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# Features



# An uncommon cold

The covid-19 virus isn't the first coronavirus to jump from animals to humans. What can we learn from previous encounters, asks **Anthony King**

**I**N 1889, a disease outbreak in central Asia went global, igniting a pandemic that burned into the following year. It caused fever and fatigue, and killed an estimated 1 million people. The disease is generally blamed on influenza, and was dubbed "Russian flu". But with no tissue samples to check for the flu virus, there is no conclusive proof.

Another possibility is that this "flu" was actually a coronavirus pandemic. The finger has been pointed at a virus first isolated in the 1960s, though today it causes nothing more serious than a common cold. In fact, there are four coronaviruses responsible for an estimated 20 to 30 per cent of colds. Only recently have virologists begun to dig into these seemingly humdrum pathogens and what they have found suggests the viruses have a far more deadly past. Researchers now believe that all four of these viruses began to infect humans in the past few centuries and, when they did, they probably sparked pandemics.

The parallels with our current crisis are obvious. And it turns out that our growing knowledge about these other coronaviruses could be vital in meeting the challenge of covid-19. Insights into the origins, trajectories and features of common cold coronaviruses can provide crucial clues about what to expect in the coming months and years. Understanding these relatively benign viruses may also help us avoid another pandemic.

Coronaviruses are a big family of viruses that are mainly known for causing diseases in livestock. Until recently, few virologists paid them much attention. "Human coronaviruses were recognised in the 1960s," says Frank Esper at the Cleveland Clinic in Ohio. But the two strains that were discovered then merely caused the common cold. "We pushed them

to the side," he says. "We had more important viruses to work on."

This blasé attitude evaporated in 2002 when a new member of the coronavirus family began infecting humans. By the time the epidemic of severe acute respiratory syndrome (SARS) was brought under control the following year, the SARS-CoV-1 virus had affected 26 countries and killed one in 10 of the 8000 plus people it infected. The fact that a coronavirus could be so deadly was a wake-up call. A sleepy backwater in the world of virology was suddenly in the spotlight.

SARS-CoV-1 was soon traced back to its roots. Related viruses were discovered in bats, animals whose unusual physiology allows them to live with a cornucopia of coronaviruses without falling ill. The SARS outbreak seems to have been sparked when one of these bat viruses started infecting civet cats, and moved from this intermediate host to humans.

Coronaviruses have proteins on their surface, which act like a key that unlocks different cells in different host species. These proteins can shape-shift as a result of genetic mutations, or when the viruses swap genetic material with one another, opening new doors to new hosts. That these hosts might be humans was made worryingly clear by the SARS outbreak. Caught off guard, virologists embarked on a coronavirus safari, tracking

them down in people and wildlife in an attempt to understand how these changes might happen and the potential future risks.

One virus hunter was already ahead of the game. Lia van der Hoek at the University of Amsterdam in the Netherlands had been perfecting a genetic technique to discover unknown viruses and had recently found another coronavirus, HCoV-NL63, in a 7-month-old child with bronchiolitis. "I found NL63 by accident, before we knew about SARS, and the whole world starting screening," she says. A decade of subsequent research revealed that NL63 is widespread, turning up in between 1 and 9 per cent of people with respiratory tract infections around the world. It causes fever, coughs, sore throats, bronchitis and pneumonia. Children are invariably infected with it in the first years of life. "The loud cough that children can get, like barking seals, that is typical of NL63," says van der Hoek. In other words, NL63 is another coronavirus associated with the common cold.

Relatives of NL63 have since been found in pigs, cats and bats. In 2012, genetic comparisons between the human virus and those found in bats indicated that they shared a common ancestor between 563 and 822 years ago. This suggests that the virus made the leap to humans sometime in the 13th to 15th century. When it did, the result was probably a pandemic, says virologist Ralph Baric at the University of North Carolina. Like SARS-CoV-2, the virus that causes covid-19, the original NL63 would have been deadly in a human population lacking any immunity. Both viruses latch on to the same cell receptor, angiotensin-converting enzyme 2, which is plentiful in the lungs and intestines. "This would look like a flu-like disease," says Baric. ➤

**"An estimated 20 to 30 per cent of common colds are caused by four coronaviruses"**

# What causes the common cold?

The average adult has two or three colds a year, and children have more. These are caused by a gang of viruses, including four coronaviruses (see main story) that account for around a quarter of all such infections.

Most often, however, the culprit is a rhinovirus, literally “nose virus”. There are about 100 different types, that are together responsible for half of all colds. As well as the usual coughs and sniffles, rhinoviruses have been linked to ear and sinus infections.

Two other related viruses, respiratory syncytial virus and human metapneumovirus, home in on the respiratory tract. In severe cases, they can cause pneumonia and bronchitis.

If you contract a summer cold, the likely perpetrator is human parainfluenza, which comes in four varieties. These sometimes lead to serious illness too. Nevertheless, as with most colds, the usual outcome is that you will recover in a week or so.

“But one that caused more severe disease in the elderly compared to the young.”

Baric would like medical historians to search for evidence of a medieval pandemic, but there is no guarantee they would find any. Back then, people experienced myriad infections, including viruses like flu and bacterial diseases like tuberculosis, says van der Hoek. “I’m not sure a SARS pandemic in the Middle Ages would even be noticed,” she says. However, it is possible that such evidence exists for another, more recent, human coronavirus pandemic. This is where Russian flu enters the story.

## Rethinking Russian flu

Following the SARS outbreak, there was renewed interest in the two seemingly unexciting common cold coronaviruses discovered in the 1960s, HCoV-229E and HCoV-OC43. “These viruses don’t have fancy names, which means they have not been studied very much,” says Marc Van Ranst at KU Leuven in Belgium. “OC43 and 229E were orphan viruses for a long time.” In 2003, he and his team became the first to sequence the genome of OC43, which was discovered in 1967 at the Common Cold Unit in Salisbury, UK. By comparing its sequence with strains found in other animals, the researchers concluded that OC43 must have originated in cattle or pigs. Accounting for expected mutation rates and working backwards, they calculated that the jump into humans occurred around 1890. Sound familiar?

That date isn’t the only thing linking OC43 with Russian flu. Many patients of that pandemic had pronounced symptoms affecting their central nervous system. Today, although mostly associated with mild colds, OC43 is also known to infect nervous tissue. It is a suspect in nervous system conditions such as chronic demyelinating disease and multiple sclerosis. What’s more, a 1994 report of a 6-year-old child contracting a bovine coronavirus suggests cattle strains can indeed sneak into people. If OC43 was the culprit in the 1889/90 pandemic, it has clearly lost its sting in the past 130 years. “It probably lasted a fair number of years, like bad flu seasons, until it slowly lost pathogenesis,” says Van Ranst.

What about 229E? First isolated in the mid-1960s, subsequent experiments indicated that half of volunteers infected with 229E fell ill with a cold after two to five days. In 2007, it stepped back into the limelight when a close relative was discovered in the lungs of alpacas with respiratory disease. Meanwhile, researchers led by Christian Drosten, then at the University

of Bonn in Germany, had been investigating an array of 229E-related coronaviruses from leaf-nosed bats in Ghana. Their studies indicated that 229E left bats on its path to people some time between 1686 and 1800.

The pieces of the puzzle started to fit together in 2012 when a mysterious and deadly new coronavirus first struck in Saudi Arabia, causing what was named Middle East respiratory syndrome (MERS). The virus responsible, MERS-CoV, was traced back to dromedary camels and, while digging into this link, Drosten and others discovered that 5.6 per cent of these camels in Arabia and Africa are infected with viruses akin to 229E.

Genetic comparisons of 229E and related viruses in animals suggest that it originated in African bats and moved to camels, before infecting people in or around the late 18th century. Like MERS, it probably sparked a pandemic when it arrived in humans as they would have had no immunity to it. As with NL63, nobody has looked for evidence in historical records.

The idea that common cold coronaviruses were far more deadly when they first appeared in humans is supported by animal studies. In 2016, for example, scientists caught a coronavirus in the act of jumping species into pigs. “The genetic sequence was closely related to coronaviruses in bats, so it looked like the virus had spilled over directly from bats,” says Linda Saif at Ohio State University. That virus killed 25,000 piglets in China in just a few

## A 19th-century flu pandemic may have been caused by a coronavirus



months. Such events are common, says Saif, who has been investigating new coronavirus outbreaks in animals for decades. In the 1990s, for instance, a respiratory coronavirus devastated cattle herds with “shipping fever”. And in 1977, a diarrhoeal disease caused by a coronavirus emerged in pigs in Europe, later spreading to China and then the US, where it killed an estimated 8 million pigs.

“It is quite possible that when these [common cold] coronaviruses first jumped over to humans, they would have caused episodes of severe disease,” says Saif. What is surprising, however, is how infrequently such leaps seem to have occurred. “When SARS happened,” says Esper, “people like myself started looking for other coronaviruses that might cause respiratory infections.” Only one new one turned up. In 2005, the fourth common cold coronavirus was discovered in a 71-year-old pneumonia patient in a Hong Kong hospital. HCoV-HKU1 causes respiratory illnesses and has been recorded worldwide. Its closest relative appears to be a rodent coronavirus. We don’t know when it began infecting humans. Esper points out, though, that people are less likely to be hospitalised with HKU1 and NL63 than with 229E and OC43, possibly indicating that the former pair have more ancient roots in human populations.

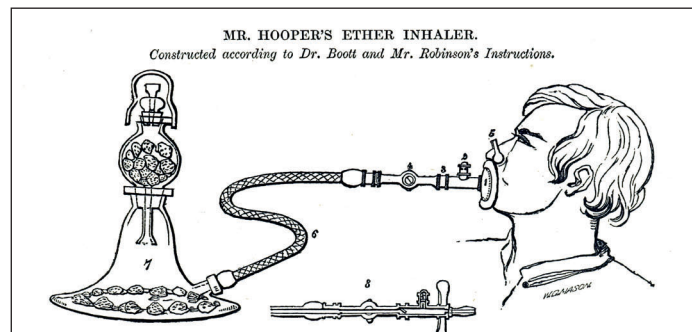
HKU1 attracts little attention, but Esper took a special interest in it when it was found in several patients in a local Ohio hospital. He discovered that older people are especially hard hit by this coronavirus. Indeed, while the common cold viruses are often thought of as childhood ills, Esper says his team has found that adults account for 70 per cent of infections by these coronaviruses. That is different from most viruses, but matches what we are discovering about the covid-19 virus. “All these coronaviruses seem to be acting very similarly,” says Esper. “Understanding why they infect adults so much may be one of the key questions that will give us an understanding of the current coronavirus pandemic, as well as future ones.”

## Inter-viral competition

Our four common cold coronaviruses have another intriguing feature: they ebb and flow. “For NL63, you have high years and low years,” says van der Hoek. “We found it more or less peaks every two years.” In addition, between 2000 and 2010, NL63 and OC43 infections were more common in children than 229E and HKU1 infections. “They are in competition,” she says. Esper has also observed the viruses hitting in relays. “Here in Ohio, we just had a banner year



**People infected with Russian flu in 1889 may have found themselves on elegant hospital wards (above) with rudimentary treatments (right)**



for HKU1,” he says, with 160 confirmed cases. OC43 was also quite common, but there were almost no cases of NL63 or 229E. “Maybe it’s because our immune system revs up, gives protection for a couple of years, and then goes away,” he says.

But there could be something darker going on. One experiment done in 1990 found that volunteers infected with 229E were vulnerable to reinfection a year later. If that happened, they experienced no symptoms but could still pass on the virus. Van der Hoek thinks this has worrying implications for coping with covid-19. “Can you imagine what this means for protecting vulnerable people when we have even more asymptomatic people shedding the virus without knowing,” she says. People with antibodies to SARS-CoV-2 must be studied, she says, to see if the same is true for covid-19.

Nevertheless, research on our common cold viruses provides some grounds for optimism too. The coronavirus family tree consists of four subfamilies, with the human ones occupying two of these. NL63 and 229E are in a group called alpha, along with feline and canine coronaviruses. OC43 and HKU1 belong to the beta subfamily, which also includes the viruses that cause MERS, SARS and covid-19. Antibodies for one virus might be effective

against a related one, says van der Hoek.

“We should definitely investigate whether people have a little bit of protection already [to covid-19] when they have just experienced an OC43 or HKU1 infection,” she says. However, the reverse may be true, warns Van Ranst.

“Maybe if you are older and have some residual immunity against some coronaviruses, there’s a greater chance that your body will overreact.”

In the longer term, virologists cannot predict how SARS-CoV-2 will evolve. It may continue to cause severe illnesses for some years yet, especially among older people. However, it seems likely that one day it will be just another common cold coronavirus. These are hit-and-run viruses, says Esper. “They infect you, make a million virus babies and spread them all out”, but our immune system usually kills them off within five days. If the viruses are too deadly, they won’t get a chance to spread, so it is in their interests to become more benign. “If SARS-CoV-2 persists, which I expect it will, it may get milder over time,” says Esper. ■



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