Emerging viral diseases

The concept of 'emerging viral disease' was proposed at the end of the 1980s in response to the appearance of the AIDS pandemic. The term has been used (and abused) ever since to encompass a range of viral infections often associated with 'Andromeda-style' headlines. This brief review provides examples, and identifies predisposing factors associated with their emergence.

By the end of the 1960s it was felt that most pathogenic human viruses had been described and classified. The ensuing decades produced some surprises, and revealed our shortsightedness, with the emergence of Lassa fever, HIV, Marburg and Ebola viruses. Emerging viral diseases have become a major public health problem during the 1990s. Are they increasing in the world or are we seeing the results of better reporting of persistent problems? Both these and several other factors are probably at work. The globalisation of trade; the mass movement internationally of huge numbers of people whether as tourists, business travellers, migrants or refugees; the growth of cities and changes in ecology and climate, are all creating new opportunities for the emergence of viral diseases.

From the point of view of human disease, there are at least two types of 'emerging' viruses:

- those previously unknown, and consequently perceived as novel viruses
- those previously recognised as enzootic or endemic infections, but which suddenly emerge as epidemics in humans when environmental or societal changes occur (Fig 1).

Key Points

- Modern molecular analytical methods can explain the origins of emergent viruses
- Most emerging virus diseases are caused by 'old' rather than newly evolved viruses
- Predisposing factors in the emergence of viral diseases are increasing
- Viral diseases emerge for finite periods, but opportunities for emergence persist

The choice of examples presented in this review is intended to be representative. It is, however, arguable that viruses such as influenza could be included. Influenza is one of the best examples of a disease that emerges through change and adaptation of the aetiological agent. The recent outbreak of avian influenza in Hong Kong, in which six people died, is a reminder of this.

The emergence of novel viruses

HIV1 and HIV2

The appearance of AIDS in the 1980s initially appeared to be one of the great mysteries of the 20th century and raised public awareness of emerging diseases to an unprecedented level. Epidemiological studies indicated that an apparently unique infectious agent could be transmitted in several ways:

- during sexual intercourse with male or female partners
- through intravenous drug abuse
- by the use of blood products for therapy to relieve various diseases
- by vertical transmission from mother to child.

This group of viruses is now widespread in Africa, Asia, Europe and both North and South America. By the mid-1980s, HIV1 was shown to be the aetiological agent of human AIDS. HIV2 is found predominantly in West Africa, and produces a slightly milder disease with a longer period of latency and lower morbidity.

The current explanation for the mysterious emergence of HIV1 and HIV2 is that, in several separate evolutionary events, the viruses transferred from African monkeys and chim-
panzees to humans\textsuperscript{2-4}. Possible circumstances surrounding these events include human exposure to infected animals during butchery for food, exposure to the viruses as contaminants of vaccines prepared in simian cell cultures, or keeping the infected animals as pets. Urbanisation, promiscuity and extensive worldwide travel fuelled the initial flames of human infections.

\textit{Equine morbillivirus}

In September 1994, a new virus appeared in Brisbane, Australia, killing a veterinarian and 14 horses. A similar virus killed another man and two horses in 1995\textsuperscript{5}. The virus caused hyperacute respiratory disease, and was identified as a unique paramyxovirus related to, but different from, measles and rinderpest virus. Although antibodies to equine morbillivirus have been found in fruit bats, the origin of the virus is still unknown.

\textit{Filoviruses}

Despite its bad press, the number of reported cases of Ebola haemorrhagic fever has been fewer than 1,000 since the disease emerged in Zaire and Sudan in 1976\textsuperscript{6}. Ebola virus, named after a river in Zaire, is related to Marburg virus, a virus that simultaneously caused outbreaks of haemorrhagic fever in Germany and Yugoslavia in laboratory workers processing kidneys from African green monkeys and which was spread through nosocomial infections. The spread of Ebola virus is dependent on close contact with clinical cases, and the epidemics ended when quarantine measures were introduced. An Ebola-like virus, which caused deaths in non-human primates imported into Reston, VA, in 1989 and 1996, seems less virulent.

Efforts to trace the natural reservoir hosts of filoviruses have been largely unsuccessful, although bats are prime suspects for Ebola virus. Thus, it is not known whether filoviruses are novel viruses. The suggestion that Ebola virus caused the plague of Athens (430–425 BC) may indicate that they have haunted us for some time.

The emergence of epidemic viruses from naturally enzootic viruses

\textit{Rift Valley fever virus}

The mosquito-borne virus, Rift Valley fever (RVF) virus, emerged from its enzootic cycle in 1977–1978 when some 200,000 people in Egypt were infected and 568 deaths were reported. Prior to this time, the disease was limited to sub-Saharan Africa where the virus is maintained by infected flood water mosquito eggs in pools known as ‘damboes’. Environmental changes to improve irrigation provide ideal conditions for the emergence of this febrile illness, which may also involve haemorrhagic fever, encephalitis and ocular disease. In 1987, two years after completion of the Diama Dam, the predicted RVF epidemic occurred in the Senegal river basin. Agricultural development appears to have precipitated the emergence of RVF in Madagascar, and there is now concern about
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Figure 2. Emergence of dengue viruses compared with human population growth.

proposed irrigation projects in southern parts of the country.

Dengue haemorrhagic fever

Dengue (DEN) virus is transmitted to humans by infected Aedes mosquitoes when they take a blood meal. Failure to maintain mosquito eradication programmes has seen the emergence of a global health problem associated with DEN virus. There are four distinct DEN virus serotypes, each of which has spread throughout the mosquito-infested tropical regions of the world during the past 40–50 years, causing 35–60 million human infections each year. As a result, the possibility of exposure to more than one DEN virus serotype during the first 5–10 years of life has increased significantly. There is good evidence that low level immunity to one or more DEN virus serotype after recovery from dengue fever predisposes an individual to dengue haemorrhagic fever or dengue shock syndrome following infection with a second or third DEN virus serotype. This is known as antibody-dependent enhancement (ADE), and represents a predisposing factor in the emergence of the disease which is increasing in frequency as the human population density increases (Fig 2). Whilst ADE is most commonly recognised for DEN virus infections, the phenomenon has also been observed with other viruses such as respiratory syncytial virus. The wider significance of ADE may become apparent as more viral diseases emerge.

Hantavirus pulmonary syndrome

During the Korean War thousands of troops developed a mysterious disease marked by fever, headache and acute renal failure, with a mortality rate of 5–10%. Eventually, a virus named Hantaan was isolated from rodents, the ‘zoonotic pool’ of this virus group. Related viruses responsible for many fatal infections have recently been found worldwide. Hantaviruses are transmitted to humans primarily by inhalation of aerosolised urine. In May 1993, a cluster of deaths in the

South-Western USA led to the definition of yet another new clinical syndrome, hantavirus pulmonary syndrome. This disease has a 60% fatality rate and is characterised by fever, an abrupt onset of acute pulmonary oedema and shock. Although human cases are spillover infections from rodents, a new threat has arisen, namely, person-to-person transmission.

Monkey pox virus

With the successful eradication of smallpox virus from the world, the need to immunise against that disease disappeared. However, monkey pox, a related virus, has begun to emerge as a human epidemic virus in Africa. The absence of immunity to smallpox combined with the immunosuppressant effects of HIV provide an opportunity for the emergence of monkey pox, effectively filling the void left by the eradication of smallpox virus.

Conclusions

Predisposing factors in the emergence of viral diseases are increasing. Urbanisation, agricultural development, transportation and travel are expanding. Climate change is providing new habitats for arthropod vectors. Viruses are evolving rapidly, generating variants that exploit new niches. Although ‘emerging disease’ may be a transient phenomenon, the underlying problem must be taken seriously.

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Tuberculosis: an international perspective

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This article summarises a comprehensive review of the global tuberculosis (TB) epidemic and the impact of the human immunodeficiency virus (HIV). There is also a brief description of the World Health Organization (WHO) recommended TB control strategy, an update on the current status of TB control worldwide, and a look at future prospects for global TB control. An accompanying article by Drobniewski covers the increasingly important issue of drug resistance.

The global tuberculosis burden: notifications and estimates

Case notifications often represent only a fraction of the true incident cases, particularly in those developing countries where access to effective TB care is limited. WHO estimates of incidence are derived:

- for developing countries, from the annual risk of TB infection
- for low prevalence, industrialised countries, from notification data.

Figure 1 shows estimated TB incidence rates by country in 1996.

The impact of HIV on tuberculosis

HIV is the most important risk factor for progression of Mycobacterium tuberculosis infection to clinical disease. WHO estimated that 30.6 million people were living with HIV infection worldwide at the end of 1997, 20.8 million (68%) of them in sub-Saharan Africa. The HIV pandemic has magnified the TB epidemic where there is overlap between M. tuberculosis- and HIV-infected populations.

Using estimates of the prevalence of M. tuberculosis and HIV infections in various regions, WHO has estimated that at the end of 1997 there were about 15 million persons with M. tuberculosis and HIV co-infection worldwide, of whom the great majority were in sub-Saharan Africa (12 million) and most of the rest in South-East Asia (3 million). These estimates are likely to be conservative because the risks of infection with M. tuberculosis and HIV were assumed to be independent, but it is likely that they share common risk factors. The annual risk of progression to TB among persons infected with both HIV and M. tuberculosis is 5–15%, depending on the degree of immunocompromise, compared with an estimated 10% lifetime risk in persons infected with M. tuberculosis alone.

Many countries in Eastern and Southern Africa (eg Uganda, Malawi, Zambia and Tanzania) have reported nationwide HIV seroprevalence rates among new TB patients of at least 30%15. In Asia, Northern Thailand12,13 and certain urban areas of India14 have reported rapidly-increasing HIV seroprevalence rates among TB patients. The number of reported cases of TB has increased dramatically since the 1980s in areas where HIV seroprevalence has increased among TB patients. The increased number of cases poses a challenge to health services, TB control programmes and clinicians15. Tables 1 and 2 show estimated TB incidence and deaths respectively, including those attributable to HIV.

Studies in various regions have shown that about 25% of patients had TB during the course of HIV infection in Latin America17, Mexico18 and Haiti19.