



Emerging viral infections in a rapidly changing world

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Emerging viral infections in both humans and animals have been reported with increased frequency in recent years. Recent advances have been made in our knowledge of some of these, including severe acute respiratory syndrome-associated coronavirus, influenza A virus, human metapneumovirus, West Nile virus and Ebola virus. Research efforts to mitigate their effects have concentrated on improved surveillance and diagnostic capabilities, as well as on the development of vaccines and antiviral agents. More attention needs to be given to the identification of the underlying causes for the emergence of infectious diseases, which are often related to anthropogenic social and environmental changes. Addressing these factors might help to decrease the rate of emergence of infectious diseases and allow the transition to a more sustainable society.

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Abbreviations

EID	emerging infectious disease
hMPV	human metapneumovirus
PCR	polymerase chain reaction
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus
WHO	World Health Organization
WNV	West Nile virus

Introduction

For much of the twentieth century, infectious diseases in human populations of Western countries have been in retreat, as we learnt to sanitize our cities, cleanse our water supplies, improve domestic hygiene, use antibiotics, control vector organisms and vaccinate. As a result, the developed world became rather complacent, naively welcoming the false dawn of a life mostly free of infectious disease. Since the 1980s things have looked much less secure, however, with the emergence of many previously unrecognized infectious diseases, and the re-

emergence of known infectious diseases that were thought to be under control. This trend has continued until the present time and many infectious pathogens, predominantly viruses, have been newly identified in recent years [1^{**}]. In this review, we describe recent advances in our understanding of several selected viruses of particular concern, and discuss underlying factors for their emergence.

Severe acute respiratory syndrome-associated coronavirus

The emerging infectious disease (EID) that has attracted by far the most attention in recent years was first reported in the fall of 2002 from Southern China as a contagious and severe atypical pneumonia in humans. This syndrome, named severe acute respiratory syndrome (SARS), became a global health problem within two months and prompted the World Health Organization (WHO) to issue a global alert for the first time in more than a decade [2]. Most cases occurred in mainland China, Hong Kong, Taiwan, Canada, Singapore, Vietnam, the USA and the Philippines. By the end of the outbreak in July 2003, 8098 SARS cases had been reported, of which 774 were fatal [3].

The identification and characterization of the etiologic agent of SARS was expedited by an unusually open cooperation of an international WHO network of laboratories that made use of a wide range of disciplines and diagnostic techniques. Specifically, recent advances in polymerase chain reaction (PCR) technology and nucleotide sequencing sped up this process. After following a few false leads, a hitherto unknown coronavirus was identified as the possible cause of SARS [4^{**},5,6]. Within a few weeks, the full genome sequence of this SARS-associated coronavirus (SARS-CoV) was published [7^{*},8^{*}]. On the basis of phylogenetic analyses, SARS-CoV was found neither to be a member of the three recognized coronavirus groups, nor the result of a recombination between known coronaviruses. Therefore, it was placed in a new coronavirus group — group 4 [7^{*}]. Replication of the pulmonary lesions of SARS in experimentally infected macaques, together with the diagnosis of SARS-CoV infection in the majority of 436 SARS patients examined in detail, provided the final proof that SARS-CoV was the primary cause of SARS [9^{**},10^{**}].

Exposure to the virus appears to be through direct or indirect contact and possibly through droplet infection [4^{**}]. The primary lesion in SARS patients is diffuse alveolar damage, which corresponds clinically to acute respiratory distress syndrome [10^{**}]. The pathogenesis is poorly understood, particularly of the severe pulmonary

disease that some patients develop in the second week after the onset of symptoms, when SARS-CoV is not detectable in lung tissue [5]. Hypotheses include an overexuberant host response resulting in generalized hypercytokinemia [11^{*}] and pulmonary fibrosis owing to virus-induced damage at an early stage of the disease [10^{**}]. Clarification of the pathogenesis is important to guide therapy. Antibiotics, corticosteroids, ribavirin and oseltamivir have been used in treatment, but their efficacy is not known [4^{**}].

The natural reservoir of SARS-CoV is likely to be one or more species of wild animal, because it is improbable that its presence would have gone unnoticed in domestic animals or humans. A coronavirus, genetically similar but not identical to SARS-CoV, has been isolated from four Himalayan palm civets (*Paguma larvata*) and a raccoon-dog (*Nyctereutes procyonoides*) from a market in Southern China, where they were intended for human consumption. However, because several wildlife species are kept together in captivity and during transport to such markets, it is still uncertain which species maintain SARS-CoV [12^{**}] (see also Update).

SARS-CoV could re-emerge in the human population by various mechanisms. Firstly, it might be circulating subclinically among humans and emerge owing to improved circumstances for the virus; for example, it may have a seasonal cycle and reappear in the winter season, as with influenza. Secondly, the virus might again be transmitted from its wild animal reservoir to humans. Thirdly, SARS-CoV could inadvertently be released from a hospital or laboratory holding samples of the virus; this is believed to be the source of infection for a Singapore researcher, who contracted SARS three months after the WHO declared the outbreak over [13].

Influenza A virus

The continuing threat of a new influenza pandemic hangs like the sword of Damocles over humankind. The conventional wisdom is that aquatic birds are the reservoir for the existing hemagglutinin (H1 to H15) and neuraminidase (N1 to N9) subtypes of influenza A virus, and that domestic pigs act as an intermediate host for the transmission of a new strain of virus to humans. On the basis of recent findings, this concept has changed in two areas.

First, the domestic chicken can act as an intermediate host for the transmission of influenza A virus from aquatic birds to humans. This was first shown in Hong Kong in 1997, when six deaths out of 18 human cases resulted from the direct transmission of highly pathogenic avian influenza A virus (H5N1) from chickens to humans. By slaughtering 1.5 million chickens and other poultry in Hong Kong, the source of viral infection for humans was removed. Direct chicken-to-human transmission happened again in 1999, when avian influenza A virus (H9N2) was isolated for the first time in two children

hospitalized with upper respiratory tract illness. The unusual ability of this H9N2 virus to replicate efficiently in both chickens and humans can be explained by its preferential binding to sialyl(α 2,6)galactose-terminated receptors on host cells. This type of receptor is found on both human and chicken cells, but not on duck cells [14].

The most recent example of direct chicken-to-human transmission of influenza A virus occurred during an epidemic of highly pathogenic avian influenza virus (H7N7) in poultry in the Netherlands in spring 2003 and caused considerable morbidity and one fatal case in humans. Infections with this virus were confirmed in 83 people handling poultry, and in three cases there was subsequent transmission between humans. Although most infected people suffered only a conjunctivitis or mild influenza-like illness, one person died of pneumonia [15]. A major concern during the outbreak was that the avian H7N7 virus would reassort with the human H3N2 virus that was circulating in the human population at the same time, with the potential to spark off a new influenza pandemic. Fortunately, this did not occur (R Fouchier, unpublished data).

The second finding to alter our concept of influenza transmission, was the realization that the gene pool for influenza A viruses is likely to be broader than that found in aquatic birds alone and more dynamic than previously thought. On the basis of recent studies in Southern China, H9N2 influenza virus lineages — that originated from domestic ducks and became established in chicken and quail in the mid-1990s — have been transmitted back to domestic ducks. In the process, reassortant viruses have been generated containing nucleic acid segments from both H9N2 viruses and influenza viruses resident in ducks. This suggests that the gene pool of influenza A viruses includes various species of aquatic and terrestrial birds, with easy transmission among species. The diversity of virus genotypes and host receptor specificities results in a continuous flux, conceivably with an increased opportunity for a new pandemic influenza virus to develop [16^{*}].

Human metapneumovirus

Human metapneumovirus (hMPV) is a good example of a pathogen that ‘emerged’ as a result of increased and tenacious diagnostic efforts rather than through expansion of its range or transmission to a new host species. One of the reasons that it was not found previously is that the virus does not replicate well in the cell lines used for the virological diagnosis of respiratory tract infections in humans up to that time. Although most children are infected by five years of age and the virus has been circulating in the human population since at least 1958, hMPV was only identified in 2001 [17^{**}]. It is a paramyxovirus most closely related to avian pneumovirus, and is associated with a substantial proportion of hitherto unexplained respiratory tract illnesses [17^{**},18^{*}]. Since

its discovery in the Netherlands, hMPV infection has been reported elsewhere in Europe, North America, Asia and Australia [19]. Respiratory tract disease associated with hMPV infection occurs both in children and adults, suggesting that hMPV is capable of causing clinically important reinfection of individuals later in life. The spectrum of clinical disease includes rhinitis, pharyngitis, bronchitis, bronchiolitis and pneumonia, and resembles that of human respiratory syncytial virus infection. Severity of the disease varies from the common cold to death, with very young children, the elderly and immunocompromised patients being predisposed to severe lower respiratory tract disease [17^{**},19,20^{*},21].

West Nile virus

West Nile virus (WNV) infection is mosquito-borne and is maintained and amplified in birds. It is occasionally transmitted to humans, horses and other mammals in which disease may occur. The virus attracted major attention when it spread from its original range (Africa, the Middle East and Europe) to North America, where it first appeared in New York in 1999 [22,23^{*}]. By phylogenetic analysis, the 1999 New York isolate most closely resembles that of a WNV isolate from Israel in 1997, suggesting that it originated from the Middle East, but how this occurred is not known [24]. The virus has spread rapidly since its arrival in North America, and by August 2003 had reached as far west as Alberta in Canada [25] and California in the USA [26] and as far south as Mexico [27,28] and the Caribbean [29]. It is likely to spread further south into Central and South America. Modeling shows that this pattern of spread is most likely due to long-distance transport of WNV in infected birds along their migratory flyways, combined with local dissemination by mosquitoes [30]. The mortality of infected birds in North America is unexpectedly high, particularly in corvids, and contrasts with the low pathogenicity of WNV for birds in its original range [31^{*}]. Passive surveillance of wild bird mortality has proved to be the most effective method to monitor the spread of WNV in North America, and has resulted in a unique integration of public health and wildlife health agencies [31^{*}]. In addition to mosquito bites, novel routes of transmission to humans include blood transfusion, organ transplantation, feeding of breast milk and through the placenta. As expected in a previously unexposed human population, a relatively high proportion of people infected with WNV in North America develop neurological disease, which is occasionally fatal [22]. In 2002 and 2003 (up to 12th September), 8245 human cases of WNV infection were reported in the USA and Canada, of which 369 were fatal (compiled from Health Canada [32] and the Centers for Disease Control and Prevention [33]).

Ebola virus

Ebola virus is one of the most pathogenic viruses for humans, causing severe haemorrhagic fever with a high

rate of mortality [34]. Its danger to humans is compounded by limited knowledge of its pathogenesis, an unknown natural reservoir, and limited preventive and therapeutic measures. In addition, Ebola virus infection threatens the survival of gorillas (*Gorilla gorilla*) and chimpanzees (*Pan troglodytes*) in their last stronghold in western equatorial Africa, where declines in population of more than 50% between 1983 and 2000 are partly blamed on Ebola outbreaks [35^{**}]. To manage Ebola virus infection, it is important to discover its natural reservoir. Fruit bats are likely candidates, because they are the only experimentally infected species showing long-term excretion in absence of the clinical disease. However, attempts to diagnose Ebola virus infection in free-living fruit bats have been unsuccessful so far [36].

Mitigation efforts

Research efforts to mitigate the effect of the above-named EIDs have concentrated on four main areas: improved surveillance (e.g. a worldwide network of WHO laboratories for influenza surveillance and a global electronic reporting system for outbreaks of EIDs and toxins, ProMED-Mail); improved diagnostic methods (e.g. a more rapid and efficient test to detect WNV [37]); the development of vaccines (e.g. for Ebola virus infection [38^{**}]); and the development of antiviral agents (e.g. interferon for the treatment of SARS [39]). Advances in molecular biology will play a large part in facilitating and accelerating these efforts. These include sophistication of PCR-based tests and the use of reverse genetics. The development of robotic PCR machines allows high-throughput screening of samples for surveillance purposes, while real-time PCR assays permit a more rapid diagnosis. Vaccine development will be accelerated by the use of reverse genetics, which is becoming more efficient, more widely available, and applicable to more viruses. This technology allows the production of recombinant virus by transfection of susceptible cell cultures with plasmids encoding the viral genome or complementary copies thereof. Reverse genetics can be used to construct either recombinant vector-based vaccines or live attenuated virus vaccines.

Underlying causes

The underlying causes for the emergence of infectious diseases are anthropogenic social and environmental changes. These result from the combined weight of human numbers and their consumption patterns that are overloading the planet's biophysical and ecological capacity. Some of these causes are summarized in Box 1.

Although the effects of these human-caused changes on the emergence of infectious diseases are known in principle, surprisingly little attention has been given in the scientific literature to the association between the emergence of the diseases described above and potential underlying factors. For example, the emergence in

Box 1 Underlying causes for the emergence of infectious diseases.

Generalized social changes (worldwide urbanization, intravenous drug abuse and changing sexual practices).

Demographic changes (increased and accelerated human mobility and increases in refugee populations).

Medical care (infections in hospitals and nursing homes) and medical technology (blood transfusion, organ transplantation, re-used syringes for antibiotic injections, contamination of vaccines and antibiotic resistance).

Economic and commercial trends (intensive food production, extended irrigation and liberalized trading patterns).

Climatic changes (global warming and regional changes).

Ecosystem disturbance (deforestation, eutrophication of waterways and reduction in predators of disease vector organisms) [1**].

humans of SARS-CoV infection could be associated with changes in the scale of the exotic meat trade (both from farmed and wild-caught animals) in recent years. Likewise, the repeated emergence of highly pathogenic avian influenza in humans in Hong Kong could be related to the rapid growth of the poultry industry in China — 160% for chickens and 190% for ducks — between 1991 and 2001 [40]. The recent outbreak of highly pathogenic avian influenza in the Netherlands might also be associated with the rapid increase in the number of free-range chickens, from 0 in 1991 to 305 000 in 2001 (data from Statistics Netherlands [41]); there is an association between the presence of free-range poultry farms and highly pathogenic avian influenza outbreaks in North America and the UK [42]. Furthermore, outbreaks of Ebola virus infection in humans and great apes in western equatorial Africa could have resulted from the rapid expansion of mechanized logging and bushmeat trade in that area [35**].

Conclusions

The emergence of viral diseases continues, and affects humans in both developed and developing countries, as well as domestic and wild animals. Earlier detection of outbreaks will be facilitated by improved surveillance methods and should include wildlife, because they are often the source of EIDs. However, on the basis of past experience and the complexity of the interactions between these predisposing factors, it is virtually impossible to predict the emergence of future infectious diseases. Despite this uncertainty, we do have the current technological capability to rapidly respond to EIDs in terms of identification and diagnostic techniques and, to a lesser degree, with vaccines and therapeutic agents. It is important to recognize that the underlying causes for the emergence of infectious diseases are human-caused social and environmental changes.

If the human impact on the ecosystem continues to escalate, the rate of emergence and re-emergence of infectious

diseases will only increase in future. By adequately identifying the underlying factors that cause specific EIDs, we can address them and so help to change this trend and allow the transition to a more sustainable society.

Update

Domestic cats (*Felis domesticus*) and ferrets (*Mustela furo*) are susceptible to experimental SARS-CoV infection and easily transmit virus to non-inoculated animals. The fact that two distantly related carnivore species can so easily be infected with SARS-CoV indicates that the reservoir for this virus may involve multiple species [43].

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