
Catastrophes after crossing species barriers

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Probably the most tragic examples of virus infections that have caused the deaths of many millions of people in the past century were the influenza and AIDS pandemics. These events occurred as a direct result of the introduction of animal viruses into the human population. Similarly, mass mortalities among aquatic and terrestrial mammals were caused by the introduction of viruses into species in which they had not previously been present. It seems paradoxical that at a time when we have managed to control or even eradicate major human virus infections like polio and smallpox we are increasingly confronted with new or newly emerging virus infections of humans and animals. A complex mix of social, technological and ecological changes, and the ability of certain viruses to adapt rapidly to a changing environment, seems to be at the basis of this phenomenon. Extensive diagnostic and surveillance networks, as well as novel vaccine- and antiviral development strategies should provide us with the safeguards to limit its impact.

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By far the most appealing achievement of modern medicine has been the worldwide eradication of smallpox in the late 1970s. This was the result of an unprecedented international collaborative effort, coordinated by the World Health Organization, using the first live attenuated vaccine that had been introduced about two centuries earlier by Jenner.

Similarly, considerable progress has been made with the worldwide eradication of poliomyelitis, which is expected to be achieved within the coming years. Also a start has been made with the eradication of measles, which has now virtually disappeared from the Americas. From time to time, however, the virus is re-introduced into industrialized countries, which are considered to be free, as was recently shown in The Netherlands where two independent outbreaks were observed. The first resulted from the introduction by an immunocompromised child in an intensive care hospital ward (De Swart *et al.* 2000) and the second by the spread of measles virus among children who had not been vaccinated on religious grounds.

It seems paradoxical that at a time when we are capable of eradicating virus infections that over the centuries have killed millions of people and wrecked the lives of many millions more, we are apparently confronted with several new or newly emerging virus infections of man and animals. The influenza and AIDS pandemics of the past century are probably the most striking examples, but especially in the last decade many more new virus infections seem to have emerged. The obvious question is whether this observed increase is indeed real, or whether it is the result of the scientific and lay press paying increasing attention to these issues. The major changes that may have contributed or predisposed us to this apparent increase over the last decades are related to changes in human behaviour, increase in human mobility, demographic changes, human exploitation of the environment,

decreased attention to infectious disease research and control and the ability of certain viruses to adapt rapidly to a changing environment. In fact all of these predisposing factors have largely contributed to the worldwide spread of HIV-1 and HIV-2 from primate reservoirs in the past two decades: changing mores and taboos, intravenous drug abuse, travel, wars, increases in population density and urbanization, greater contact with wild primates, breakdown of public health infrastructure and the extreme variability of these viruses.

The increase in contact between humans and wild or feral animals due to, for example, changing habitats or climatological conditions, may directly or indirectly lead to the emergence of virus infections in humans. The close relatedness between humans and primates allows many viruses to cross the species barrier between the two. Besides the introduction of HIV-1 and HIV-2 into the human species, many other primate viruses have caused major problems in humans: outbreaks of monkeypox and filovirus infections are recent examples that have attracted considerable media attention. The ongoing identification of previously unrecognized retro-, hepadna- and herpesviruses, which all proved to be closely related to human viruses of the same virus families, illustrates the existence of virtually unlimited primate reservoirs of potential human pathogens. Contact between humans and wild rodent populations that have increased due to climatological changes may also lead to severe outbreaks of virus infections, like the recent hantavirus infections with high case-fatality rates in the Americas.

The increased distribution of arthropods like *Aedes aegypti* (Egyptian mosquito) has led to massive outbreaks of dengue virus infection with high mortality rates due to dengue haemorrhagic fever and dengue shock syndrome in middle America and South-East Asia. Recently,

another flavivirus transmitted by mosquitoes, West Nile virus, was introduced in North America where it caused outbreaks of encephalitis among inhabitants of New York and New Jersey. The virus was introduced into avian reservoirs about one year ago.

Birds also play an important role in the epidemiology of influenza of humans. In the past century, three major influenza pandemics resulted in the loss of many millions of lives. The Spanish flu alone caused the deaths of more than 20 million people by the end of World War I, which itself resulted in about eight million deaths. Following the introduction of a new pandemic influenza A virus from an avian reservoir, influenza A viruses have been shown to continue their circulation, which eventually leads to more deaths than those caused by the initial pandemic outbreaks. It is probable that after introduction of an influenza A virus from an avian reservoir into a mammalian species, the virus needs to reassort with an existing mammalian influenza A virus to become a real pandemic virus. After the recent episode of the H5N1 so-called 'chicken' influenza virus outbreak in Hong Kong (de Jong *et al.* 1997; Claas *et al.* 1998), in which six people died, it became clear that such a reassortment event could probably also take place in humans (Claas & Osterhaus 1998). It is quite likely that influenza pandemics will also occur this century. It is, however, impossible to predict when they will happen and which influenza A virus will be involved. Any predictions in influenza epidemiology seem to be spurious. Recently we showed that, in contrast to what was generally accepted, influenza B virus did not only infect humans, but could also be found in seals (Osterhaus *et al.* 2000). We speculated that the influenza B virus that we found in seals in 1999, which was actually identical to a human influenza B virus of 1995, could pose a future threat to humans if indeed it were to remain in an evolutionary stasis as observed.

Emerging virus infections may also have a major impact on domestic and wild animals. Again the main origin of emerging viruses in animals is their introduction from other animal reservoirs. Recently a whole range of previously undiscovered and well-known morbilliviruses was identified as the primary cause of mass mortalities in aquatic mammals like seals and dolphins. The mass mortality of *ca.* 50% of the total harbour seal population of north-western Europe in the late 1980s was caused by the introduction of a 'new' morbillivirus: phocine distemper virus (PDV) (Osterhaus & Vedder 1988). Probably due to the profound immune suppression that infection with this virus caused, a plethora of other viruses was isolated from affected animals (Osterhaus 1988). Vaccination-challenge experiments and serological screening were needed to prove that the PDV infection was indeed the primary cause of that outbreak (Osterhaus *et al.* 1989a). Interestingly, a similar disease outbreak that occurred among Lake Baikal seals at approximately the same time was caused by the interspecies transmission of canine distemper virus (CDV) from local domestic dogs (Osterhaus *et al.* 1989b).

Two years after these morbillivirus outbreaks among seals, mass mortality was observed among striped dolphins in the Mediterranean Sea. The primary cause was, again, a previously undiscovered morbillivirus: dolphin morbillivirus (DMV). This virus proved to be

closely related to a virus that had previously been found to be a cause of mortality in porpoises (porpoise morbillivirus (PMV)), and it was more distantly related to PDV and CDV (Barrett *et al.* 1993). Subsequently, we discovered a DMV-like virus in highly endangered Mediterranean monk seals that had died off the coast of Mauritania and in Greek waters (Osterhaus *et al.* 1997).

A mass mortality among lions in the Serengeti also proved to be caused by a CDV infection that had spilled over from Massai dogs and probably via hyenas (Harder *et al.* 1995). It had not been realized that lions were indeed susceptible to CDV infection.

The multitude of morbillivirus infections in aquatic mammals inhabiting heavily polluted coastal waters, has left lingering concerns that persistent organic pollutants (POPs), many of which are demonstrated immunotoxicants, including PCBs, dioxins and furans, played a contributory role to these mass mortalities by rendering the animals more susceptible to the effects of these infections. We have therefore carried out a 30-month captive feeding study of two groups of harbour seals in which 22 seals were fed herring from either the relatively uncontaminated Atlantic Ocean or the contaminated Baltic Sea. POPs disrupted immune function in seals that were fed the Baltic Sea herring, causing diminished T-cell function *in vitro* and *in vivo*, and reduced natural killer cell function, both of which are crucial to anti-virus defences in vertebrates (Harvell *et al.* 1999; Ross *et al.* 2000).

Recently a new group of paramyxoviruses, closely related to but distinct from the genus *Morbillivirus*, which apparently cause persistent infections in frugivorous bats, has caused mortality among horses and pigs. These closely related viruses, which were identified in Australia (Hendra virus) and Malaysia (Nipah virus), respectively, were also shown to cause fatal infections in humans exposed to horses or pigs. Introduction of intensive pig farming in areas where these bats are common has probably been the direct cause of the introduction of Nipah virus in the intensively farmed pig populations.

Changing agricultural methods have also been at the basis of the emergence of a new variant of Creutzfeldt–Jakob disease (vCJD), which so far has caused the deaths of approximately 70 individuals in the UK. The causative agent proved to be indistinguishable from that of bovine spongiform encephalopathy, which has infected almost a million cattle in the UK during the last two decennia. The feeding of cattle with protein concentrate containing bovine meat and bone meal that had not been adequately sterilized allowed the agent to re-circulate within the cattle population, thus exposing the human food chain to this newly discovered agent. Given the long incubation period of the disease in humans, uncertainties about the extent and ways of exposure and the efficacy of the preventive measures taken, it is hard to predict how many more cases of vCJD may be expected to occur in the UK and the rest of Europe.

Finally, it should also be realized that newly emerging medical techniques, like blood transfusion, vaccinations, transplantation of organs or tissues between humans (allotransplantation) or between animals and humans (xenotransplantation) might, if performed without the necessary precautionary measures, also contribute to the emergence of virus infections in humans and animals.

In conclusion, it may be stated that during the past decades, a complex mix of social, technological, ecological and viral changes has predisposed humans and animals to the emergence or re-emergence of virus infections that have crossed species barriers. The establishment of well-coordinated national and international surveillance networks, as well as the development of novel vaccine and antiviral development strategies should provide the safeguards needed to limit their impact.

REFERENCES

- Barrett, T., Visser, I. K. G., Mamaev, L., Goatley, L., Van Bresse, M. F. & Osterhaus, A. D. M. E. 1993 Dolphin and porpoise morbilliviruses are genetically distinct from phocine distemper viruses. *Virology* **193**, 1010–1012.
- Claas, E. C. J. & Osterhaus, A. D. M. E. 1998 New clues to the emergence of flu pandemics. *Nature Med.* **4**, 1122–1123.
- Claas, E. C. J., Osterhaus, A. D. M. E., Van Beek, R., de Jong, J. C., Rimmelzwaan, G. F., Senne, D. A., Krauss, S., Shortridge, K. F. & Webster, R. G. 1998 Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *The Lancet* **351**, 472–477.
- de Jong, J. C., Claas, E. C. J., Osterhaus, A. D. M. E., Webster, R. G. & Lim, W. L. 1997 A pandemic warning? *Nature* **389**, 554.
- De Swart, R. L., Wertheim-van Dillen, P. M., Van Binnendijk, R. S., Muller, C. P., Frenkel, J. & Osterhaus, A. D. M. E. 2000 Measles in a Dutch hospital introduced by an immunocompromised infant from Indonesia infected with a new genotype virus. *The Lancet* **355**, 201–202.
- Harder, T. C., Kenter, M., Appel, M. J. G., Roelke-Parker, M. E., Barrett, T. & Osterhaus, A. D. M. E. 1995 Phylogenetic evidence of canine distemper virus in Serengeti's lions. *Vaccine* **13**, 521–523.
- Harvell, C. D. (and 12 others) 1999 Emerging marine diseases—climate links and anthropogenic factors. *Science* **285**, 1505–1510.
- Osterhaus, A. D. M. E. 1988 Seal death. [Letter] *Nature* **334**, 301–302.
- Osterhaus, A. D. M. E. & Vedder, E. J. 1988 Identification of virus causing recent seal deaths. [Letter] *Nature* **335**, 20.
- Osterhaus, A. D. M. E., UytdeHaag, F. G. C. M., Visser, I. K. G., Vedder, E. J., Reijnders, P. J. M., Kuiper, J. & Brugge, H. N. 1989a Seal vaccination success. [Letter] *Nature* **337**, 21.
- Osterhaus, A. D. M. E., Groen, J., UytdeHaag, F. G. C. M., Visser, I. K. G., Van de Bildt, M. W. G., Bergman, A. & Klingeborn, B. 1989b Distemper virus in Baikal seals. [Letter] *Nature* **338**, 209–210.
- Osterhaus, A., Groen, J., Niesters, H., Van de Bildt, M., Martina, B., Vedder, L., Vos, J., Van Egmond, H., Abou Sidi, B. & Barham, M. E. 1997 Morbillivirus in monk seal mass mortality. *Nature* **388**, 838–839.
- Osterhaus, A. D. M. E., Rimmelzwaan, G. F., Martina, B. E. E., Bestebroer, T. M. & Fouchier, R. A. M. 2000 Influenza B virus in seals. *Science* **288**, 1051–1053.
- Ross, P. S., Vos, J. G., Birnbaum, L. S. & Osterhaus, A. D. M. E. 2000 PCBs are a health risk for humans and wildlife. [Letter] *Science* **289**, 1878–1879.