Emerging viruses – is there an emerging pattern?

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The Ebola outbreak in West Africa in 2014 and the spread of Zika across the Americas in 2016 have thrust previously obscure viruses into the media spotlight. But is something new really going on? What can we expect in future? Is there anything we can do?

How to frighten children

One of the formative experiences of my childhood was Terry Nation's TV series *Survivors*, which aired on the BBC in April 1975. Even today, the first episode is still chilling in its portrayal of a London overwhelmed by a new infectious disease until, in the words of one character: "the dead outnumber the living." Nation was best known as the creator of Dr Who's perennial adversary, the Daleks, but *Survivors* was a far more serious project, growing directly from his own conviction, about which he had "no doubt", that "the disaster – in whatever form – will come" (Radio Times interview, 10 April 1975). *Survivors*' dramatization of the helplessness of humanity in the face of a relentless and virulent pestilence, instilled my lifelong fascination with pandemics.

Nation's premonition of imminent global meltdown turned out to be false (at least so far), but *Survivors* was partly prophetic in that the years immediately following its broadcast really did see the rise of many new viral diseases. The first of these appeared in the Soviet Union in November 1977, and was quickly named 'Russian flu' by the Western media. Russian flu was insufficiently severe for the World Health Organization to officially declare it a pandemic strain, but its inexplicable similarity to seasonal H1N1 influenza of the 1950s fuelled speculation that it was an escapee from a Soviet laboratory. Eighteen months previously, the opening credits of Survivors had shown a sinister scientist dropping a flask, then flying out of Moscow to another airport before collapsing and dying – implying that, as later occurred in real life, the Russians were to be blamed.

Sex, drugs and blood transfusions: the first trio of pandemics

The next media health scare was genital herpes. This was not by any means a new disease, and its causative agent, herpes simplex virus type 2, had been known since the 1960s. However, there was a considerable expansion in the incidence of genital herpes in the mid-to-late 1970s and the press were quick to portray it as a disease of sexual promiscuity. Media fascination with genital herpes has long waned, but its incidence continues to increase to this day.

Part of the reason for genital herpes losing the limelight was that a far more serious disease appeared in the US gay community in 1981, named the following year as AIDS. The isolation of the causative agent, HIV-1, in 1983 revealed a previously unknown virus. Once diagnostic tests were developed, it quickly became apparent that AIDS was by then well established in Africa, with footholds in several other continents. The AIDS pandemic had simply not been noticed until it entered a Western population. In the 21st century, Bayesian phylogenetic techniques have now revealed that HIV-1 had been spreading

in the Congo Basin in central Africa since around 1920, having entered human populations from chimpanzees, and probably arrived unheralded in New York around 1972. The process of animal-to-human host transfer, by which chimp SIV-1 became human HIV-1, is referred to as zoonosis, and it has become a recurring theme in the pandemics of the last three decades. A further recurring theme is the lateness at which pandemics are often recognized, even when the virus is previously known.

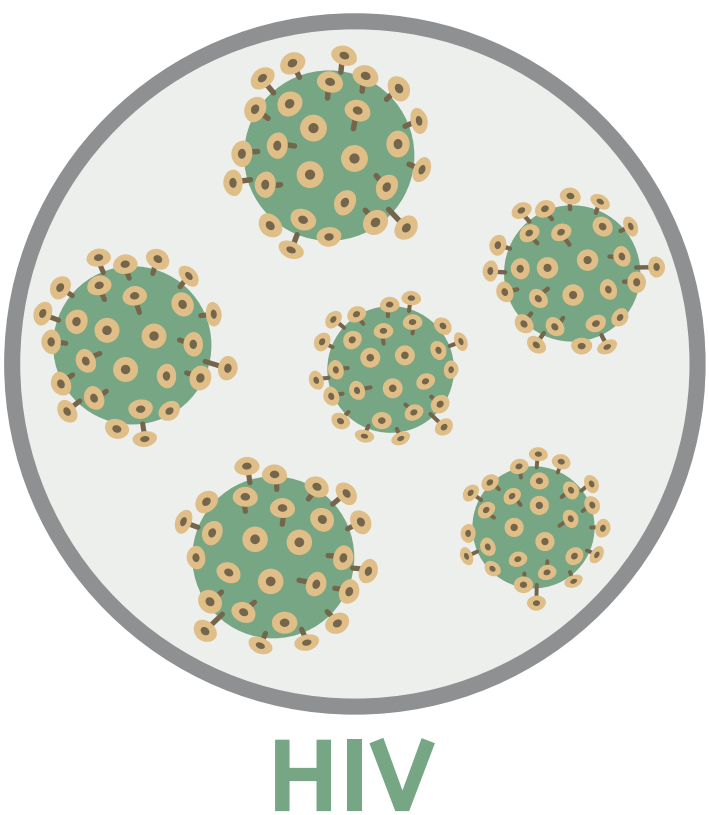
Hepatitis C virus (HCV) was finally identified in 1989, although its existence had been suspected since the mid-1970s. HCV, a blood-borne and sexually transmitted virus, spread through many of the same social networks as HIV-1, and also probably had its origins in Africa, but subsequent phylogenetic analyses have revealed a much earlier origin. HCV was not decades old like HIV-1 when it first came to public attention, but centuries old. This perhaps explained why HIV-1's zoonotic source was readily identifiable as chimp SIV-1, but HCV's ultimate origins have faded in the 500 years or more it has been spreading slowly around the planet. Nevertheless, historical timescales aside, the emergences of HIV-1 and HCV showed many parallels in geographical origins, modes of transmission and routes of travel.

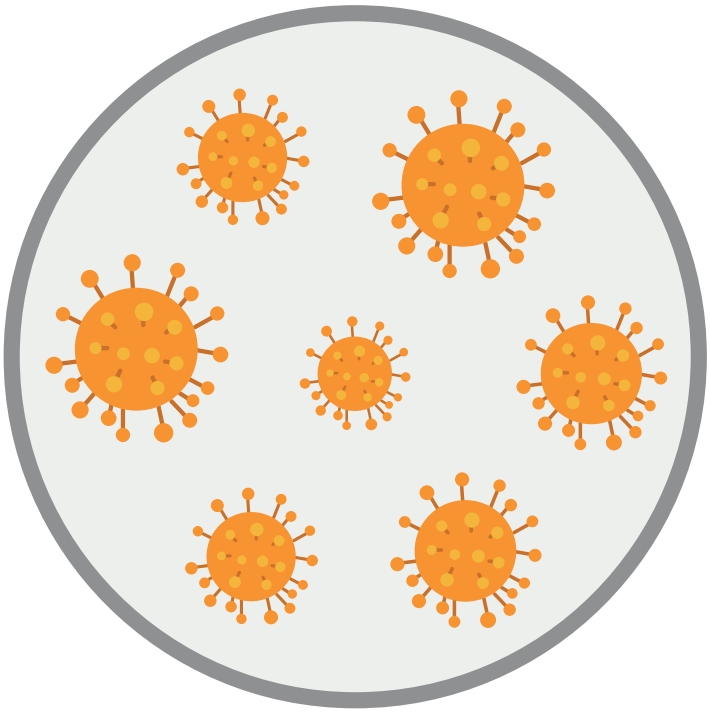
Virology's meteorite near-miss

Astronomers are fairly certain that a meteorite impact 65 million years ago led to the extinction of the dinosaurs. In January 2017, the 35 metre diameter asteroid AG13 passed between the earth and the moon, becoming the latest in a long line of near-miss events, potentially devastating if only a little nearer and larger, but otherwise simply joining the list of disasters that never quite happened.

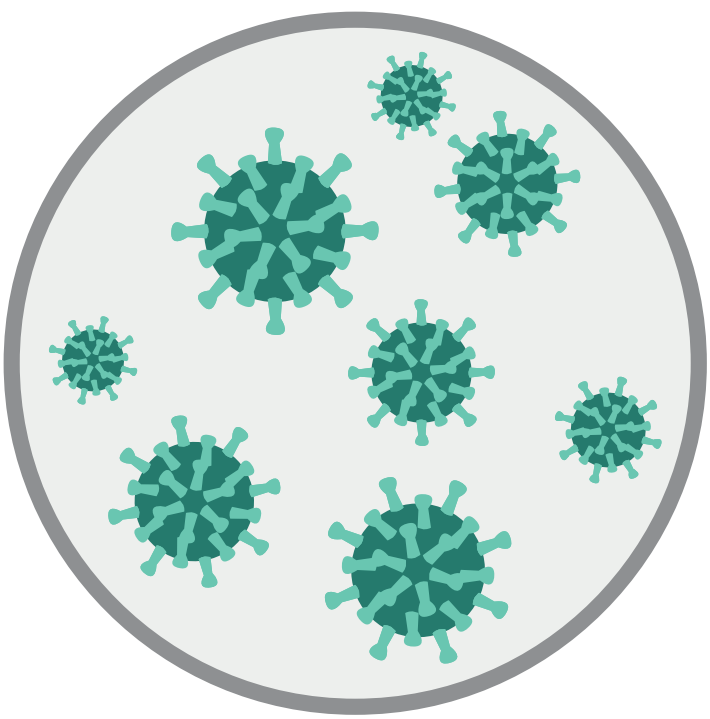
Virology's equivalent occurred in 2003, when a new and virulent flu-like illness, severe acute respiratory syndrome (SARS), began to spread in Hong Kong, having begun at the end of the previous year in mainland China. Initial observation of super-spreader events – one case in a Hong Kong hotel led to 16 new cases – and high mortality, raised fears that SARS might cause a rapid pandemic with many millions of deaths. The confirmation that SARS was a coronavirus, a family into which some common cold viruses fall, only served to deepen the conviction that SARS was at least as dangerous as HIV-1 in terms of the total number of deaths it could cause, and was likely to cause them a lot quicker. In the end, some heroic public health efforts over several countries helped contain the disease, and the final tally of cases and fatalities revealed a death rate of just under 10% of patients – not as bad as had been initially feared. Then, SARS suddenly disappeared and has not been seen since, like a meteorite heading off into the blackness of space. The zoonotic origins of SARS may be in bats, where several related viruses are found, via palm civets, where the virus was detected at the time of the outbreak, and SARS is just one of several diseases where the sale of wild animals for domestic consumption – the bushmeat trade – may represent the best candidate for the point of zoonotic entry.

In 2012, another new coronavirus, Middle East respiratory syndrome (MERS), appeared in Saudi Arabia. With a mortality rate exceeding 35% of patients, SARS paled by comparison, but fortunately MERS is not readily transmissible and most cases have occurred in a hospital setting. Travel-associated cases have appeared fairly regularly in several countries, but almost always without onward spread. The exception was in 2015 in Korea, when a traveller returning from the Gulf seeded a hospital outbreak of a magnitude similar to those previously seen in Saudi Arabia. MERS would seem to have relatively little pandemic potential in the general population but coronaviruses, with their fast evolution and easy respiratory transmission in some cases, always make virologists uneasy. Unlike SARS, the zoonotic source of MERS is clear – camels – but again several closely related viruses in bats may indicate its deeper origins.





SARS



MERS-CoV

Ebola tears up the textbooks

Although the 2003 SARS episode was one over which virologists lost more sleep than the general public, the 2014 outbreak of Ebola in West Africa provoked global alarm. Since its discovery in 1976, Ebola had been an exhibit in virology's 'chamber of horrors' – appalling but fortunately very rare and confined to isolated parts of the Congo Basin and surrounding regions. In the recriminations following the series of events that allowed Ebola to produce its first truly mass outbreak, one of the crucial factors identified in its early spread was that Ebola was not supposed to occur in West Africa. When the teams from the Guinean Ministry of Health and Medecins Sans Frontières reached the epicentre in the second week of March 2014, performing the crucial confirmatory test, the outbreak was in its fourth month and affected patients had already spread out over several localities, including two hospitals. If it had occurred to the provincial health authorities to request an Ebola test in the first two months of the outbreak, it might have been possible to contain the disease within its initial focus in Meliandou village. Such patterns of early diagnosis and quick quarantine have long been the practice in Congo, including another unrelated Ebola outbreak that occurred in northern Congo in mid-2014. But not everything was necessarily down to human error – retrospective analysis of how the Ebola virus evolved over the course of the outbreak also identified some mutations which may have assisted transmissibility.

Some determined efforts to locate the zoonotic source of the West African outbreak have so far failed to provide conclusive evidence. Nevertheless, bats remain the best candidate for Ebola's natural reservoir. Exactly why so many efforts to trace the zoonotic sources of human emerging viruses, from SARS through MERS to Ebola, end at the same destination, is not clear. Bats may well, because of their inverted roosting position, be more likely to have urine or faecal material on their bodies, and this inherent lack of hygiene may be a factor.

Viruses take wing

Just as there is a possibility that the West African Ebola epidemic may have been super-charged by a mutation occurring early in the outbreak, the rapid spread of chikungunya in the present century has also been linked to genetic changes in the virus. However, chikungunya is not the only mosquito-borne virus – collectively known as arboviruses – to have gone pandemic. Beginning with the spread of dengue into the Americas in 1977, followed by West Nile virus (WNV) in 1999, chikungunya in 2013 and Zika shortly afterwards, diseases spread by mosquito bite have moved out of their previous African and South-East Asian ranges to achieve global distribution in the

tropics and sub-tropics. WNV's transmission by cold-adapted midges means that it has spread as far north as the US–Canadian border and central Europe.

Dengue, WNV and chikungunya were all known pathogens that were on the surveillance radar following expansions elsewhere – most notably chinkungunya's spread across the Indian Ocean from Africa to South-East Asia beginning in 2005. By contrast, Zika had a mere dozen or so cases described in the medical literature prior to the beginning of its own trans-Pacific spread in 2007, and its mildness compared with the others only intensified the sense of shock when it became apparent that it was the cause of thousands of cases of birth defects across Latin America. Indeed, although death rates from Zika are lower than from the other members of the pandemic arbovirus quartet, its long-term economic and social impact is potentially larger.

The common themes

Despite the diversity of emerging viruses, several issues link many of them together. Zoonosis – the transfer of a virus from an animal reservoir to a new home in humans – is the origin of HIV-1, SARS, MERS, WNV, Ebola and probably HCV and Zika, even if the ultimate animal origin is unproven. Bushmeat consumption is probably a key point in the zoonotic process for SARS, Ebola, MERS and HIV-1. The need for bushmeat reflects increases in human population which cannot be sustained via traditional agriculture. Urban overcrowding into unhygienic shanty town slums provides the ideal environment for the spread of close-contact diseases like Ebola. Providing water supplies in shanty towns requires open storage tanks which then invite infestation with mosquitos bringing dengue, chikungunya and Zika. Absence of adequate health services ensures the continuing spread of HIV-1. The immunodeficiency brought on by AIDS renders populations vulnerable to further infection and means that they cannot adequately respond to vaccination campaigns against established viruses like yellow fever, measles and polio.

We need not necessarily share the fatalism of the late Terry Nation, penning *Survivors* in anticipation of a dramatic pandemic end to civilization, but optimism is difficult. Children no longer need fiction to frighten them.

The bigger picture

This article has focused on viruses affecting humans over the last 40 years. Although this is the part of microbiology that fills our television screens and social media channels, we should remember that viruses also affect pets, livestock and plants, and that bacteria, fungi and parasites may cause just as much trouble in their own slower, more persistent way. If all we do is treat disease, then it will return. We need to change the conditions – ecological, social, economic and political, and all the way along the food chain – that are increasingly fostering the spread of new diseases through the human environment. Solutions that deal with a single aspect of the problem will merely deflect the problem elsewhere. There are no easy answers so far, but the first step in dealing with a problem is to recognize that it exists. ■

Further reading

- Bausch, D.G. and Schwarz, L. (2014) Outbreak of Ebola virus disease in Guinea: where ecology meets economy. PLoS Negl. Trop. Dis. **8**(7), e3056. doi:10.1371/journal.pntd.0003056
  Penned almost as a work of reportage in the early days of the West African Ebola outbreak, this article has become something of a minor classic in its concise and compelling description of a disaster waiting to happen.
- *Two papers are essential reading in understanding the origins of AIDS.*
  Faria, N.R. et al. (2014) The early spread and epidemic ignition of HIV-1 in human populations, Science **346**(6205), 56–61, *traces HIV-1 back to its chimpanzee fountainhead in the jungles of colonial Africa.*
  Worobey, M. et al. (2016) 1970s and Patient 0 HIV-1 genomes illuminate early HIV/AIDS history in North America, Nature **539**(7627), 98–101. doi:10.1038/nature19827, *takes up the story of HIV-1 as it crosses the Atlantic in the 1970s.*
- Duffy, M.R. et al. (2009) Zika virus outbreak on Yap Island, Federated States of Micronesia. N. Engl. J. Med. **360**, 2536–2543
  This detailed dissection of the strange appearance of an obscure African virus on a remote Pacific island, was the first indication of the intercontinental invasion that was to follow. It can hardly be read now without hindsight producing a slight unnerving frisson.

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