineages [125]. BTVs are maintained within an enzootic cycle among biting midges in the genus *Culicoides* (family Ceratopogonidae) and various ruminant species, almost all of which are susceptible to infection. However, not all species of *Culicoides* are competent vectors and for the most part the distribution of the virus is governed by the availability of a species of *Culicoides* that permits replication of the virus [126]. The virus is believed to have its origin in Africa but occurs in semi-tropical and temperate areas where such vectors exist or periodically occur [127]. Thus virus is found for example, in southern Europe, North America and northern and eastern Australia. The frequency of invasion into new areas or non-endemic areas has increased recently in part due to climate change but also in terms of movement of its vectors and changing patterns in competence of other *Culicoides* species as vectors [111,128]. The distribution of BTV types varies widely; disease is rarely seen in wild ruminants in Africa, or in domestic cattle until recently. The disease in sheep can be severe and is strongly breed related [129]. In non-endemic areas, where *Culicoides* species do not survive throughout the year due to colder conditions, a number of theories have been postulated for overwintering of the virus but there is a lack of solid evidence for how this might occur [125-134]. Note that the primary importance of BTV infection in cattle and sheep relates to trade embargoes on export of ruminants in areas where the virus is found e.g. North America [127].y

Since 2000, increasing BTV types have been found in southern Europe with a variety of *Culicoides* species being incriminated [111, 130, 135]. In the summer of 2006 however, BTV serotype 8 (BTV-8) emerged for the first time in northern Europe, resulting in over 2000 infected farms by the end of the year [136]. This was probably due in large part to climatic changes permitting its major vector, *Culicoides imicola*, to move northwards, and to the ability of some northern *Culicoides* species to become competent to transmit the virus [111,128]. Interestingly, the initial spread from the Netherlands indicated a single point introduction of the disease into Europe, not typical of a spread by competent vectors from southern Europe. The virus subsequently overwintered and spread across much of Europe, causing tens of thousands of livestock deaths. In August 2007, BTV-8 reached the United Kingdom (UK) , threatening the large and valuable livestock industry. A voluntary

vaccination scheme was launched in UK in May 2008 and, in contrast with elsewhere in Europe, there were no reported cases in the UK during 2008. Thus whilst the global range of BTV has historically been assumed to be restricted by regional differences in vector competence amongst *Culicoides* species as well as by the temperature requirements of the virus for replication, this outbreak did not follow this pattern. It has been postulated that the use of a live attenuated BTC 8 vaccine may have been the initial cause of this outbreak [137]. Importantly on 15th January 2013, Spain proceeded to declared itself free of serotype 8 of bluetongue virus. As with other parts of Europe BTV serotype 8 appeared for the first time in Spain in January 2008 but the system of disease surveillance implemented in Spain allowed for early detection and the implementation of rapid and effective control measures based on vaccination and movement control limited spread and enabled eradication of BTV from this region [138]. This still leaves the question of the underlying reservoir of BTV 8 and the process for emergence into Europe.

A similar questions arises with the recent discovery of a new virus in Europe in 2011. Schmallenberg virus, an informal name given to an Orthobunyavirus related to Shamonda virus, was initially reported in November 2011 as a cause congenital malformations and stillbirths in cattle , sheep , goats, and possibly alpaca [139]. It appears to be transmitted by *Culicoides* spp. which are likely to have been most active in causing the infection in the northern hemisphere summer and autumn of 2011, with animals subsequently giving birth from late 2011. The virus is named after Schmallenberg, in North Rhine-Westphalia, Germany, from where the first definitive sample was derived [140]. After Germany, it has been detected in many European countries, with disease in sheep and calves [141]. At least three species of *Culicoides* appear to be capable of transmitting the virus [142]. A number of questions remain unanswered about the outbreak, its vectors, management issues and public health issues [143]. To date there appears to be no human infections from Schmallenberg virus [144]. However as with the emergence of BTC 8 in Europe, no explanation is available as to the original reservoir of either virus, a critical risk management issue.

CONCLUDING COMMENTS

Most new viruses that have the potential to cause pandemics are zoonoses, that is, they originate in animals, and then with assistance from various drivers of emergence such as ecological, behavioural or socioeconomic changes, spill over to infect humans. This is the start of the first of three stages in disease emergence described by Morse and colleagues [13], and it is at this stage that surveillance of potential reservoirs at known hot spots [8] might provide that first enigmatic indication of the potential to spill over to infect humans and thus lead to that early cross-transmission event.

Since the SARS outbreak there has been an explosion in our knowledge of novel viruses in a variety of hosts, but perhaps more in bats than other animal orders for reasons relating to their ecology and to their association with novel viruses in the preceding decade. Some of the virus isolates can be cultured, and their biology explored for possible cross-species transmission and other factors associated with assessing their pathogenic potential . Many others are known only from short genomic sequences, and it is less obvious how they can be used for determining future risk potential. Nevertheless, having sequence data from viruses in wildlife niches can be useful when tracking the origins of novel diseases, as demonstrated recently with the SARS-like virus infection in Saudi Arabia, and also in seeking information on genetic diversity and perhaps indications of host range .

Surveillance has been described as the first line of defence against emerging viruses [145]. While this is certainly so for the timely detection of outbreaks of human disease, and indeed a requirement under the terms of the new International Health Regulations, it is also important to maintain surveillance at the human-wildlife interface where that first indication of a cross-species transmission event might be detected or even suspected. Studies at the animal interface have only recently been initiated by the USAID-sponsored program 'PREDICT' and by some individual laboratories with specific disease interests (eg Nipah virus). It is still a long way finding a possible pandemic virus – it has never happened before, but the development of exquisitely sensitive genomic detection technologies and the initiation of surveillance close to the animal-human interface might just provide that rare event.

The spread of arthropod vectors around the world in used car tyres, in happy bamboo plants, in aircraft, or breeding in containers or other water traps on vessels is an ongoing problem, but one which will undoubtedly lead to the incursion and establishment of additional arboviruses to threaten human and animal health. This has demonstrated a widespread weakness in quarantine, environmental health and public health activities in many countries. Unless this is improved, further incursions are inevitable.

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