The diversity of viruses infecting humans

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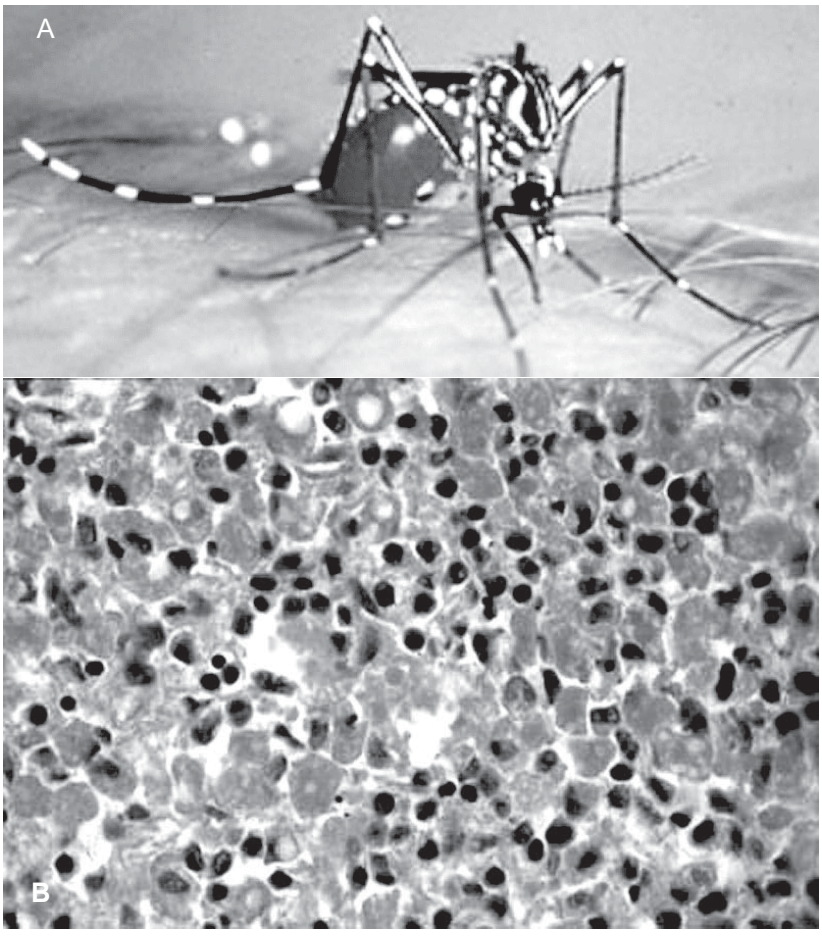
Abstract. Most human viruses have been discovered through the diseases they cause in animals, plants, bacteria or fungi. Recent finds include human bocaviruses, which now seem to have a global distribution, and cause respiratory tract disease in infants, and several new pathogenic human coronaviruses. The SARS coronavirus, genetically distinct from all previously known coronaviruses, caused a disease which was highly transmissible and very severe, eventually leading to 8000 cases worldwide with over 800 deaths. Many viruses which are transmitted to humans by invertebrates, such as insects or ticks, have the ability to infect and replicate in cells of both vertebrate and invertebrate origin. However human virology is a rapidly expanding field and recent technologies such as the polymerase chain reaction (PCR) amplification system have made it possible to look for previously unrecognized viruses which may or may not be involved in pathogenesis. For example viruses in the genus Anellovirus are found in 80% of human blood samples yet do not seem to cause any disease. This paper overviews known human vertebrate viruses, more recent discoveries, and recommends a systematic search for viruses which may already infect the human population but have so far remained undetected.

INTRODUCTION

The most recent report of the International Committee on Taxonomy of Viruses (ICTV) lists more than 6000 viruses that are classified into 1950 virus species and distributed among more than 391 different taxa (Fauquet *et al*. 2005). In general, most of these viruses were discovered through the diseases they cause in animals, plants, bacteria or fungi, although since the development of the polymerase chain reaction (PCR) amplification system it has been possible to detect the presence of viruses that do not appear to cause any disease. An example of such viruses can be seen in the genus *Anellovirus*, which contains at least three small circular single-stranded DNA viruses that can be found in the blood of humans (Biagini *et al*. 2006). These viruses are extremely widespread in the human population, with abundant anellovirus DNA being detectable in more than 80 % of human blood samples tested yet cause no clinical disease (Bendinelli & Maggi 2005). For these reasons, any consideration of the diversity of human viruses must take into account that there has been no systematic search for human viruses that may or may not be associated with disease.



A, A female *Aedes aegypti* mosquito engorged with blood while feeding. Dengue viruses are transmitted during the feeding process. (Courtesy of the CDC)

B, Dengue-infected cells

VIRUSES OF VERTEBRATES

Humans are vertebrates, and the article by Craig Pringle in this issue ("The Taxonomy of Vertebrate Viruses") describes the many virus families and species known to infect vertebrates. Very few viruses are unique to the human species, and perhaps the only well known example, variola virus, has been eradicated by vaccination and now no longer exists in nature. Other potential targets for eradication, hepatitis C virus and human immunodeficiency virus (HIV) seem only able infect humans and certain non-human primates, but no vaccines have been developed so far that might prevent or eliminate these infections. It is also clear that many viruses which are transmitted to humans by invertebrates, such as insects or ticks, must have the ability to infect and replicate in cells of both vertebrate and invertebrate origin. Some of these, such as the flavivirus yellow fever virus, cause extremely serious disease consequences in humans, where they target liver cells, with replication in Kupffer cells, causing massive necrosis of hepatocytes which leads to jaundice and in the worst cases severe hemorrhagic fever involving the gastrointestinal tract. These pathological features made yellow fever one of the worst plagues in history, particularly affecting the African and South American regions, and perhaps because of the disease severity, the epidemiology of

the disease was worked out and shown to involve mosquito borne transmission as early as 1900, when few viruses had been described (Reed 1902). This led to the development of an effective attenuated yellow fever vaccine for the protection of humans. Unfortunately a satisfactory vaccine has not so far been developed for use against a related flavivirus, dengue/ dengue hemorrhagic fever virus, which occurs in four major antigenic types. But dengue fever virus, like yellow fever virus, is spread by *Aedes aegypti* mosquitoes, and so mosquito control methods have benefited the control of both these diseases.

In addition to insect borne flaviviruses, there are also serious diseases caused by tick borne flaviviruses, such as Kyasanur Forest disease virus, found in India, Omsk hemorrhagic fever virus, found in Russia, and Alkhurma hemorrhagic fever virus, found in Saudi Arabia. The exact mechanisms involved in the infection of insect cells versus tick cells or human cells are not well worked out, but it seems clear that viruses which alternate between infections of arthropod and vertebrate hosts show a remarkable genetic stability during experimental (Bilsel *et al.* 1988) or natural (Deubel *et al.* 1985; Charrel *et al*. 2005) transmission cycles.

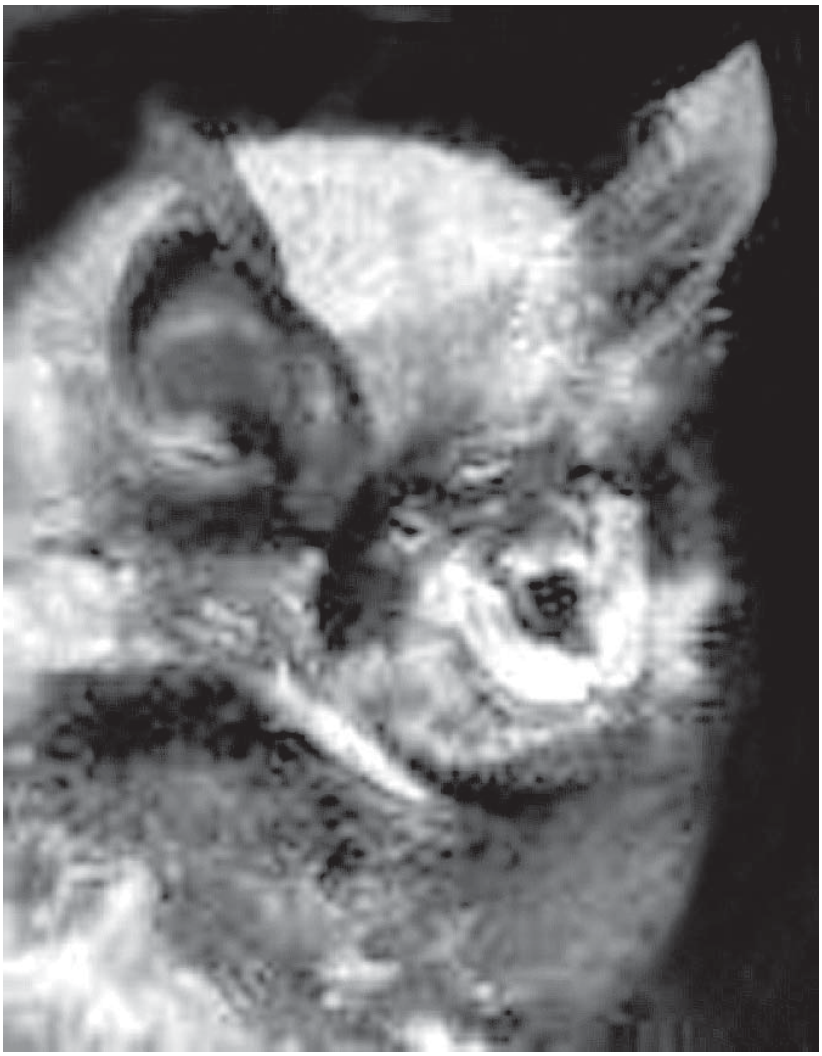
NEW HUMAN VIRUS INFECTIONS

Although human viruses have been studied for more than a century, it has become clear in the last 15 -20 years that a large number of new human virus infections have been newly recognized (Mahy and Murphy 2005). In some cases a virus has been found in association with a long-recognized disease syndrome such as acute respiratory disease syndrome (ARDS) caused by the hantavirus Sin Nombre virus (Nichol *et al.* 1993), and this led to the discovery of more than 30 related hantaviruses throughout the American continent. These virus infections are spread to humans through a vertebrate (usually a rodent) vector, but until the first one was recognized through epidemiological association and careful molecular analysis, they had remained unsuspected for decades.

Other new viruses have been recognized because of a new disease they caused in humans, such as the severe acute respiratory syndrome (SARS) coronavirus . The disease first appeared in humans in China in 2002, and by 2003 had spread to a number of neighbouring countries, The first virus isolate was made from samples taken from a physician who had died from the disease in Vietnam (Drosten *et al*. 2003; Ksiazek *et al.* 2003). The unusual feature of the SARS coronavirus was that although previously known human coronavirus infections (human coronaviruses OC43 and 229E) had long been recognized as causing relatively mild symptoms such as the common cold, genetic analysis of the SARS virus showed that it was genetically distinct from all previously known coronaviruses, and caused a disease which was highly transmissible and very severe, eventually leading to 8000 cases worldwide with over 800 deaths. The coronaviruses are currently divided into three genetic groups, with human coronavirus 229E falling into group 1 and human coronavirus OC43 into group 2. Group 3 contains only avian coronavirus species. The sequence of the SARS coronavirus placed it in group 2 (Kim *et al*. 2006). Studies on the origin of the SARS coronavirus are still ongoing: there is recent evidence of a zoonotic origin of the human disease, perhaps from palm civets, but the true natural reservoir of the virus seems most likely to be in a bat species, probably Chinese horseshoe bats (Lau *et al.* 2005; Li *et al.* 2005). What is clear, however, is that careful serological studies revealed no evidence of the presence of the virus in the human population before 2002 (Knobler *et al*. 2004), when this virus first entered the human population and caused SARS.

In addition to SARS, which was the first major international disease outbreak of the 21st century, a number of diseases of lesser importance have been newly recognized by the discovery of new virus species related to conventional virus infections. For example, it has been known for many years that the human parvovirus, a small single-stranded DNA virus known as B19, was the cause both of a rash in children called erythema infectiosum (fifth disease), and also of aplastic crisis in both children and adults with chronic hemolytic anemia. This was the only known human parvovirus until very recently, when a new parvovirus was discovered to be the cause of lower respiratory tract infections in children. The new virus was discovered by large-scale molecular virus screening of pooled human respiratory tract samples based on host DNA depletion, random PCR amplification, large-scale sequencing analysis and bioinformatics. This procedure detected one parvovirus and one coronavirus, both of which were at that time uncharacterized (Allander *et al*. 2005). The human parvovirus displayed genome nucleotide sequence similarities to known parvoviruses infecting bovine and canine animal species, bovine parvovirus and canine minute virus, which had been placed in the genus *Bocavirus* of the subfamily Parvovirinae within the family Parvoviridae (Fauquet *et al.* 2005). Thus the virus was provisionally named human bocavirus.

Surprisingly, studies carried out in Australia (Sloots *et al*. 2006) Japan (Ma *et al.* 2006) Canada (Bastien *et al*. 2006) and elsewhere (unpublished) have revealed a significant number of children whose lower respiratory tract disease appears to be caused by human bocavirus infection. The new human coronavirus detected by Allander *et al*. (2005) was found by sequence analysis to be related to another new human coronavirus identified in an elderly man who developed pneumonia in Hong Kong soon after returning from Shenzen, China (Woo *et al*. 2005a). This virus was named human coronavirus-HKU1, since it was isolated in Hong Kong University. Further



A horseshoe bat from Hubei, China of the species found to be most infected with the SARS virus. (Photo courtesy Consortium for Conservation Medicine)

studies there showed that this virus was also associated with a second case of pneumonia, this time in a 35 year old woman, and a more complete investigation involving 4 hospitals showed that HCoV-HKU1 virus was responsible for 2.4% of all community-acquired pneumonia (Woo *et al*. 2005b). Most recently, HCoV-HKU1 virus was found in Australian children (Sloots *et al*. 2006), and in 5 children and one adult in Caen, France (Vabret *et al*. 2006).

Probably as a result of the sudden world-wide interest in human coronaviruses generated by the discovery of the SARS coronavirus, other new human coronaviruses were found using more conventional approaches. In 1994, a group from the University of Amsterdam isolated a new coronavirus from a 7-month-old child suffering from bronchiolitis and conjunctivitis, and named the virus HCoV-NL63. The virus was genetically distinct from previously reported coronaviruses, but appeared to be a new group 1 coronavirus which was widely spread in the Dutch population (van der Hoek *et al*. 2004). Within a few months, this newly recognized virus was detected in association with bronchiolitis in young children in Australia (Arden *et al*. 2005) Belgium (Moes *et al*. 2005) Canada (Bastien *et al*. 2005) Japan (Ebihara *et al*. 2005) Switzerland (Kaiser *et al*. 2005) and China (Chiu *et al*. 2005; Zhu *et al*. 2006).

At the same time that the Amsterdam group were reporting their findings, a group at Yale university discovered a closely related if not identical coronavirus to NL63 which they named New Haven coronavirus (HCoV-NH) (Esper *et al*. 2005a). The Yale group admitted that their coronavirus was similar and might represent the same species as HCoV-NL63.
However, in an accompanying paper, Esper *et al*. (2005b) went on to claim an association between HCoV-NH and Kawazaki disease, a childhood systemic vasculitis long suspected of having a viral origin, though none has ever been found. The importance of this claim stimulated existing Kawasaki research groups in California and in Taiwan to look for the virus in their clinical specimens, but neither group could confirm any association of either HCoV-NH or HCoV-NL63 with the disease (Shimizu *et al*. 2005; Chang *et al*. 2006).

THE HUMAN VIROME

It is clear from these recent discoveries that the SARS epidemic catalyzed a great deal of excellent work in what had been a neglected area of virology with the result that we now have more than doubled the number of known human coronaviruses from 2 to at least 5. How many more might still be undetected?

In their seminal paper describing the discovery of the new human parvovirus, human bocavirus, Allander *et al*. (2005) suggest that it might be possible to undertake a systematic exploration to describe the "human virome". This might be based not on disease, but given our extensive data bank of virus sequences, it would be possible to carry out a systematic search for the presence of viruses in human tissues. The coronaviruses were investigated because of the intense interest in understanding SARS and its origins, but I suggest that an alternative approach might be to focus on viruses known to be important causes of disease in animals, but for which no human examples have yet been recognized. Considering the coronaviruses, we now recognize them as belonging to a family within a wider taxonomic group, the Order Nidovirales. This Order includes the related families Arteriviridae, Coronaviridae, and Roniviridae. The latter family of viruses have only been found so far in crustaceans, but there are a number of arteriviruses that may have a counterpart infecting humans. Arteriviruses infect horses, causing arterial disease, so would be a promising candidate as a cause of the vasculitis associated with Kawazaki disease. Artiviruses also include porcine reproductive and respiratory syndrome virus, (PRRSV) which causes a serious disease in pigs, and lactate-dehydrogenase elevating virus of mice (LDV)(Rowson and Mahy 1985), which usually causes

a persistent lifelong infection with no obvious pathological consequences apart from a tenfold rise in lactate dehydrogenase enzyme in the blood. But in aging mice of certain strains a form of poliomyelitis may develop. All arteriviruses, including LDV, primarily infect macrophages. The only known primate arterivirus affects monkeys, causing simian hemorrhagic fever.

Finally, in addition to the coronavirus genus, the family *Coronaviridae* includes the genus *Torovirus,* whose members are known to infect horses, bovines and carnivores. The discovery of at least one human torovirus has recently been claimed and linked to neonatal necrotizing enterocolitis (Lodha *et al*. 2005).

SUMMARY

There is no doubt that human virology is a rapidly expanding field, and technological advances have now made it possible to look for previously unrecognized viruses existing in the human population which may or may not be involved in pathogenesis. Recent examples of such newly recognized viruses include the human bocaviruses, which now seem to have a global distribution, causing respiratory tract disease in infants, and several new pathogenic human coronaviruses, As we continue to search for the causes of many human diseases of unknown aetiology, it may be prudent to undertake a more systematic search for viruses which may already infect the human population but have so far remained undetected.

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