

How and who does SARS kill?

No two cases of SARS are exactly the same. Depending on the age and fitness of the patient, the disease can run wildly different courses. Even the symptoms of fever and dry cough, initially included in the case definition for SARS, are no longer considered to be universal.

SARS facts

- **Symptoms** Initially fever, sometimes accompanied by headache; later a dry cough, trouble with breathing, nausea and diarrhoea.
- **Incubation period** 2–10 days
- **Economic cost** Nearly US\$100 billion, mostly as a result of cancelled travel and decreased investment in southeast Asia, according to Bio Economic Research Associates of Cambridge, Massachusetts.

One pivotal point seems to occur at about the beginning of the third week after infection, when some patients, especially the young, improve. Others, however, progress to a more severe form of the disease — their lungs become clogged with debris and fluid, which show up as dark lesions in chest X-rays. In about a fifth of all patients, this requires aggressive treatment such as mechanical ventilation. Even then, many of these people die.

Worldwide, the death rate from SARS seems to be about 10%. But individual risk factors vary considerably. For people over 65 years of age, more than half of those infected will die. Just about any lung ailment complicates the disease, and conditions such as emphysema are more common in the elderly. Other concurrent infections may also be involved. Although it is now well established that the SARS virus can kill on its own⁸, other viruses that have been isolated from patients with SARS⁹ could exacerbate the illness.

The ultimate cause of death also remains unclear. Does the virus kill directly by destroying cells in the lung, or does the immune system deliver a *coup de grâce* by fighting back too hard? By the time that most of the lung damage occurs, the amount of virus circulating in the blood has already peaked¹⁰, suggesting the latter. And the pattern of damage is consistent with an overload of cytokines⁹ — biochemical messengers that rev up our immune responses. But for the time being, pathologists are recording an open verdict.

Jonathan Knight

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Where did the SARS virus come from?



The SARS coronavirus is believed to have jumped over from an animal host to people in rural areas of Guangdong province in southern China. From November last year, it circulated there for several months while Chinese health authorities failed both to tackle its spread, and to provide adequate information to their counterparts in other countries about what was going on. But the path that the virus took to set up this initial hotbed of human infection — essential information for assessing the likelihood of a recurrence, even if the initial wave of SARS is over — remains a mystery.

Coronaviruses are named after their crown-like halo of protein spikes, which help them to latch on to their host cells. Those previously identified in people cause nothing nastier than common colds, but some of the coronaviruses that afflict livestock and pets cause more serious conditions.

Analysis of the complete genome sequence of the SARS virus, published in May¹¹, suggests that it is not closely related to any of the three previously identified coronavirus subfamilies, nor does it seem to have arisen through a chance genetic recombination between known coronaviruses¹². "Its unique sequence suggests that it has evolved independently from the other members of the family, in some animal host, for a long time," says Malik Peiris, a virologist at the University of Hong Kong.

Ongoing research by Peiris and his colleagues may shed light on the origins of the virus. The Hong Kong team is looking at genomic sequences of coronaviruses sampled from masked palm civets (*Paguma larvata*) and other animals sold in the markets of southern China. Comparison of the sequences of the viruses found in different animals should make it possible to trace the evolution of the SARS virus and determine which animal passed the disease to humans. Yi Guan, another member of the Hong Kong team, says that related viruses have so far been found in about half-a-dozen species — which he declines to name until the work has been published.

Knowledge of the chain of animals involved in passing the SARS virus to humans would help in the design of preventive measures. For example, when the previously unidentified Nipah virus began causing fatal encephalitis in livestock and people in Malaysia in 1998, about one million pigs were slaughtered. Later the virus was found to reside in fruit bats¹³, so farmers could take measures to isolate their livestock from this natural reservoir. "Once you find the source, you can find out how to manage it better," says John Mackenzie, a virologist at the University of Queensland in Brisbane, Australia.

It will probably be some time before we pin down the natural reservoir for SARS. Recent investigations by researchers at the China Agricultural University in Beijing, for instance, have failed to find SARS-like coronaviruses in 732 animals from 54 wild and 11 domestic species in southern China, including palm civets. As with efforts to investigate the epidemiology of SARS in people, progress may depend on the development of improved diagnostic tests. But potentially, Guan warns, revealing the origins of SARS could require decades of painstaking fieldwork.

David Cyranoski

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Why China?



SARS is not the first viral disease to burst out of China or Hong Kong. The southern Chinese region was the source of influenza pandemics in 1957 and 1968, and scares about the transmission to people of novel strains of avian flu in 1997 and 2001. Why does this region keep throwing up viruses that have the potential to threaten the lives of people around the world?

Southern China's status as the world's primary breeding ground for new strains of flu is explained by the fact that its people, pigs and domestic fowl, which all harbour influenza viruses, live cheek-by-jowl, increasing the likelihood that two strains will recombine genetically to produce a deadly new variant. "The animals walk in and out of their houses," says Kenneth Shortridge, who led the University of Hong Kong's efforts to monitor avian viruses in southern China until his retirement last year. Preliminary evidence suggests that SARS followed a different model, apparently crossing over to people from wild animals, rather than livestock. But this, too, is not terribly surprising, given that the southern Chinese make widespread use of wild species for food and traditional medicine — practices that Chinese health officials are now trying to discourage.

Another dietary issue — specific nutritional deficiency — has also been tentatively linked to the emergence of new viral strains in rural China. For instance, in many parts of the country, the diet is lacking in the trace element selenium. A team led by Melinda Beck of the University of North Carolina at Chapel Hill found that when the coxsackievirus B3 infects mice deficient in selenium, it mutates at a much higher rate and can become more virulent¹⁴. Beck suspects that this phenomenon may explain the high incidence of Keshan disease, a weakening of the heart muscle, in some Chinese populations¹⁵. She has also observed increased mutation rates in flu viruses infecting selenium-deficient mice¹⁶. "The fact that China has widespread selenium-deficient areas may play a role in the emergence of new viral strains," Beck claims.

Other scientists regard Beck's findings as speculative, and doubt whether they offer a general explanation for the emergence of viral diseases in China. When you have the world's largest population interacting closely with livestock and wild animals, say experts, it's hardly surprising that China seems to be the origin of so many viral outbreaks. "It's a matter of exposure probability," suggests Mei-Shang Ho, an epidemiologist with Academia Sinica's Institute of Biomedical Sciences in Taipei, Taiwan.

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