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Feature

Virus outbreak crosses boundaries

The current outbreak of coronavirus disease COVID-19 is showing up vulnerabilities in many aspects of the globalised world we live in. The suggestion that it may have originated in the endangered pangolin also puts animal trafficking in the spotlight. The human–wildlife interface remains an important risk factor for further disease outbreaks. **Michael Gross** reports.

By Thursday February 20th, as this article went into production, there have been more than 75,000 confirmed cases and more than 2,000 deaths from the novel coronavirus disease COVID-19. The vast majority of the cases and deaths were recorded within mainland China, but other accumulations of cases have emerged in the South Korean city of Daegu and on the cruise ship Diamond Princess docked at Yokohama, Japan. The World Health Organization (WHO) is issuing daily situation reports, with a risk assessment of ‘very high’ for China and ‘high’ at the global level. Both travel and manufacturing industries are already feeling the effects of the outbreak.

Like other virus infections that have caused concern in the last two decades, COVID-19 has crossed the species barrier from an animal reservoir and demonstrated the ability to spread between humans, making it a further example of a zoonosis. Many zoonotic diseases that have established themselves in the human population, such as today’s childhood infections like chickenpox, have evolved to become relatively harmless, enabling them to spread without endangering the survival of their host population.

This relatively peaceful co-evolution between some zoonotic pathogens and human populations is thought to have originated when agriculture enabled people to live in larger communities, creating effective population sizes big enough to sustain a permanent equilibrium with a weakened pathogen. By contrast, viruses that have made the transition more recently may still be more lethal. Thus, Ebola virus disease, which occasionally causes outbreaks in tropical Africa, where its natural reservoir is in bats, typically causes a very high rate of mortality among those infected and therefore has to be confined at all costs (Curr. Biol. (2018) *28*, R51–R54).

A few outbreaks of severe respiratory disease caused by coronaviruses have caused concern since the beginning of this century. They came from different animal sources and the course of the epidemics has highlighted problems in the response systems.

Caves to markets

Coronaviruses, a group of spherical RNA viruses with an envelope that in the electron microscope can appear like a star’s corona, were discovered in the 1960s in the context of human respiratory diseases like the common cold. They were also found to cause respiratory disease in some animal species, diarrhoea in others.

The first major outbreak of a new and dangerous zoonotic disease linked to a coronavirus was the epidemic of severe acute respiratory syndrome (SARS) in 2002–2003. Starting in November 2002 in southern China, the disease affected more than 8,000 people, with a mortality rate of just under 10%. After spreading to 17 countries, the outbreak could be contained and no cases of SARS have been reported since 2004.

Initial studies into the source of the SARS version of the coronavirus identified the Asian palm civet (*Paradoxurus hermaphroditus*) as a carrier. This small mammal of the tropical forests was on sale for its meat at the local meat markets in Yunnan province.

Further studies indicated that the civets may have been infected by bats. In 2017, the teams of Shi Zheng-Li and Cui Jie at the Wuhan Institute of Virology, China, discovered a mixed population of several species of horseshoe bats in a cave in the Yunnan province carrying a coronavirus variant with precisely the same genetic elements that were found in the pathogen of the SARS outbreak (PLoS Pathog. (2017) *13*, e1006698).

Bats are known to have a remarkable tolerance of viruses that may cause serious disease in other species. This feature has been linked to the dampened inflammation response to stress factors such as DNA present in the cytosol, which can be an indicator of viral infection but in the case of bats can also be linked to the stress caused by the high amount of energy needed for powered flight (Curr. Biol. (2019) *29*, R1163–R1165). Keeping the inflammation response under control enables the bats to mount a robust immune reaction against the virus while avoiding the side effects such as swelling and fever.

Point made: The 2019–2020 outbreak of coronavirus disease has highlighted the vulnerability of the increasingly connected world population to newly emerging zoonotic diseases. (Photo: zhizhou deng/Flickr (CC BY 2.0).)

Animal wrongs: Markets in Asia selling a wide variety of wild and domesticated animals have been identified as a risk factor for the spread of zoonotic diseases such as SARS and COVID-19. (Photo: Daniel Case/Wikimedia Commons (CC BY-SA 3.0).)

In a recent study of bat resistance to viral disease, Cara Brook from the University of California at Berkeley, USA, and colleagues analysed and modelled these effects in detail using cell cultures derived from two different species of bats (eLife (2020) *9*, e48401). The authors conclude that viruses respond to robust bat immunity by establishing more rapid cell-to-cell transmission rates than do comparable viruses in other groups of mammals. Therefore, when they transfer to humans, they may become more deadly than established human viruses.

People don't often mingle with bats, but Brook and colleagues note that the diseases are often transferred from bats to humans via another mammalian host, like the palm civet in the case of SARS. Moreover, they note that disturbing bat habitat may stress the bats and make them shed more viruses via their saliva and excretions. Their Bat One Health field project, currently operating in Madagascar, Bangladesh, Ghana and Australia, explores the link between the loss of bat habitat and the transfer of their viruses into other animals and humans.

Camel connections

The next significant outbreak of coronavirus disease was the Middle East respiratory syndrome (MERS), first identified in Saudi Arabia in 2012. Like SARS, this disease is caused by a virus of the genus *Betacoronavirus*, but of a clearly distinct lineage from that pathogen.

Compared with SARS, it is more deadly but less infectious in the transmission between humans. According to WHO figures from January 2020, there have been just over 2,500 cases so far, causing 862 deaths. In spite of the high mortality of 34%, this virus is not regarded as a major global health threat, as its spread can be contained relatively well.

Virus strains identical to the one in MERS patients were discovered in dromedary camels. The virus appears to have passed from camels to humans on several occasions, causing further outbreaks in 2015 and 2018. Following the first outbreak in 2012, government advice to avoid close contact with camels has led to a backlash among farmers in Saudi Arabia. The BBC reported in 2014 that farmers kissed their camels in defiance of health advice. This kind of resistance to medical advice might explain the later recurrence of the disease. As recently as November 2019, several new cases of MERS were reported from Saudi Arabia, and in each of these cases the infected people were known to have had contact with camels, but not with other patients infected with the virus.

In a recent study, Sohail Hassan from the University of Veterinary and Animal Sciences at Lahore, Pakistan, and colleagues tested for MERS-specific antibodies in camel handlers and their families in Pakistan, where no cases of MERS infection have been reported (Emerg. Infect. Dis. (2019) *25*, 2307–2309). Of 91 ELISA tests, more than half were positive for MERS-CoV antibodies. With a 50% reduction plaque-reduction neutralization test ($PRNT_{50}$), 12 participants tested positive for exposure to the coronavirus, and 10 of these were confirmed by immunofluorescence. While the authors interpret the high ELISA result as possible cross-reaction from other coronaviruses, they consider the ten positive tests obtained by the other two methods as an indication that exposure to MERS-like coronaviruses is widespread among camel handlers in Pakistan.

A separate study conducted in Sudan detected MERS-CoV antibodies in nearly all of the dromedary camels tested but not in humans exposed to them (Emerg. Infect. Dis. (2019) *25*, 2333–2335).

As transmission between humans mainly occurs within healthcare environments, Emmie de Wit and colleagues at the National Institute of Allergy and Infectious Diseases at Hamilton, USA, have tested the prophylactic use of the antiviral drug remdesivir (Proc. Natl. Acad. Sci. USA (2020) *117*, https://doi.org/10.1073/pnas.1922083117). In a study using rhesus macaques, the researchers found that the compound, if given before infection with the virus, protects the animals from becoming ill. The researchers conclude that its usefulness for the protection of healthcare professionals in the current coronavirus outbreak should be tested.

A pangolin pandemic?

The current outbreak of coronavirus disease is, according to the results available so far, less deadly than MERS and SARS, but also more infectious. Even with a death rate below one percent, it could kill millions if it establishes itself in the global human population. This fear motivates the dramatic protection and quarantine measures that have been taken since the disease was first identified.

This new outbreak emanated from the city of Wuhan, the capital of the Hubei province in China, and has been traced back to the Huanan Seafood Market, where numerous animals ranging from fish, chickens, and pheasants to wild animals such as bats, marmots, venomous snakes, and deer are on sale.

At this point it appears certain that the outbreak, like SARS and MERS, is a new zoonotic transfer, but the animal source remains to be confirmed. Sequencing of virus genomes from five of the first cases identified established that the same virus was present in all five patients, that it was new in that it had limited similarity to the SARS virus (79%) and to the MERS one (52%), and that it may have originated in bats, as it showed higher similarity (87%) to viruses found in Chinese horseshoe bats, ZC45 and ZXC21 (Chinese Medical Journal (2020) https://doi.org/10.1097/CM9.0000000000000722).

The connection between horseshoe bats and humans may again have passed through another carrier species. A new zoonotic connection emerged in the shape of the endangered Asian pangolin.

In October 2019, Ping Liu, Wu Chen and Jin-Ping Chen from the Guangdong Institute of Applied Biological Resources, Guangzhou, China, reported that they had discovered high loads of coronavirus in blood samples of 21 Malayan pangolins (*Manis javanica*) that had been confiscated from wildlife traffickers (Viruses (2019) *11*, 979). Many of these animals were ill and 16 of them died despite rescue efforts. Although the motivation of the study was rooted in conservation concerns, as the Malayan pangolin is critically endangered, the discovery of the viruses led the researchers to conclude: “Malayan pangolins could be another host with the potential of transmitting the SARS coronavirus to humans. As a consequence, the viral metagenomic study of Malayan pangolin is meaningful both for the conservation of rare wild animals and public health.”

At a press conference held on February 7th, researchers Shen Yongyi and Xiao Lihua from the South China Agricultural University in Guangzhou reported that they compared the coronavirus sequences from the pangolins to those of the recent outbreak and found them virtually identical. This work, currently submitted for publication, might assign the pangolin a role as an intermediate host between a bat reservoir and the human outbreak, in analogy to the role that palm civets played in the SARS epidemic.

Curling up: The four endangered Asian pangolin species are widely poached and trafficked. As yet unpublished analyses of coronaviruses in pangolins confiscated from traffickers suggest they may have been carriers in the transmission of the new coronavirus from bats to humans. (Photo: Shukran888/Wikimedia Commons (CC BY-SA 4.0).)

The suggestion casts a spotlight on one of the most endangered and most trafficked groups of mammals. Pangolins, which are armoured with tough scales like armadillos, have the defence strategy of curling up into a ball like a hedgehog. Unfortunately, this makes them vulnerable to human hunters who can just pick them up and take them home. Hunted both for their meat and for the use of their keratin scales in traditional medicine, the four species of Asian pangolins are all endangered, three of them critically. The four African species (two of genus *Phataginus*, two of *Smutsia*) are listed as vulnerable or endangered.

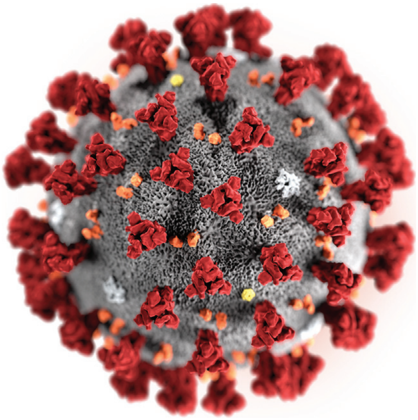
The critically endangered Asian pangolin species *Manis pentadactyla* and *Manis javanica* are featured on the EDGE of existence list of unique and endangered mammals (Curr. Biol. (2018) *28*, R1283–R1286). The Zoological Society of London (ZSL), UK, which compiled this ranking, has championed the case of pangolin conservation, which until 2012 didn’t find much attention.

One might hope that the news of pangolins carrying coronaviruses might help deter the poachers and traffickers, but then again the reports of farmers kissing their potentially virus-infested camels suggest that rational arguments don’t always win at the human–animal interface.

What to do

As the ultimate fate of the current outbreak hangs in the balance between successful containment and the possibility that the virus establishes itself in the human population with seasonal returns like influenza, a few lessons are already apparent. An initial phase where Chinese authorities attempted to silence doctors warning of a new emerging disease seems to have helped the outbreak to grow beyond the size of SARS.

Nahid Bhadelia from the Boston University School of Medicine, USA, who has worked as a clinician during past outbreaks of Ebola virus disease and H1N1 influenza, highlights that the success of fighting a pandemic comes down to three decisions (Nature (2020) *578*, 193): “How to quickly identify infected people, how to isolate and care for them and how to keep health-care workers safe.”



Global threat: This illustration shows the ultrastructural morphology of the novel coronavirus responsible for the 2019–2020 outbreak of the COVID-19 coronavirus disease. (Photo: Alissa Eckert, MS, Dan Higgins, MAM.)

In the current globalised economy, where the entire world seems to be connected to Wuhan, identifying people who may have been exposed to the virus without causing a panic among those who have no real reason to worry may be the deciding factor. The current news of repatriation flights, stricken cruise ships, and rapidly spreading misinformation — a second epidemic opportunistically following the viral disease — illustrate how hard it may become to get all these decisions right and get the disease under control.

As researchers have warned repeatedly, there are many more virus strains out in nature that could jump the species barrier and cause further outbreaks. Disturbing habitats, hunting wild animals, whether it happens to be for food or medicine, as pets or as trophies, living too closely with domesticated animals from camels to poultry, all these human actions could lead to further outbreaks, which, due to the growing interconnectedness of a growing world population will be even harder to control than the previous ones.

To cause a global pandemic, a virus has to cross many boundaries, from those between species to those between countries. Respecting both wild and domesticated animals and rethinking travel may help to stop pandemics before they go global.

Michael Gross is a science writer based at Oxford. He can be contacted via his web page at www.michaelgross.co.uk

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Obituary

David Hogness (1925–2019)

Michael W. Young

David Hogness, formerly Emeritus Professor at the Stanford University School of Medicine, died at the age of 94 on December 24, 2019. Hogness's enormous impact on the fields of genetics and molecular biology can be traced to a program of research that he initiated over 50 years ago. With the birth of recombinant DNA in the early 1970s, it became possible to study purified segments of DNA. As this new technology was emerging, Hogness proposed and developed a series of methods for the collection, ordering, and functional characterization of cloned DNA segments to produce maps of complex eukaryotic chromosomes. In doing so, he was the first to envision the field of genomics, explicitly laying out the fundamental steps by which entire eukaryotic genomes would be described.

David Swenson Hogness was born on November 17, 1925 in Oakland, California. In 1930, his family moved to Chicago where his father became a professor of physical chemistry at the University of Chicago. David majored in Chemistry as an undergraduate at Caltech, staying on to earn a PhD for studies in biochemical genetics with Herschel Mitchell. He then became a postdoctoral fellow with Jacques Monod at the Pasteur Institute, where he was involved in the lab's early studies of the mechanism of β-galactosidase induction by lactose in *Escherichia coli*. In 1955, Hogness was recruited to the Department of Microbiology at Washington University in St. Louis by Arthur Kornberg and moved with several of his colleagues to Stanford University School of Medicine in 1959, forming a new Department of Biochemistry. Hogness married Judith Gore in 1948, and the two remained together until her death in 2014. Judy and Dave had two sons, Peter and Chris.

David Hogness: Taken during a speech at the February 1976 NIH Director's Advisory Committee Meeting on recombinant DNA. (Photo: courtesy of the US National Academy of Sciences.)

In a detailed and widely distributed grant application to the National Institutes of Health in 1972, Hogness set forth the rationale through which complex genomes would be physically mapped, specifically focusing on *Drosophila melanogaster* as his model: libraries of total genome DNA would be cloned in prokaryotic vectors. These would first be ordered by *in situ* hybridizations to sections of the chromosome (with exceptional resolution afforded by the polytene chromosomes of *Drosophila*) and subsequently arranged within a physical map by iterative hybridizations among neighboring clones. Transcribed sequences could be delineated by hybridizing a specific RNA — even contained within a heterogeneous RNA sample — to cloned DNA. This would establish the boundaries of functional elements. Hogness realized that this approach would permit a correspondence among physical, transcriptional, and genetic maps. He specifically pointed out how chromosome aberrations could be used to jump between segments of the same or different chromosomes, and he suggested a procedure that, in later years, would become more widely known as positional cloning. As demonstrated in the conclusion of his proposal, he clearly anticipated a mapping