Chapter 14
Bird Flu, SARS and Beyond

Abstract  In the politically sensitive year of 1997, Hong Kong experienced an outbreak of avian flu when the deadly H5N1 virus unprecedentedly jumped the species barrier from chickens and infected human beings. Hong Kong decided to slaughter over a million chickens, and the virus was stopped in its tracks. In 2003, Hong Kong was the epicenter of the SARS pandemic, which originated in Guangdong province. The Faculty of Medicine played key roles in both instances, with its Microbiology Department successfully identifying a novel coronavirus as being responsible for SARS. Hong Kong learned from its experience and took action to combat the emergence of new infectious diseases. Such vigilance paid off in 2009, when swine flu swept the world, and in 2013, when a novel avian flu H7N9 emerged in China.

Respiratory Infections Raise Awareness of Need for Vigilance

All the preparations to entrench medical autonomy in Hong Kong after the British departure did little to help the freshly minted Hong Kong Special Administrative Region deal with the first medical emergency in the post-colonial period: an outbreak of what was widely called the bird flu, which for the first time saw the virus jump the species barrier to infect human beings, sickening 18 people, of whom six died, an inordinately high mortality rate of 33%. Hong Kong gained the distinction of being the only place where this event, which scientists had thought could not happen, actually happened.

It was previously thought that avian influenza viruses could not directly attack humans, requiring a mammalian intermediary such as a pig, wherein host adaptation or genetic reassortment could take place, before a virus capable of infecting humans would emerge. That was thought to have been the pattern of previous pandemics, such as the Asian Flu of 1957 and the Hong Kong Flu of 1968, which together claimed more than 1.5 million human lives.
As for the Great Flu of 1918, which infected an estimated 500 million people worldwide—about a third of the world’s population at the time—and killed 20–50 million people—there is still no agreement on its origins, although the U.S. Surgeon General alluded to an Asian origin saying, “Some writers who have studied the question believe that the epidemic came from the Orient.”

**First Signs of Trouble**

In March, 1997, the first signs of trouble in Hong Kong appeared when chickens on a Yuen Long farm started to die. Then those on a second farm started dying, and a third, with about 7,000 birds succumbing to influenza. Although farmers were concerned, health authorities were not too worried because the virus from which the chickens suffered was never known to cross the species barrier and infect humans. That is, not until two months later.

On May 9, 1997, a three-year-old boy, Lam Hoi-ka, fell ill. He had a sore throat and a fever. When he hadn’t recovered after five days, he was taken to Queen Elizabeth Hospital, where he died on May 21. The cause of death was noted as acute respiratory failure, liver and kidney failure and “disseminated intravascular coagulopathy.” In effect, his blood had curdled.

As soon as the chickens started to die, officials from the Agriculture and Fisheries Department contacted Professor Kennedy Shortridge, Chair of Microbiology at the University of Hong Kong, who had been studying influenza viruses in southern China since the 1970s. Shortridge had been doing pioneering research on the role of domestic animals in the genesis of human influenza virus strains. The Microbiology Department was designated a World Health Organization (WHO) Collaborating Laboratory for Animal Influenza Viruses in the mid-1970s and Shortridge himself was appointed an adviser to the organization’s Committee on Ecology of Influenza Viruses.

As early as 1982, Shortridge had labeled southern China, where humans and domestic animals lived in close proximity, “an epicenter for the origin of pandemics.” Ten years later, he called southern China a “virus soup” and warned that pandemic influenza was a zoonosis, that is, it could be transmitted from animals to humans and, in 1995, he warned that influenza in southern China could not properly be

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1 Madeline Drexler, *Secret Agents: The Menace of Emerging Infections* (Washington D.C.: Joseph Henry Press, 2002), 164.
2 Pete Davies, “The Plague in Waiting,” *Guardian*, August 7, 1999.
3 Ibid.
4 Erik Larson, “The Flu Hunters,” *Time*, 24 June 2001.
5 K.F. Shortridge and C.H. Stuart-Harris, “An Influenza Epicentre?” *The Lancet*, 320, no. 8802 (1982):812–13.
6 K.F. Shortridge, “Pandemic influenza: A Zoonosis?” *Seminars in Respiratory Infections*, 7, no. 1 (1992):11–25.
called an “emerging” infection because it was constantly lurking. “Elusive might be more apt,” he wrote.7

The virus affecting the three-year-old boy was isolated after his death by the Hong Kong government. Although the Microbiology Department was a WHO Collaborating Laboratory for Animal Influenza Viruses, in terms of equipment the small university laboratory could not match those in Atlanta, headquarters of the U.S. Centers for Disease Control and Prevention (USCDC), and other major collaborating centers of the WHO. So Hong Kong knew it was some kind of influenza A virus, that is, it came from birds, but exactly which kind neither the Department of Health nor the University of Hong Kong could determine.8 Specimens were thus despatched to the U.S. and to Europe.

**Experts Decided Death Was a Fluke, and Went Home**

There, the specimens patiently waited until it was their turn to be examined. The National Influenza Centre in Rotterdam was the first to respond with the shocking news that the virus was an H5N1. This means that it was an avian flu that had never before infected a human being anywhere in the world. The alarming news spread through the small community of flu virus researchers and, in August, specialists, including Keiji Fukuda, Chief of Epidemiology in the Influenza Branch of the U.S. Centers for Disease Control and Prevention, descended on Hong Kong to find out what was happening. But nothing much seemed to be happening. Since the boy’s death in May, there had been no other human cases. Everyone decided that whatever happened to the boy was a fluke. The experts went home.

But then, in November, a second human case emerged. A two-year-old boy from Kennedy Town became sick. He was admitted to Queen Mary Hospital with a fever, a sore throat and a cough. The hospital took a specimen from his nose and throat. The boy recovered but tests showed that he had the H5N1 virus. A third case followed, this time a 37-year-old man. Soon, more cases were reported: a 13-year-old girl in the New Territories followed by a 54-year-old Kowloon man.

Quickly, the international experts returned, including Fukuda in December at the head of a US CDC field team as well as the virologist Robert Webster of St. Jude Children’s Research Hospital in Memphis, Tennessee in the United States and an old friend and colleague of Shortridge’s. Webster brought with him a young Chinese researcher, Guan Yi (管轶), who was working in his laboratory and had studied in Hong Kong in the early 1990s and who, at that time, was completing a Ph.D. under Shortridge. In fact, Guan Yi had presented his doctoral thesis, “Molecular epidemiology of swine influenza A viruses from southern China,” at Hong Kong University in September 1997. He had just returned to Memphis from Hong Kong in late

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7K.F. Shortridge, “The Next Pandemic Influenza Virus?” *The Lancet*, 396, no. 8984 (1995): 1210–212.
8Drexler, *Secret Agents*, 175.
November when he received a call from Webster, his mentor, who told him: “Don’t unpack your bags—we’re sending you back to Hong Kong.” So, in December 1997, he was back in Hong Kong with Webster. “We wanted to know where the virus was hiding,” Guan Yi recalled. One man who met him at the time, Keiji Fukuda, said, “It was already clear by then that Professor Guan Yi was a major talent.”

Actually, even before his Ph.D. training in Hong Kong, Guan Yi had almost ten years’ training and practical experience as a specialist in respiratory infectious diseases, including a period of specialist training at Capital Institute of Pediatrics and the Peking Union Medical College Hospital from 1986 to 1989.

Webster was appointed a distinguished visiting scholar by the University of Hong Kong. In December, Webster and Shortridge jointly established an international H5N1 task force of world class influenza virologists. In one month, the group established the infrastructure for a center of excellence for influenza virus research in Hong Kong. Just before the Christmas holidays began, Shortridge and Webster personally oversaw the testing of birds in Hong Kong’s wet markets and found that 20% of the chickens were infected with H5N1; ducks and geese also harbored the virus.

Guan Yi was part of the team testing poultry in the wet markets, but he was also valuable in another way: being a native of mainland China, he knew the people and culture there and was able to obtain crucial information, an ability that was to serve the university, and Hong Kong, well a few years down the road when a much bigger health crisis erupted. Guan received his Doctor of Philosophy degree in 1998 and joined the staff of the University of Hong Kong in early 2000.

Fukuda remained with the USCDC until 2005 before moving over to the World Health Organization. Thus, during Hong Kong’s bird flu and SARS epidemic, he assisted while wearing his USCDC hat. But, after joining the WHO, he was involved in tackling later health issues, such as H1N1 in 2009 and H7N9 in 2013.

**Legislators Demand Action**

Meanwhile, during the chicken flu crisis, anxiety gripped Hong Kong. The legislature demanded action. Asked by a legislator, Cheng Kai-nam (程介南), about the possibility of a ban on imports of mainland chickens and of destroying some of the chickens in Hong Kong, the Secretary for Health and Welfare, Katherine Fok (霍羅兆貞), replied: “It may not be necessary for us to ban the supply of chicken and poultry…. However, we will consider all options. But for the time being, we do not

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9 Kevin Voigt, “Avian Flu: Preventing a Pandemic,” *The Wall Street Journal*, 28 October 2005.
10 Meeting with Guan Yi, 22 September 2016.
11 Interview with Keiji Fukuda, 20 February 2017, after he joined the School of Public Health of the University of Hong Kong.
12 *Medical Faculty News*, Vol. 3, Issue 3, December 1, 1998, 6.
13 Ibid.
14 K.F. Shortridge, J.S.M. Peiris, and Y. Guan, “The Next Influenza Pandemic: Lessons from Hong Kong,” *Journal of Applied Microbiology*, 94, no. 51 (2003):70–79.
intend to ban the supply of chicken.” No mention was made of the possible slaughter of chickens in Hong Kong, suggesting that even in the second week of December, the government did not contemplate taking extreme measures.

But H5N1 cases continued to mount throughout December. Director of Health Margaret Chan was in the habit of reassuring people that there was nothing to worry about and habitually said that she ate chicken every day. Even she, however, changed her tune and said, “It seems we are entering a competition with the virus. We are working at breakneck speed” (Fig. 14.1).

Academic researchers, too, were working day and night, with Malik Peiris, Professor of Microbiology, toiling in his lab until 11 p.m. almost every night, examining tissues from patients in Hong Kong and Kowloon. Peiris had joined the University in 1995 as a senior lecturer and one of his prime tasks at the time was to establish a clinical diagnostic and public health virology laboratory at Queen Mary Hospital. Knowing the lethality of the virus, Shortridge did not want it to spread beyond Hong Kong. Recalling the toll taken by the Asian pandemic of 1957 and the Hong Kong Flu of 1968, both of which started off as bird flus, he wanted to stop the disease before it could spread. “It was absolutely terrifying,” he said. “You could feel the weight of the world pressing down on you.”

His sense of urgency was galvanized by the fact that the normal flu season was starting early, with the H3N2 virus variant starting to circulate within the human population in late December. Thus, there was a possibility that the H5N1/97 virus might reassort with the H3N2 virus in the human host to give rise to a virus better able to transmit from human to human, thus leading to a pandemic. “Given that H5N1/97 was so widespread within the poultry markets, this meant that the only means of stopping further exposure of the human population to it was to slaughter all poultry in the markets and farms of Hong Kong,” he explained in a 2003 paper.

One Sunday morning, information from the Department of Agriculture indicated that a large number of birds tested in open poultry markets were infected. Increasing numbers of people were getting sick, a third of birds had died and infected birds were around the whole city. Although she realized that a lot of people would be upset, Director of Health Margaret Chan still decided on killing all chickens, infected or not. Fukuda recalled, “We all felt that was the right thing to do.”

Beginning December 29, three days of slaughter were launched during which 1.5 million birds—primarily chickens but also ducks and geese—were killed. The government was widely criticized for the way it handled the operation but, once all the chickens were gone, there were no further cases of bird flu. Six of the 18 people stricken by the highly pathogenic avian influenza had died but a pandemic was averted.

The relationship between the government and local academics was described thus by Fukuda, who was, in a sense, an outsider. “The government’s role is really

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15 Drexler, Secret Agents, 178.
16 Gina Kolata, Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus that Caused it (New York: Simon and Schuster), 237.
17 Shortridge et al., The Next Influenza Pandemic.”
18 Interview with Fukuda. 20 February 2017.
to coordinate, and to articulate to the public what is going on,” Fukuda said. “Meet public expectations and marshal all scientific expertise you need. Make sure agriculture was involved. Dr. Margaret Chan was clearly overseeing everything.”

Shortridge himself felt subsequent events justified the cull. “The last human case of H5N1 disease was recognized the day before the commencement of the slaughter on 29 December, vindicating the controversial slaughter policy,” he wrote. “It is reasonable to believe that this intervention prevented an incipient pandemic progressing to an actual pandemic and thus a pandemic was averted. The H5N1/97 virus was possibly one or two mutational events from achieving pandemicity. However, as with all measures that successfully prevent an adverse outcome there is no definite way of proving their efficacy.”

The unusual clinical severity and high mortality of infected patients in the outbreak of avian influenza H5N1 in Hong Kong was first reported in the *Lancet* in February 1998 by Yuen Kwok-yung (K.Y. Yuen) of Hong Kong University’s Department of Microbiology. He was the lead writer, whose co-authors included K.F. Shortridge and Malik Peiris. Yuen had attended to H5N1 patients and devised a rapid diagnostic test known as RT-PCR used in testing the respiratory secretions from these patients. This was the first time that the test was used for rapid diagnosis of such patients in a clinical setting. He also analyzed the case notes of 12 patients, ranging in age from 1 to 60. “Whether avian viruses can infect human beings directly or need to reassort in an intermediate host (e.g., pigs) is a matter of debate,” he wrote, adding: “Until recently, a purely avian virus had not been isolated from people with respiratory disease, although conjunctivitis caused by an avian H7 virus has been reported.”

### A Shared Award

While decisions regarding the slaughter of chickens were made by the government, the university played a major role. This was known to the outside world as well. Thus, the following year, when Thailand announced the winner of the Prince Mahidol Award for outstanding achievements in medicine and public health, the award was shared jointly by Margaret Chan, the Director of Health, and Professor Shortridge.

In the aftermath of the 1997 events, tight surveillance of the live poultry retail markets revealed that the highly pathogenic H5N1/97 virus was no longer detected. However, the precursor viruses remained, including the H5N1-like virus in the Guangdong goose identified in 1996 and other viruses in quails. Live chickens continued to be sold in Hong Kong but the government after 1997 instituted a policy of

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19 Ibid.
20 Shortridge et al., “The Next Influenza Pandemic.”
21 K.Y. Yuen et al., “Clinical Features and Rapid Viral Diagnosis of Human Disease Associated with Avian Influenza A H5N1 Virus,” *Lancet* 351, no. 9101 (1998), 967–71.
central slaughter of geese and ducks. For three years, Hong Kong’s retail markets remained free of the H5N1 virus.22

But in 2001, the H5N1 virus was back. On April 11, the government announced that it had isolated Goose/96-like H5N1 virus from a chicken cage in the poultry stall of a market, but suggested that this mild type of virus would not pose a major threat to public health. However, the surveillance program of the university detected a new strain of H5N1 virus and the sample was confirmed by the World Health Organization as having the potential to be highly pathogenic.23

The viruses were initially detected in apparently healthy chickens but, not long afterward, the chickens began dying in one market after another, although there were no human victims. Professor K.Y. Yuen, who had been Chair of Infectious Diseases since 1999 and was a member of the consultation committee of the Health and Welfare Bureau, held detailed discussions with Lily Yam, Secretary for Environment and Food, on measures to deal with the outbreak (Fig. 14.2). He fully supported her decision to make a pre-emptive move and slaughter more than a million chickens, ducks and geese to prevent further reassortments, possibly into pathogens that can threaten people. The influenza research team, established after the H5N1 outbreak in 1997, was led by Professor Shortridge and included Dr. Malik Peiris and Dr. Guan Yi, as well as ten local research assistants, all of whom worked closely with the government to identify new influenza viruses and stop them before they could infect humans. The team also cooperated with the World Health Organization, the U.S. National Institute of Health and other international health bodies.24 Yam explained that the slaughter was ordered “to avoid the possibility, no matter how remote, of this particular strain combining to form a new strain that may affect human beings.” K.Y. Yuen proposed a monthly rest day for retail markets, when all unsold poultry would be killed and the markets cleaned, left empty for the day, then restocked the following day. The measure was adopted by the government.

Shortridge and his colleagues found that virus isolation rates were significantly lower following the rest day. The pre-emptive depopulation decision halted the continuing reassortment of viruses within the poultry population and prevented the emergence of any that could attack humans.

In 2002, another incident occurred that confirmed the rapid adaptation of the H5N1 virus. In early January, a new subset of H5N1-like viruses was detected in the retail markets. They were isolated from dead chickens. Subsequently, a series of reports were received of chicken farms found to be infected as well as in chicken stalls in retail markets. The farms were quarantined and depopulated. A total of 950,000 chickens were slaughtered. The handling of this 2002 incident showed that

22 Shortridge et al., “The Next Influenza Pandemic.”
23 Poon Ping-Yeung, “A Study of the HKSAR Government’s Strategy to Manage Avian Flu Outbreaks.” University of Hong Kong Master’s Dissertation, June 2003. https://hub.hku.hk/bitstream/10722/28343/1/FullText.pdf?accept=1 p. 8.
24 “How HKU Scientists Helped Save Hong Kong’s People,” Convocation Newsletter, Issue 3, 2001, 24.
with the cooperation of vigilant operators of chicken farms, disease recognition can take place earlier, before the chickens went to market. As Shortridge observed, it was now possible to have a higher level of baseline preparedness for the next influenza pandemic.25

An Unknown Deadly Virus Emerges in Guangdong

At the end of 2002, unknown to anyone in Hong Kong, another deadly virus was circulating in neighboring Guangdong Province, propagating a disease that had no name but which was preliminarily dubbed atypical pneumonia in China and later renamed Severe Acute Respiratory Syndrome, or SARS, by the World Health Organization.

The first cases emerged in Foshan city in mid-November. It spread within the province to Heyuan and Zhongshan. It was difficult to know what was going on in the mainland, especially where a sensitive issue like the emergence of a new disease was concerned. No announcements were made either by Beijing or by local authorities in Guangdong Province. However, the controlled media did, at times, publish articles from which some information could be gleaned. Thus, Guangdong newspapers in early January 2003 published a handful of articles denying the existence of any epidemic but, by doing so, enhanced speculation of a deadly new disease. On January 4 an article appeared in Heyuan Daily headlined “Epidemic is only a rumor.” In Guangzhou, News Express ran an article “No reason to worry” on January 10 and “Heyuan back to normal” on January 14.26 Such articles were meant to reassure the public that the situation was under control and that there was nothing to worry about. But the articles themselves were not that reassuring. Thus, the Heyuan Daily article described panic buying of drugs, with long lines at pharmacies. It said that the “terrifying rumor of a serious infectious disease” had resulted in a rush to purchase certain antiviral tonics. “This irrational purchasing has driven prices of these drugs to ridiculous levels: a tonic that usually costs 10 yuan now costs 450 yuan. Antibiotics have also become more expensive, the price rising to 30 yuan. Yet no matter the price, as of 9 p.m., these medicines were sold out at most pharmacies. Until yesterday morning there were long lines waiting to buy these drugs with customers purchasing up to 10 boxes each.”

The article also revealed that parents were keeping their children at home rather than sending them to kindergarten. “In the Central Kindergarten, two classes contained a total of 20 kids, less than half the usual attendance,” the article said. “Kindergarten officials said they had also heard the rumors of a disease but didn’t believe it. But just in case, they added, they had prepared a cold elixir tea to ward

25 Shortridge et al., “The Next Influenza Pandemic.”
26 Heyuan Daily and News Express articles cited in Karl Taro (Grenfeld, China Syndrome: The True Story of the 21st Century’s First Great Epidemic, New York, HarperCollins, 2006), Chapter 10, 77–79. Also see note, 410.
off any sickness.” So even teachers who “didn’t believe” the rumors were taking precautions.

As for the disease itself, the article had this to say: “People’s Hospital of Heyuan received two patients from Zijin Hospital on the fifteenth of last month. The patients were transferred to Shenzhen and Guangzhou. Specialists from hospitals in Guangzhou were sent to Heyuan to help in the treatment. The Hospital Director said that after the meeting of provincial experts it was proven that the disease is a very common disease: atypical pneumonia. This disease is not infectious and is caused by changing weather. The symptoms are high fever, coughing and spots in the lungs. This disease is not similar to any communicable disease identified by the government so there has been no reason to report it to provincial authorities.” So it seemed that Heyuan was not able to look after its own patients and had to send them to other cities, and had to seek help from specialists in Guangzhou. Also, while saying that “the disease is very common,” the article seemingly contradicted itself by saying, “This disease is not similar to any communicable disease identified by the government.” There was a mysterious illness about, not just a rumor.

A team of health experts had been sent to Heyuan in mid-December and, on January 2, 2003, these health personnel diagnosed the disease as an infection caused by a certain virus.27 “Guangzhou is fighting an unknown virus,” the mainland media reported.28 On January 27, the Guangdong health department received a “top secret” document from a government health committee. However, because no one with sufficient security clearance was there, the document, which contained information about a new pneumonia-like illness spreading in the region, lay unread for three days. Eventually, a bulletin was sent to hospitals across the province, but by then many health workers were on vacation because of holidays to celebrate the Chinese New Year, which fell on Saturday, February 1.29

The Chinese public, and the rest of the world, was kept in ignorance. Under Chinese law, any occurrence of infectious diseases should be classified as a state secret before they are “announced by the Ministry of Health or organs authorized by the Ministry.” That is to say, until the government made the information public, any doctor or journalist who disclosed information on the disease was liable to prosecution for leaking state secrets.30 On February 8, reports about a “deadly flu” began to be sent via text messages on mobile phones in Guangzhou. In the evening, words like bird flu and anthrax started to appear on some local Internet sites.31 That same

27Yanzhong Huang, “The SARS Epidemic and Its Aftermath in China: A Political Perspective,” in Learning from SARS: Preparing for the Next Disease Outbreak, ed. Stacey Knobler et al. (Stanford University Press, 2006).
28“Guangzhou Is Fighting an Unknown Virus,” Southern Weekend, February 13, 2003.
29John Pomfret, “China’s Slow Reaction to Fast-Moving Illness,” The Washington Post, April 3, 2003.
30United States Congress Senate, “Dangerous Secrets: SARS and China’s Healthcare System,” Roundtable before the Congressional-Executive Commission on China, 108th Congress, May 12, 2003. Published 2010.
31February 11, 2001, South China Morning Post, cited by Yanzhong Huang.
day, two major Guangzhou newspapers, the *Nanfang Daily* and the *Yangcheng Wanbao*, carried short news reports about a “mysterious illness” that had hit the hospitals in Guangzhou. The next day, February 9, a delegation of experts from the Ministry of Health and the Chinese Center for Disease Control and Prevention (China CDC), led by the Vice Minister of Health and the Deputy Director-General of Health, went to Guangdong. On February 10, a circular appeared in the local media that acknowledged the presence of the disease and listed some preventive measures, including improving ventilation, using vinegar fumes to disinfect the air, and washing hands frequently. Responding to the advice, residents in Guangzhou and other cities cleared pharmacy shelves of antibiotics and flu medication. In some cities, even white vinegar was sold out. The panic spread quickly in Guangdong, and was also felt in other provinces.

The information blackout imposed by the mainland meant that the health authorities in Hong Kong were kept in ignorance of what was going on in neighboring Guangdong. It wasn’t until February 10, 2003, when six newspapers in Hong Kong carried reports on the atypical pneumonia outbreak that Hong Kong’s Director of Health, Dr. Margaret Chan, and Secretary for Health, Welfare and Food, Dr. Yeoh Eng-kiong, became aware of the epidemic next door. It was also on February 10 that the WHO country office in Beijing received an email message describing a “strange contagious disease” that had “already left more than 100 people dead in Guangdong Province in the space of one week.” The Global Public Health Intelligence Network of the WHO also picked up media reports of an unusual epidemic of fatal pneumonia-like illness in Guangdong.

**WHO Gets Reports of Alarming Outbreak**

February 10 was the first working day for many people after the weeklong Chinese New Year holiday. On that day, the WHO Representative in China, Dr. Henk Bekedam, received reports about an alarming outbreak in Guangdong Province. The son of a former WHO staff member sent an email to Alan Schnur, the Communicable Disease Team Leader of WHO China: “Am wondering if you would have information on the strange contagious disease (similar to pneumonia with invalidating effect on lung) which has already left more than 100 people dead in … Guangdong Province, in the space of one week. The outbreak is not allowed to be made known to the public via the media, but people are already aware of it (through hospital workers) and there is a ‘panic’ attitude, currently, where people are emptying

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32 Thomas Abraham, *Twenty-First Century Plague: The Story of SARS* (Hong Kong: Hong Kong University Press, 2004), 20.
33 “SARS: How a Global Epidemic Was Stopped,” (Manila, WHO Regional Office for the Western Pacific, 2006), 5.
34 Yanzhong Huang.
35 WHO, Update 95—SARS Chronology.
pharmaceutical stocks of any medicine they think may protect them.” Mr. Schnur forwarded the email at once to the Ministry of Health, and sought information. He added that the American embassy had passed on a similar rumor about a strange disease that was causing bleeding and many deaths in Guangzhou.

Once the Hong Kong Government learned from the newspapers about this health crisis, it attempted to obtain additional information, aware that previous waves of diseases, such as the global pandemics of 1957 and 1968, had entered Hong Kong from Guangdong province before spreading into the rest of the world. The Department of Health tried to telephone health officials in Guangdong to find out what exactly the position was, but it failed to reach anyone in authority.

When Dr. E.K. Yeoh asked Dr. Chan about the outbreak in Guangdong, she told him about the department’s failure to obtain any response to its enquiries. He then asked her to contact the Ministry of Health in Beijing, since this was the established channel of communication between Hong Kong and the Chinese government where infectious diseases were concerned (Fig. 14.3). It turned out that under the policy of “One Country, Two Systems,” only the central government was supposed to communicate with Hong Kong and not the provincial government in Guangdong. Dr. Chan then successfully contacted the Director General of the Department of International Cooperation of the Ministry of Health by telephone and expressed concern about the reported epidemic in Guangdong. The director general promised to look into the matter.

The following morning, the Guangzhou city government held a press conference at which the Director of the Bureau of Health, Huang Jiongjie, explained the situation in the provincial capital. Director Huang said that towards the end of 2002, atypical pneumonia cases were reported in certain parts of Guangdong Province. To date, he said, more than a hundred cases had been reported in Guangzhou, with many of the patients being healthcare workers. There had been two deaths. Despite its quick onset, he said, the risk of fatality is low. There was, he said, no need to panic.

In the afternoon, the Guangdong provincial government held its own press conference. Health officials reported a total of 305 atypical pneumonia cases in the province, with five deaths. But they, too, spoke reassuringly about how the situation was under control although they acknowledged that there were no effective drugs to treat the disease and that the outbreak was only tentatively contained. A third of the cases were health workers who contracted the disease while caring for patients. That same information, that there had been about 300 cases and five deaths in Guangdong province as a result of an outbreak of acute respiratory syndrome, was also passed on to the WHO by the Chinese Ministry of Health.

Professor Yuen Kwok-yung, Head of the Microbiology Department, had kept his ear to the ground to find out what was going on in Hong Kong’s neighborhood. Unlike the government, which did not bother to monitor what appeared in

36 “SARS: How a Global Epidemic Was Stopped,” 75.
37 “Guangzhou is fighting an unknown virus,” Southern Weekly, February 13, 2003, cited by Huang.
Guangdong newspapers, Professor Yuen, also known as K.Y., was very concerned about the increasing reports in the media about unusual outbreaks of mysterious diseases. University of Hong Kong researchers were ahead of the government, which was oblivious to what hints had appeared in the mainland press. They, too, sought additional information but they, unlike government officials, had the necessary contacts.

As Professor Yuen subsequently explained to the Legislative Council Select Committee set up to look into the government’s handling of the disease, the Microbiology Department convened a meeting attended by four persons: K.Y. Yuen, the Head of Department, Professor Malik Peiris, Dr. Guan Yi and Dr. B.J. Zheng. At the meeting, Guan Yi expressed his concern that the atypical pneumonia outbreak in Guangdong might be linked with H5N1 influenza, as had happened in Hong Kong in 1997 (Fig. 14.4). He proposed a more in-depth field investigation to ascertain the infectious agents responsible for the outbreak by conducting a foray into Guangzhou to find out what was actually going on and, if possible, to bring back specimens from patients suffering from this mysterious ailment for analysis in Hong Kong. The consensus at that meeting was that Dr. Guan and Dr. Zheng should try to contact authorities in Guangzhou to facilitate the investigation (Fig. 14.5). As Peiris said, “We knew the disease was going to come over to Hong Kong,” so it was vital to learn as much as possible before it arrived. Guan and Zheng were both from the mainland and knew its culture and its people. So, when a mysterious disease was reported in Guangdong, it was natural that they were the ones to plunge deep into the heart of the infected areas and to shine a light into the dark corners. They left the following day, February 11. Peiris’s role was to supervise the virological investigations into the patient specimens. He would also liaise with researchers in other countries. Yuen himself focused on Hong Kong.

**HKU Experts Head for Guangdong**

Ever since the avian flu outbreak in Hong Kong, the Department of Microbiology had conducted frequent exchanges with mainland doctors and scholars. When this mysterious new disease emerged, researchers both in Hong Kong and the mainland suspected that it was again some form of bird flu. During their visit, Dr. Guan and Dr. Zheng met Professor N.S. Zhong (鐘南山), or Zhong Nanshan, a prominent educator and researcher who was head of the respiratory research center at the First Affiliated Hospital, Guangzhou Medical College. Dr. Zheng knew him personally, so it wasn’t difficult to arrange to discuss the atypical pneumonia situation with him. Dr. Zhong, who had received his early training in Beijing Medical University and had done advanced work at St. Bartholomew’s Hospital in London and the University of Edinburgh Medical School, was in charge of the management of atypical pneumonia cases at his hospital (Fig. 14.6).

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38 K. Y. Yuen, “Report to the Legco Select Committee,” 23 December 2003, 1–2.
39 Meeting with Malik Peiris, 26 September 2016.
During their visit, Dr. Zhong told the two Hong Kong researchers that the atypical pneumonia outbreak might be caused by flu-like viral infection because all routine laboratory examinations for infectious agents were negative. He suggested collaboration between his institution and the University of Hong Kong and agreed to provide specimens from patients with atypical pneumonia for viral isolation and identification. While strictly speaking this could be interpreted as a violation of China’s state secrets laws, it also could be labeled an “academic exchange” between health specialists in the mainland and Hong Kong.

Obtaining the specimens was in itself risky, since it meant direct physical contact with patients suffering from the mysterious disease. In the hospital of the Guangzhou Institute of Respiratory Diseases, the two Hong Kong doctors, wearing full protective gear, walked amid the patients, all in critical condition, accompanied by a nurse. Some sense of what happened is provided by this account: “She [the nurse] elevated the back of the man’s bed, removed his oxygen mask, and ordered him to open his mouth. Tentatively reaching a wooden stick with a Q-tip-like bulb at the end into the oral cavity, the nurse dabbed at the patient’s tongue twice, removed the swab, and handed it to Guan Yi. He broke the top of the stick and dropped the swab into a vial of medium. He didn’t say anything, but he could already see that this wasn’t going to work. In order for it to be an effective screening, he would need mucus and phlegm from further down the patient’s throat, as well as some nasal aspiration. The nurse was too frightened to gather anything but the faintest of saliva samples.” Guan Yi decided to take over and so, at the next station, he asked the nurse to step aside as he held a female patient up, ordering her to open her mouth, and then began slapping her back gently to encourage her to expectorate mucus. “This time the swab was pressed so far down the patient’s throat that when Guan removed it, it was coated with a satisfactory blob of mucus that glistened under the white lights. He managed to take twelve swabs, each of which he sealed in a vial of suspension medium so that they appeared almost like miniature moth cocoons preserved in formaldehyde.”

So the specimens were obtained and brought back to the Microbiology Department to be analyzed by Malik Peiris and his associate, Chan Kwok-hung (陳國雄), or K.H. Chan. In fact, Dr. Zhong subsequently said that samples were not given out to other researchers simply because they didn’t ask.

Professor Yuen kept the Hong Kong Government informed of his department’s activities through telephone calls to Director of Health Margaret Chan. The microbiologist told her about the investigation into the possible infecting agent responsible for the atypical pneumonia outbreaks in Guangdong and of the visit to Guangzhou by two members of his department and their return with specimens. He also conveyed to her his concern that large numbers of healthcare workers were being infected. So the University and the Government were in close contact from the earliest days. The Department of Health started a surveillance system for severe com-

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40 Statement by Professor K.Y. Yuen to Legislative Council Select Committee, 23 December 2003.
41 Greenfeld, China Syndrome, 134.
42 John Wong and Zheng Yongnian, ed., The SARS Epidemic: Challenges to China’s Crisis Management (Singapore: World Scientific, 2004), 168.
43 “Report of the Legislative Council Select Committee,” 28.
munity acquired pneumonia. All hospitals were required to report such cases. Nineteen cases were identified in February.

Hong Kong University researchers tried to isolate the virus causing the outbreak in Guangdong. They were the only ones in Hong Kong with specimens, but then they hit a stone wall. The specimens brought back were inoculated into chicken embryo and other cell lines. After several days, various viruses were isolated, including the H3N2 influenza virus, a virus that causes the common cold and one that causes respiratory infections called metapneumovirus, but there was nothing that was identifiable as the pathogen responsible for the Guangdong outbreak.

Because bird flu, especially of the H5N1 variety, was the chief suspect, attempts to cultivate the specimens used cell lines set up for this purpose. But they failed. A predisposition to suspect avian flu was totally natural. After all, on February 19, Hong Kong reported to the World Health Organization another outbreak of H5N1 when the avian flu virus was detected in a nine-year-old boy, whose family had been visiting Fujian Province when he fell ill. His father had died two days previously from an infection with the same virus, and his sister had died in Fujian earlier in the month, but was not tested for the virus. The WHO, too, saw a possible link between avian influenza and the outbreak in Guangdong. However, by mid-February, Malik Peiris was thinking of testing for other virus groups, but was hobbled by the limited resources of his modest virology lab. He made enquiries with overseas colleagues regarding techniques for picking up other virus groups, such as coronaviruses, hantaviruses and adenoviruses.44

Meanwhile, Guan Yi and B.J. Zheng continued to travel to Guangzhou to collect additional samples from patients. But it wasn’t long before it became unnecessary to travel to Guangdong to look for the virus. The virus had come to Hong Kong.

**Arrival of the Index Patient**

The date it happened can be pinpointed. On February 21, Dr. Liu Jianlun, a 64-year-old professor of nephrology from a teaching hospital in Guangzhou, arrived in Hong Kong and checked into the Metropole Hotel. Dr. Liu had contact with patients suffering from atypical pneumonia and then developed a fever and cold, which was treated by antibiotics. Though he still felt unwell, he decided to go ahead with his Hong Kong trip on February 21 to take part in the wedding of his nephew.

After arriving in Hong Kong, Dr. Liu and his wife had lunch with his sister and brother-in-law in a restaurant near the Mong Kok Railway Station. It was their son who was getting married. Then he went shopping in Central with his brother-in-law and had dinner in his home before going to the Metropole Hotel in Kowloon to spend the night.45 The next morning, February 22, a Saturday, he walked into the

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44 Personal communication from Malik Peiris, 13 February 2017.

45 “The Guangzhou Visitor (1 of 2),” DH Staff News No. 2, Government of the Hong Kong Special Administrative Region Department of Health.
Accident and Emergency Department of Kwong Wah Hospital, which was close to his hotel. He told hospital staff that he had been in contact with patients suspected to have atypical pneumonia during February 11–13 and had developed flu-like symptoms with sharp chest pain on February 15. Chest X-rays had showed left lower zone haziness. He said he treated himself with antibiotics (levofloxacin) and penicillin and improved. He said he had fully recovered before leaving for Hong Kong. But in Hong Kong, his fever came back and he had shortness of breath.\(^46\) The Accident and Emergency Department realized this was a serious case and requested an immediate transfer to an intensive care unit. Dr. Watt Chi-leung (屈志亮), ICU director, was aware of reports of an epidemic in the mainland and put Dr. Liu in isolation. He also instructed ICU staff to put on N95 surgical masks, gloves and gowns when caring for this patient.\(^47\) Dr. Watt also asked ICU staff to take Tamiflu as a precautionary measure.\(^48\)

On February 24, there was an unexpected telephone call from Guangzhou. The caller was a Ms. Tong, the secretary of the medical superintendent of the First Affiliated Hospital of Zhongshan Medical College in Guangzhou. She told Dr. Andrew Yip Wai Chun (葉維晉), Chief of Service of the Department of Surgery of Kwong Wah Hospital, that a member of her hospital group (the Second Affiliated Hospital), was in the ICU with severe respiratory illness. She asked Dr. Yip to check and see if the patient required expert care. Dr. Yip found out from Dr. Watt that the patient’s condition was critical. He suggested approaching Professor Yuen for medical advice. But because Professor Yuen himself was not feeling well, he suggested that Associate Professor Ho Pak-leung (何栢良) be approached instead\(^49\). Professor Ho went to Kwong Wah Hospital together with a colleague, Dr. Kenneth Tsang (曾華德), a respiratory physician from the University Medical Unit of Queen Mary Hospital (Fig. 14.7). At the hospital, they went over in considerable detail with hospital doctors the clinical history, examination findings, case notes, computer records, chest X-rays, laboratory results and infection control measures relating to the patient. So the Faculty of Medicine was involved in the treatment of the very first SARS patient from mainland China, who became known as patient zero, an extremely infectious patient who brought SARS to Hong Kong and, from Hong Kong, the disease rapidly spread around the world. It is believed that Dr. Liu infected 16 other guests in the hotel and, through them, something like 4,000 people in various countries became infected in less than four months as a result of travel by these hotel guests.\(^50\) This showed how rapidly a disease can spread in the twenty-first century. As long as the disease was bottled up in China, its impact was limited to

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\(^{46}\) “Report on a SARS Patient from Guangzhou who was admitted to Kwong Wah Hospital,” SC2 Paper No. A80.

\(^{47}\) “Written statement of Dr. Watt Chi Leung,” SC Paper No.: W6(C).

\(^{48}\) Statement by Kwok Lai Yin, Nurse Specialist, ICU Unit, Kwong Wah Hospital, to Legislative Council Select Committee dated 31 December 2003.

\(^{49}\) Written Statement of Dr. Yip Wai Chun, SC2 Paper No.: W31(C).

\(^{50}\) *Bulletin of the World Health Organization*, 81, no. 8 (2003).
one country. But as soon as it spilled over into Hong Kong, a hub of international air travel, it quickly spread around the world.

Professor Yuen himself participated in the treatment of the Liu case. He initiated a course of Ribavirin, a broad-spectrum viral agent, which is effective against respiratory, hepatitis and hemorrhagic fever viruses.\footnote{51} Despite all efforts, Dr. Liu died on March 4, ten days after he sought treatment at Kwong Wah Hospital. By then, his brother-in-law, Y.P. Chan, had been admitted to Kwong Wah for exactly the same condition. As Professor Yuen said, the illness of the brother-in-law was a turning point, since another family member had been infected by the same mysterious illness. “We had,” he said, “a real crisis on our hands.”\footnote{52}

Time was pressing. On March 12, the World Health Organization issued a global alert about cases of atypical pneumonia. It recommended that “patients with atypical pneumonia who may be related to these outbreaks be isolated with barrier nursing techniques.” At the same time, WHO also recommended that “any suspect cases be reported to national health authorities.” Three days later, it issued a rare emergency travel advisory calling the disease “a worldwide health threat.” It also gave the mystery ailment a name, Severe Acute Respiratory Syndrome (SARS). For the Special Administrative Region, it was an unfortunate choice of names, tarnishing the image of Hong Kong at best and, at worst, suggesting that the disease and Hong Kong were somehow synonymous. Hong Kong suggested a name change to the WHO but eventually gave up such efforts. On March 16, WHO released a list of “affected areas” with local transmission of SARS. Hong Kong was on that list. However, as far as the WHO was concerned, SARS was not named after Hong Kong. Indeed, the world health body, in describing the new disease, said it was “first recognized in late February, 2003, in Hanoi Vietnam.”

**Collaboration with Imperial College, London**

With the SARS epidemic’s arrival in Hong Kong, the University’s Department of Community Medicine became closely involved. Professor Anthony J. Hedley, the Chair Professor of Community Medicine since 1988, had focused on issues such as smoking, air pollution and other noninfectious health problems. SARS, of course, was quite different, with its rate of infection and case fatality rate yet unknown. Hedley turned to Imperial College, London, for help. In an email to Roy M. Anderson, the Head of the Department of Infectious Disease Epidemiology, he acknowledged that his department didn’t have much experience in this area. I know your work, Hedley said, could I persuade you to get interested in SARS? Could you come over and visit us?\footnote{53} (Fig. 14.8).

\footnote{51}{K.Y. Yuen and M. Peiris, “Facing the Unknowns of SARS in Hong Kong,” in *The New Global Threat: Severe Acute Respiratory Syndrome and Its Impacts*, ed., Tommy Koh et al. (Singapore: World Scientific, 2003), 176.}
\footnote{52}{Ibid.}
\footnote{53}{Personal communication from Roy Anderson, 5 April 2017.}
Anderson needed little persuasion. He had already been asked by David Heymann, Deputy Director of the World Health Organization, to be a member of its SARS emergency committee. His department had a lot of experience dealing with past epidemics, ranging from AIDS to foot-and-mouth to influenza. As it was, Heymann had asked Anderson to join him on a trip to Beijing to talk to the Chinese authorities about sharing data on how the epidemic started, what progress there was and control measures. Soon, Anderson was on a plane bound for Hong Kong. Beijing came next.

In Hong Kong, Hedley arranged for Anderson to meet his colleagues, including Gabriel Leung, who established and directed the university’s Infectious Disease Epidemiology Group, and Dr. Margaret Chan, the Director of Health. Together, they worked out a protocol for capturing data, analyzing the data and some public health interventions. So the Department was collaborating with both Imperial College and with the Hong Kong Government. The Department, Anderson said, “played an important role in helping the Hong Kong Government construct additional databases of cases, their contacts and basic demographic and epidemiological data from the midpoint of the epidemic onwards.”

More trips followed for Anderson and members of his team. Soon, Imperial College and HKU scholars were writing papers together. One early paper, whose principal researchers were Anderson and Christl A. Donnelly, also of Imperial College, was somewhat controversial, asserting that the case fatality rate was significantly higher than health authorities had thought, possibly up to 55% in people 60 and above, and 13.2% in younger people. As The New York Times reported, this was the first major epidemiological study of the disease. The paper’s authors included seven Imperial College experts, seven specialists from the Department of Community Medicine of the University of Hong Kong, two from the Hong Kong Department of Health, two from the Hong Kong Hospital Authority and one from the Chinese University of Hong Kong. They explained that estimating fatality rates by simply “dividing the current cumulative number of deaths by the current cumulative number of hospital admissions” was not satisfactory because “among patients still recorded as being in hospital, it is impossible to ascertain who will eventually die or be discharged.” Because of the public health importance of the article, the Lancet posted it online on May 7, 2003, more than two weeks before it appeared in the journal itself.

The Imperial College–Hong Kong University collaboration continued after the re-emergence of SARS in mainland China in 2004. In a paper where Anderson was the principal author, the group reviewed the understanding of the epidemiology, transmission dynamics and control of the aetiological agent of SARS. It concluded that the low transmissibility of the virus, combined with the onset of peak infectiousness following the onset of clinical symptoms of disease, “transpired to make

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54 Ibid.
55 Lawrence K. Altman, “The SARS Epidemic: Front-Line Research; Study Suggests a Higher Rate of SARS Death,” The New York Times, 7 May 2003.
56 C.A. Donnelly et al., “Epidemiological Determinants of Spread of Causal Agent of Severe Acute Respiratory Syndrome in Hong Kong,” Lancet, 361, no. 9371 (2003): 1761–66.
simple public health measures, such as isolating patients and quarantining their contacts, very effective in the control of the SARS epidemic.”\textsuperscript{57} If the time from infection to symptoms is about two days and the time from infection to peak infectiousness is also two days, then “by the time a patient reports to a physician it’s too late to quarantine him” because transmission has already occurred, Anderson explained. But, with SARS, “the incubation period from infection to first fever is five days, the time from infection to peak infectiousness is about 18 days, so you had a long interval and if you isolated or quarantined that patient you could stop transmission dead.”\textsuperscript{58} That, he said, was essentially what was done since Roman times with ships arriving at ports, and “sailors were put in quarantine until they were certain that they were not transmitting anything obnoxious from their travels.”

Anderson observed that the Department of Community Medicine, which was subsequently absorbed into the School of Public Health, had been transformed by the SARS experience. “What SARS did,” he said, “was to shift its attention a little bit more to infectious diseases. And infectious diseases epidemiology is slightly different—it involves transmission dynamics, it involves contact tracing, we have a primary case, you had to understand who that person has had contact with, so it has influenced the way the people thought about infectious diseases and how best to study them.” Speaking of his own institution, Anderson said, “We are a very quantitative group with a high computational, mathematical and statistical capability, so we probably switched them on a little bit towards more quantitative side of understanding transmission and control.”

The paper on the epidemic case fatality rate, he said, may well have been one of the department’s first infectious disease epidemiology papers, which was followed by many more. “When you deal with noninfectious diseases, you can take your time,” he observed. “Epidemics happen quickly and when they start to take off they grow exponentially. The SARS epidemic had a doubling time of about five to seven days, so things were moving very, very quickly. A very large number of staff in the department was switching from their normal research interest to thinking how to combat and study SARS.” This transformation, he said, was successful. “Some very high quality work has been coming out of there in the last 13 years,” he said, which has had “a very substantial influence internationally.”

\textbf{WHO Set Up Global Network of Labs and Scientists}

As soon as the emergency travel advisory was issued in mid-March, the WHO set up a network of scientists from 11 laboratories around the world to try to identify the causal agent and develop a diagnostic test, similar to a network for influenza set up by Klaus Stohr. The laboratories were in Canada, France, Germany, Japan, the

\textsuperscript{57}Roy M. Anderson et al., “Epidemiology, Transmission Dynamics and Control of SARS: The 2002–2003 Epidemic,” \textit{Philosophical Transactions of the Royal Society of London B}, 359, no. 1447 (2004): 1091–105.

\textsuperscript{58}Interview with Anderson, 5 April 2017.
Netherlands, Singapore, the United Kingdom, the United States and, of course, Hong Kong. All were approached by telephone during the weekend of March 15–16 and all agreed to participate and to observe the WHO’s ground rules. The purpose of the network was to unite laboratories with different methods and capacities to rapidly fulfill all postulates for establishing a virus as the cause of the disease. Scientists agreed to share results in real time via a secure website and discuss findings in daily conferences. As Klaus Stohr wrote, “Laboratories in the influenza network ruled out all influenza virus strains and other known causes of pneumonia from samples taken in Hanoi, Singapore and Hong Kong. SARS looked increasingly like a new disease.”

Of the 11 laboratories, three were in Hong Kong. These belonged to the Hong Kong Government, the University of Hong Kong and the Chinese University of Hong Kong. At Hong Kong University, the team included medical technologist Chan Kwok-hung, pathologist John Nicholls and Leo Poon Lit-man. The Hong Kong University virology lab was the smallest, with only about six people, easily dwarfed by the government’s virology lab, not to say the U.S. CDC’s lab, where hundreds of people worked. In other words, the odds were stacked against Malik’s team in the race to identify the SARS virus. Dr. Chan set up cell lines for the testing of specimens, Dr. Poon helped develop molecular diagnostic tools for fishing out unknown pathogens, and Dr. Nicholls (Fig. 14.9) used electron microscopy to help identify viruses. K.Y. Yuen did PCR tests on the positive cell culture with cytopathic effect to exclude the presence or contamination by any bacteria that may cause atypical pneumonia, including chlamydia and mycoplasma.

The situation in Hong Kong was worsening. By March 18, 111 hospital workers and relatives of what authorities believed to be the index patient were diagnosed with atypical pneumonia, now renamed SARS. Most were in the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong, and four were in intensive care. Of the 111 cases, 44 were doctors, nurses, and other hospital personnel at the Prince of Wales Hospital, where Hong Kong’s major outbreak began on March 8. Concern heightened in late March when a major outbreak of SARS erupted in Amoy Gardens, a high-rise housing estate.

Actually, even before the Prince of Wales Hospital breakout on March 8, Malik was actively looking at the possibility of the villain of the piece being a coronavirus among other possibilities. In an email on that day to a colleague in the United Kingdom, he asked for information on “coronavirus control material to be used in molecular detection assays.” Disappointingly, the colleague knew no one in the U.K. who was actively working on coronaviruses.

Very quickly, the WHO’s global network produced results. On March 18, the day after the network began functioning, German laboratories reported paramyxovirus

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59 K. Stöhr, “A Multicentre Collaboration to Investigate the Cause of Severe Acute Respiratory Syndrome,” *Lancet*, 361, no. 9370 (2003):1730.
60 Ibid.
61 Mary Ann Benitez, “Hong Kong Bears Brunt of Latest Outbreak,” *Lancet*, 361, no. 9362 (2003).
62 Malik Peiris’s email to Maria Zambon.
from a SARS patient. The Chinese University of Hong Kong also found paramyxovirus-like particles in respiratory samples. China was not part of the network but on March 19, WHO received a letter from China’s Ministry of Health announcing that chlamydia was found by electron microscopy in five SARS patients. Actually, as early as February 19, the Ministry of Health had said to the WHO: “It is almost ascertained that the causal agent for the atypical pneumonia outbreak in Guangdong is chlamydia.”63 This was based on the work of Hong Tao, a senior microbiologist at China’s Center for Disease Control and Prevention.64 He had announced that the causative agent was chlamydia and, because of his standing, the Ministry of Health accepted his finding and maintained that the causal agent for SARS had already been identified.

The Microbiology Department at Hong Kong University had had a head start, with specimens brought back to Hong Kong at the risk of their lives by Guan Yi and B.J. Zheng. But after attempting to culture about 50 specimens, it was still unable to identify the virus involved. Of course, there was no guarantee that any of the specimens brought back from Guangzhou contained the pathogen in question. Where the index patient Dr. Liu was concerned, no bacteria, virus, fungus or parasite could be found in his respiratory secretions, blood or other body fluids. As K.Y. Yuen acknowledged, “Basically we failed to save him and also failed to make a microbiological diagnosis.”65 But the infection of Dr. Liu’s brother-in-law presented another opportunity. Here was a patient who was suffering from exactly the same disease. The researchers wanted lung tissue from the new patient, which, they acknowledged, was an extremely invasive surgical procedure to perform on a sick patient. But after consideration by Dr. Andrew Wong, Chief of Service in Medicine at Kwong Wah, the operation was performed and the lung tissue sent to Queen Mary Hospital for microbiological analysis.66 This time, at least, the microbiological team knew for sure that the specimen had come from a patient with the mystery disease.

**New Cell Lines Tried**

With the failure of previous attempts, almost all the team members realized that there was now a need to try other cell lines. As K.Y. Yuen wrote in a joint article with Malik Peiris: “Our colleague, Dr. Chan Kwok-hung was encouraged to try as many new cells lines (animal cells as medium for viral culture) as possible, beyond the standard four or five that were normally used. What we needed next were luck and lots of patience.”67

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63 SARS: How a Global Epidemic Was Stopped,” 2006.
64 Abraham, *Twenty-First Century Plague*, 123–24.
65 Yuen and Peiris, “Facing the Unknowns of SARS in Hong Kong.” 176.
66 Ibid.
67 Ibid, 179.
Dr. Chan decided to use a cell line of fetal kidney cells from rhesus monkeys. It was rarely used except to grow hepatitis A virus but it had also proved useful in growing a range of respiratory viruses.\(^{68}\) This was done on March 13. Two days later, there was a visible reaction as the cells appeared to be dying, that is to say, there was a virus taking over. This was confirmed through multiple tests that eliminated the possibility of contamination. “The use of this cell line (FRhk-4) was probably the most important decision in the discovery of the pathogen behind SARS,” Yuen and Peiris wrote. “The lung tissue of Mr. Chan YP (the brother-in-law of the index patient) was inoculated into this cell line for viral culture together with other specimens from patients with pneumonia associated with recent travel to Guangdong. Miraculously, significant changes were observed in this cell line.”\(^{69}\)

But was the virus that was killing the cells the SARS virus, that is, was it the cause of the disease, or did it just happen to be present? To determine this, the Hong Kong University team tested their virus against blood serum samples from patients at different stages of the disease, from early onset to the late stages. The test results confirmed their suspicions. As Peiris said, “We had the virus growing well, it was reacting in the expected way to early and late serum samples. We were quite sure this was the virus causing SARS.”\(^{70}\) By March 21, Peiris was ready to share his findings with researchers around the world. That day, he had missed the daily conference call linking SARS researchers globally. But, in an email late that night, Peiris indicated that Hong Kong University had isolated an agent from two patients with SARS. The agent was isolated in continuous rhesus monkey kidney cells. It had a cytopathogenic effect, that is to say, it caused structural changes in host cells, which indicated the growth of a virus. “In conclusion,” Malik wrote, “we are confident that the agent in the cell cultures are associated with the SARS syndrome. The identification of this agent is under way.”\(^{71}\) Klaus Stöhr of the WHO subsequently published a paper on the “multicenter collaboration to investigate the cause of Severe Acute Respiratory Syndrome” in which he recalled Malik Peiris’ report on the agent that had been cultured in rhesus monkey kidney cells. “In addition, in an immunofluorescence assay of virus-infected cells, done in a blinded trial, sera from SARS patients had rising antibody titres to the new virus isolate,” he wrote. “By contrast, sera from blood donors taken long before the disease emerged in Hong Kong had no antibody to this virus. Furthermore, virus-like particles in the cytoplasm and at the cell membrane were seen in thin electron microscopic sections from infected cells.” Stöhr concluded: “These findings proved to be the turning point in the search for the SARS causative agent.”\(^{72}\)

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\(^{68}\) J.S. Malik Peiris and Yi Guan, “Confronting SARS: A view from Hong Kong,” in SARS: A Case Study in Emerging Infections,” ed., Angela Mclean et al. (Oxford University Press, USA, 2005), 37.

\(^{69}\) Ibid.

\(^{70}\) Abraham, Twenty-First Century Plague, 114.

\(^{71}\) Text of Email Provided by Malik Peiris.

\(^{72}\) Stöhr, “A Multicenter Collaboration to Investigate the cause of Severe Acute Respiratory Syndrome,” 1730.
**Malik Describes ‘Tricky Virus’**

The day after he informed the WHO network of researchers, Malik Peiris held a press conference in Hong Kong and reported that the University had identified a virus associated with SARS but that his team did not yet know what kind of virus they were dealing with. “What we have here is a new, I think it is quite a tricky disease and a tricky virus,” Peiris said. “It is quite important for us to study this in detail before we can come to a conclusion.” The *South China Morning Post* headline proclaimed: “Genetists link ‘tricky virus’ to pneumonia outbreak.”

Four days later, Peiris held another press conference and identified the virus as a coronavirus, so called because of the crown-like spikes on its surface. The Hong Kong University virologist said that his team had completed the genetic sequencing of the virus, isolated from Hong Kong patients. “It is not one of the two known human coronaviruses and not even any animal coronavirus,” Professor Peiris said. “We are dealing with a type of virus which we have never come across before.”

The Hong Kong University discovery was the culmination of a worldwide race to uncover the agent that causes SARS. Scientists all over the world had been working around the clock and those at the University of Hong Kong had succeeded at being the first to identity the elusive culprit. This was a real triumph, subsequently confirmed by the WHO.

The Centers for Diseases Control and Prevention in the U.S. also announced the discovery of a coronavirus without mentioning Hong Kong’s breakthrough, apparently unaware that it had occurred. It issued a press release announcing that “a previously unrecognized virus from the coronavirus family is the leading hypothesis for the cause of severe acute respiratory syndrome.” However, the WHO took it upon itself to set the record straight. Dr. David Heymann, WHO’s Executive Director for Communicable Diseases, said at a press briefing: “Just so you’re clear. The virus was first found in Hong Kong, first identified in Hong Kong. And then it was identified at CDC. And now it’s been identified by all the other laboratories.” Also, just as Hong Kong University publicized its breakthrough before the CDC’s announcement, so the university was able to get its scientific discovery into print first, with the publication of a paper in the online *Lancet* on April 8, 2003, “Coronavirus as a possible cause of severe acute respiratory syndrome.” The success was very much the result of a group effort, as the list of authors shows, with Malik Peiris as the lead writer, K.Y. Yuen as the last writer and others, including

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73 “Genetists Link ‘Tricky Virus’ to Pneumonia Outbreak,” *South China Morning Post*, 23 March 2003.

74 “New Virus Believed to Be Responsible,” *South China Morning Post*, 27 March 2003.

75 “CDC Lab Analysis Suggests New Coronavirus May Cause SARS,” 24 March 2003, Office of Enterprise Communications, Centers for Disease Control and Prevention.

76 “Severe Acute Respiratory Syndrome Press Briefing,” 11 April 2003. [http://www.who.int/csr/sars/Press_2003_04_11/en/](http://www.who.int/csr/sars/Press_2003_04_11/en/)
Guan Yi, Leo Poon, John Nicholls and K.H. Chan, in between. In the same issue, *Lancet* published a commentary that said: “In today’s *Lancet*, Joseph Peiris and colleagues provide strong evidence that SARS is associated with a novel coronavirus that has not been previously identified in human beings or animals, and begin the process of eliminating the many unknowns from this new syndrome. … One of the strengths of their report, and an important means of establishing causality, is their analysis of specimens from control patients. None of the 40 respiratory secretions from patients with other respiratory diseases contained the coronavirus RNA, and none of 200 serum samples from blood donors had serum antibody to this new coronavirus. These findings significantly strengthen the tentative aetiological association reported by other investigators from the Centers for Disease Control and Prevention in Atlanta and from Toronto, who have also isolated a novel coronavirus from patients with SARS.” Two days later, the CDC article appeared in the online edition of the *New England Journal of Medicine*, “A novel coronavirus associated with severe acute respiratory syndrome.” The university’s lead over the CDC, with incomparably greater resources, was clear.

**Mainland Scientists Achieved Feat First?**

Paradoxically, it emerged later that Chinese scientists on the mainland may well have been the first to identify the SARS coronavirus. This apparently happened in mid-March, 2003, even before the World Health Organization had issued a global alert. Scientists with the Chinese Academy of Military Medical Sciences had discovered a new virus in samples from patients in Guangdong Province. “The virus, they had noticed, had a distinctive halo of spikes that put it in a family not known to kill humans: the coronaviruses,” the magazine *Science* reported in July 2003, by which time the World Health Organization had declared all countries SARS-free. “By the first week of March, the group had tentative evidence that the new virus might indeed be linked to the epidemic.”

The problem, as is frequently the case in China, was politics. Since the highly respected senior microbiologist Hong Tao had made the pronouncement in February that chlamydia was responsible for the mystery ailment, the Ministry of Health had accepted this view and the official Chinese establishment would accept no other view. So the academy’s microbiologists kept their mouths firmly shut. “These scientists were the first ever to see the SARS virus,” Klaus Stohr of the WHO said after

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77 J.S. Peiris, et al., “Coronavirus as a Possible Cause of Severe Acute Respiratory Syndrome,” *Lancet* 361, no. 9366 (2003): 1319–25.
78 A.R. Falsey, et al., “Novel Coronavirus and Severe Acute Respiratory Syndrome,” *Lancet* 361: no. 9366 (2003): 1312–13.
79 T.G. Ksiazek, et al., “A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome,” *New England Journal of Medicine*, 348, no. 20 (2003).
visiting the academy, “and we had no idea.” Just like the outbreak in Guangdong, when Chinese patients and medical workers lacked information because of the Communist Party’s penchant for secrecy, China was a victim of its own policies, this time of obstinately sticking to a position just because someone in a position of authority had made a pronouncement.

The discovery of the SARS coronavirus was a huge step forward in the war against the deadly disease, but by no means did it mark the end of the war. In fact, things were to get much worse before they got better. The Hong Kong Director of Health made SARS a statutorily notifiable disease by revising the Quarantine and Prevention of Disease Ordinance so as to provide the legal basis for mandating close contacts of SARS patients to report daily to one of four medical centers. All secondary and primary schools and preschools were temporarily suspended. The Rolling Stones canceled their concert, scheduled for March 28 and 29. On April 2, the World Health Organization issued the most stringent travel advisory in its 55-year history. It recommended that “persons travelling to Hong Kong and Guangdong Province consider postponing all but essential travel until further notice.”

Once the SARS virus was grown in the laboratory and identified, it became possible to decode its genome and identify its genetic makeup. It also was possible to identify it in the body. Tests could be carried out to see what effect potential treatments had. For example, in response to demand for an antiviral cure for SARS, various drugs were tested. In one test, the clinical response of patients with SARS to a combination of lopinavir/ritonavir and ribavirin was examined and compared with patients treated with ribavirin only who served as historical controls. The treatment was found to be significantly more effective than that provided in the historical control group.

Just about this time, Hong Kong received a rare visit from a Chinese leader. Premier Wen Jiabao visited the city in mid-2003, the first national leader to do so since the devastation of SARS. The Premier went to the University of Hong Kong and praised its role in the battle against the killer disease. The Premier met the key figures involved, the Head of Microbiology Professor K.Y. Yuen, the Chief of Virology Professor Malik Peiris, and virologist at the Department of Microbiology, Dr. Guan Yi. The Premier was briefed by Professor Yuen on how, despite limited resources, the university was able to track down the agent of SARS while Dr. Guan explained how animal viruses were discovered.

Within weeks of the discovery of the SARS coronavirus, the viral genome had been completely sequenced, with Hong Kong University coming third in that race, following researchers in Canada and the United States. The sequencing showed a virus that had begun life in an animal before it mutated and began to infect people. The question then became: what animal housed this virus? That is to say, what

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80 Martin Enserink, “SARS in China: China’s Missed Chance,” *Science*, 301, no. 5631 (2003): 294–96.
81 C.M. Chu et al., “Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings,” *Thorax* 59, 3 (2004): 252–56.
82 “Premier Wen Jiabao visited the University of Hong Kong,” Press release, The University of Hong Kong, *30 June 2003*. 
animal—or animals—carried the virus that mutated and was able to infect people? In order to prevent a recurrence of SARS, it was important that an answer be found to this question. In the case of avian flu, chickens and ducks were the culprits. Were domestic animals also responsible for SARS?

Professor Zhong Nanshan had reported that one of the earliest SARS cases in Heyuan was a chef who had come into regular contact with several types of live caged animals used as exotic game food. Because of this, Guan Yi and B.J. Zheng, who led the effort to identify the animal host of the SARS virus, focused their attention on wild animals recently captured and marketed for culinary purposes. While Malik Peiris and his people were toiling in their labs, Guan Yi was busy testing animals being sold in wet markets in Guangdong to see what viruses they harbored. On May 23, 2003, the results of a joint study by research teams in Hong Kong and Shenzhen of wild animals taken from a market in southern China were released. The study detected coronaviruses closely related genetically to the SARS coronavirus in two of the animal species tested—the masked palm civet and the raccoon dog. The study also found that a Chinese ferret badger elicited antibodies against the SARS-CoV. The study provided for the first time an indication that the SARS virus exists outside a human host.

“Sequencing of viruses isolated from these animals demonstrated that, with the exception of a small additional sequence, the viruses are identical with the human SARS virus,” it said. “Information on the potential role of animals in the transmission of SARS is important to overall understanding of SARS. At present, no evidence exists to suggest that these wild animal species play a significant role in the epidemiology of SARS outbreaks. However, it cannot be ruled out that these animals might have been a source of human infection.” The wild animals sold at markets are traditionally considered delicacies and are available throughout southern China, the study reported.

Largely because of the findings of this joint study, conducted with the Shenzhen Centers for Disease Control, the Guangdong government temporarily banned the sale of civet cats and closed down wildlife markets. But the ban was lifted a few months later after another mainland team challenged the findings and after the war on SARS was believed to have been won.

Guan Yi and B.J. Zheng Hunt for the Source

Nevertheless, Guan Yi and B.J. Zheng persevered, conducting further researches in Guangdong’s live-animal retail markets. “Animals were held, one per cage, in small wire cages,” they reported about one Shenzhen market. “The animals sampled included seven wild, and one domestic, animal species. They originated from

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83 N.S. Zhong, et al., “Epidemiology and Cause of Severe Acute Respiratory Syndrome (SARS) in Guangdong, People’s Republic of China,” *Lancet*, 362, no. 9393 (2003):1353–58.

84 “Consensus document on the epidemiology of Severe Acute Respiratory Syndrome,” Department of Communicable Disease Surveillance and Response (2003), World Health Organization, 28–29.
different regions of southern China and had been kept in separate storehouses before arrival to the market. The animals remained in the markets for a variable period of time, and each stall holder had only a few animals of a given species. Animals from different stalls within the market were sampled. Nasal and fecal samples were collected with swabs and stored in medium 199 with bovine serum albumin and antibiotics. Where possible, blood samples were collected for serology.85

Sampling was carried out in Shenzhen from the end of October and in Guangzhou from early December 2003. Altogether, 179 wild animals were sampled between October 2003 and January 2004 by Guan and his team. Of these, 52 were positive for SARS-CoV-like virus, with palm civets found to be the most often infected.86 They discovered that “the recent SARS-CoV sequences from wild animal specimens collected from southern China from October 2003 to January 2004 are much more like the human SARS-CoV sequences from May 2003. This indicates that the SARS CoVs present in wild animals in southern China are heterogeneous, are continuing to evolve, and have also acquired mutations making them potentially infectious for humans.”

As it turned out, because of Guan Yi’s efforts, not only was an animal link to the SARS virus uncovered but another SARS outbreak in Guangdong was narrowly averted. On December 27, 2003, a suspected human case of SARS was reported in Guangzhou and the patient was quarantined. The Center of Disease Control and Prevention of Guangdong confirmed the case as SARS. The viral genomic sequence from this new SARS case was almost identical to that from palm civets, suggesting that the human patient might have acquired the infection from palm civets or other wild animals in the wet markets in Guangdong.87

So great was the danger of another SARS outbreak in Guangdong among the human population that Guan Yi decided to appeal directly to the powers that be. As the year 2004 began, he sat down and wrote a letter to China’s Hong Kong and Macau Affairs Office, copies of which were also sent to the Ministry of Health and China’s Centers for Disease Control. “With winter coming, the wildlife markets have reopened, providing the perfect conditions for another outbreak of SARS,” he wrote. He listed his findings on the civet cat as a major carrier of the SARS coronavirus, as well as the fact that other wild animals, too, carry the virus. He enclosed four pages of genetic sequences taken from civets. The letter was hand delivered on January 2.88

The very next day, he was invited to Guangzhou to make his case in front of the most eminent scientists in the province, including Professor Zhong Nanshan, and clinicians who had treated patients during the SARS outbreak the previous year. While they were speaking, the amino-acid sequences of the human patient recover-

85 Y. Guan, et al., “Isolation and Characterization of Viruses Related to the SARS Coronavirus from Animals in Southern China,” Science, 302, no. 5643 (2003):276–78.
86 Y. Guan, et al., “An Averted SARS Outbreak,” in Challenges of Severe Acute Respiratory Syndrome, ed., Jane CK Chan (Singapore: Elsevier, 2006), 94–100.
87 Ibid, 96.
88 Karl Taro Greenfeld, “The Race to Contain a Virus,” Time, January 11, 2004.
ing from SARS in a Guangzhou hospital were sent to Hong Kong for sequencing. In an hour, the results were in: the SARS patient’s virus sequences were almost identical to that of the virus sequences of the palm civets. That is to say, the virus in the wild animal markets had somehow infected a human. The group decided then and there to contact the provincial governor and recommend a cull of all civet cats. Professor Zhong telephoned Governor Huang Huahua recommending the slaughtering of all civet cats in the markets.89 The order to carry out the slaughter was given on January 5, 2004, involving an estimated total of 10,000 civet cats.

At a news conference in Hong Kong the day the order was issued, Dr. Zhong joined Hong Kong University microbiologists to announce that they had jointly completed a detailed study of SARS-like viruses in civet cats together with a genetic analysis of viral samples taken from a 32-year-old man in Guangzhou who was suspected to have SARS.90 K.Y. Yuen said that while research the previous spring had shown that the SARS virus that infected more than 8,000 people around the world was genetically very similar to a virus in civet cats, new research shows that the virus in civet cats “has mutated to form a new ‘sublineage’ of the virus.” He said that a genetic sequencing of samples from the infected man in Guangzhou had found that the main “spike” of protein was exactly identical, down to the last amino acid, to the new sublineage of the virus found in civet cats. Professor Zhong warned that civet cat feces could dry up and become windblown dust that would raise a risk of airborne infection. He said the feces carry extremely high concentrations of the virus, which can still be detected even when the feces are diluted as much as one billion times. Professor Yuen’s conviction of the role of civet cats in the transmission of the SARS virus to humans was reflected in testimony he gave in early January 2004 to the Legislative Council Select Committee set up to inquire into the handling of the Severe Acute Respiratory Syndrome outbreak by the Government and the Hospital Authority. At one point, Legislator Chan Kwok-keung (陳國強) asked about the origin of the virus and this exchange took place:

Legislator: “Professor Yuen, I want to ask, just now you said virus came from… some came from hospitals, some came from the community. In reality, did the virus originate from the community or from hospitals?”

Professor Yuen: “This virus? If your question is how did the thing get here, you would never get an answer. By way of example, we currently believe that the most important source is civet cats, but in reality we cannot be 100% certain unless in the same second, we can give all animals in the world a one-off examination. Then, we can be very certain. But still this is only a 99.99% probability that it is civet cats. Because you cannot be sure that a virus has not suddenly arrived on earth from Mars and entered a certain civet cat, so you can never know for sure. But if you are asking about likelihood, about probability, then I feel that

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89 Ibid.
90 Keith Bradsher and Lawrence K. Altman, “China to Kill 10,000 Civet Cats in Effort to Eradicate SARS,” The New York Times, January 5, 2004.
based on the evidence we have at the moment it mainly started from wild animals.”

The Guangdong culling operation of civet cats began on January 7 and the last case of SARS appeared on January 9. After that, no new cases of SARS emerged, despite the Chinese New Year which, as usual, saw large numbers of people traveling as they returned home for the holidays. Thus, the January 2004 cull in Guangdong, like that of December 1997 in Hong Kong, must be deemed a success in averting a pandemic. However, farmers of civet cats suffered economic disaster. Researchers found that civets on farms were largely free from the virus, though those in overcrowded retail markets, where civets are put in close proximity with other species, are often infected. This raised the question whether the civet cat was the main conduit for SARS or whether it was infected by another animal, which was the real reservoir of the virus. Professor Yuen decided to turn his attention to other animal species in the wilderness that may be carriers of similar viruses.

Not everyone was as enthusiastic as Yuen in his efforts to gather evidence that might in effect exonerate the civet cat, after so much publicity had gone into slaughtering civet cats in Guangdong. But Yuen persevered, doing his research in Hong Kong, screening for coronaviruses in wild animals within the territory. In this he was successful. He found that the Chinese horseshoe bat was the natural reservoir of SARS coronavirus-like viruses. So the bats might well have infected civet cats, possibly via yet a third animal.91 The public health implication was that animals, such as bats, should not be mixed together with other species in wildlife markets, as was the case before 2003. The Microbiology Department did not stop there. It went on to sample animals for novel viruses and, by 2017, had identified 60 novel animal viruses. Most of them were named after Hong Kong or after Hong Kong University, such as the bat coronavirus HKU4 found in Lesser Bamboo bat and the bat coronavirus HKU5 found in the Japanese Pipistrellus bat. Not much notice was taken of these novel viruses but, after the emergence of Middle East Respiratory Syndrome, both were mentioned in a paper about a man who died in Saudi Arabia. “A previously unknown coronavirus was isolated from the sputum of a 60-year-old man who presented with acute pneumonia and subsequent renal failure with fatal outcome in Saudi Arabia,” began an article in the New England Journal of Medicine in 2012. “The virus (called HCoV-EMC, later MERS-CoV) replicated readily in cell culture, producing cytopathic effects of rounding, detachment, and syncytium formation. The virus represents a novel betacoronavirus species. The closest known relatives are bat coronaviruses HKU4 and HKU5.”92 Thus, Hong Kong University identified novel animal coronaviruses prior to the emergence of this highly fatal infection in the Middle East and subsequently Korea.

91 K.P. Susanna et al., “Severe Acute Respiratory Syndrome Coronavirus-like Virus in Chinese Horseshoe Bats,” Proceedings of the National Academy of Sciences of the United States of America, 102, no. 34 (2005):19040–45.
92 Ali M. Zaki, et al., Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia,” New England Journal of Medicine, 367 (2012):1814–20.
A Bauhinia Star for Yuen

Hong Kong paid a high price for SARS, with more than 1,700 people laid low by the disease, with 299 deaths. In 2004, the government awarded Professor Yuen a Silver Bauhinia Star for his discovery of the coronavirus that causes SARS. Professor Yuen modestly said the award was recognition for all members of his team. “The award has helped boost the morale of my team,” he said. “My colleagues, including Malik Peiris and Guan Yi, put a great deal of effort into tracing the source of the SARS virus to civet cats. There are many more people who have made a lot of contribution.”

The University gave all three men—Professor Yuen, Professor Peiris and Dr. Guan—the Special Research Achievement Award in recognition of the team’s groundbreaking discovery of the coronavirus responsible for the outbreak of SARS. One interesting achievement of his team, Professor Yuen said, was that at one stage it collected the highest number of flu strains in the world; but, he added with his customary modesty, by now “the Beijing and the Harbin group should have superseded us already.”

Quite aptly, members of the entire team of scientists were called “Heroes of the SARS Wars” by Bloomberg. “Asia also has the global scientific community to thank for quickly mobilizing to understand the mysterious new virus,” Bloomberg observed. “Microbiologists in Hong Kong were in the lead. HKU doctors such as Malik Peiris and K.Y. Yuen worked almost around the clock and were the first to identify the SARS bug as a corona virus.” Yuen and his team were also called “Asian heroes of the Year” by Time Asia magazine.

The Chinese Government, too, recognized the university’s achievements. In 2005, the Ministry of Science and Technology established the first State Key Laboratories outside the mainland. One was a State Key Laboratory of Emerging Infectious Diseases while the other was a State Key Laboratory of Brain and Cognitive Sciences. Both were established at The University of Hong Kong. Professor Yuen and Dr. Guan were named co-directors of the one on emerging infectious diseases. Though Guan Yi was not yet a full professor at the time, it was a richly deserved honor. Two years later, in 2007, Professor Yuen was also conferred the honor of being named an Academician in the Chinese Academy of Engineering. He was honored for the development of tests for more rapid diagnosis of human disease associated with avian influenza A (H5N1) virus and for his leadership of the team in the successful effort to identify the SARS coronavirus and, subsequently,
his identification of the Chinese horseshoe bat as the natural host for the virus (Fig. 14.11).

Malik Peiris, too, received a wealth of awards. Reflecting his international outreach, the honors bestowed on him came from overseas, including the United Kingdom, where in 2006 he was elected a Fellow of the Royal Society of London, the highest scientific honor in the Commonwealth. The following year, he was awarded the Chevalier de la Legion d’Honneur by France as well as the Mahathir Science Award by Malaysia for the role he played in the discovery of the aetiological agent of SARS. Recognition from the Hong Kong Government came in 2008 when he received the Silver Bauhinia Star for “outstanding achievements in the field of virology and pathology, in particular his contribution to the prevention and control of infectious diseases.”

**HKU Researchers Among World’s Top 1%**

Today, all three men are listed among the world’s most frequently cited researchers in the field of microbiology. That is to say, they are among the top 1% of researchers in their field internationally. In 2015, Thomson Reuters listed Professors Yuen, Peiris, Guan and Poon among the “World’s Most Influential Scientific Minds” (Fig. 14.12).

So the microbiologists achieved recognition both within the University and from society at large, in Hong Kong and internationally. “In 1997, we only had 42 or 43 people,” K.Y. Yuen recalled. “Now, Microbiology has over a hundred people.” At the same time, the School of Public Health has well over 330 staff. “So,” Yuen said, “you can see the power of money. As a result, we can do much more research, and we have much better output.” Without the title of State Key Laboratory, Yuen said, they would never have received this money. The people working on microbiology today include both those in the department itself and in the public health school. While both the Department and the School do virology and pathogenesis, the department works more on clinical diagnosis and treatment while the school focuses more on epidemiology. They share the teaching load for medical students.

K.Y. Yuen was promoted to chair professor in 1999, Malik Peiris moved up from senior lecturer to become professor and, after SARS, to chair professor. Guan Yi has risen from a research assistant professor when he first joined the university to professor to Co-Director of the State Key Laboratory of Emerging Infectious Diseases and Professor of Virology. In January 2015, he was promoted to Chair Professor.

Such growth in personnel, plus internal promotions, would not have been possible without greatly increased funding. The designation of State Key Laboratory in mainland China would ordinarily come with substantial funding but, because the university is in Hong Kong, it cannot directly receive such funds from Beijing. From

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98 2008 Honours List, *Hong Kong Government Gazette*, 1 July 2008.
99 Interview with Professor Yuen, 5 January 2017.
2005, when the title was granted, until 2011, it could only apply for limited funding within the mainland, which had to be spent on collaborative projects with mainland researchers. However, beginning in 2011, the Hong Kong government started to provide funding to the State Key Laboratory through what is now its Innovation and Technology Bureau, to the tune of $5 million a year. This was a highly appreciated windfall and, with this additional funding, the department has grown much faster in recent years.

The physical laboratory at the university has also been upgraded. Laboratories are graded by biosafety levels, measuring the biocontainment precautions required to isolate dangerous biological agents in an enclosed facility, ranging from 1 to 4. At the time of SARS, the laboratory was at a biosafety level of P2+ and, in 2007, it was upgraded to a P3. Yuen thinks it may never become a P4 – the kind of lab where all the researchers wear astronaut suits because they are working on something very dangerous, like ebola.

**Post SARS: The Calm Before the Next Storm**

In the aftermath of such traumatic events as the H5N1 outbreak of 1997, followed by SARS six years later, Hong Kong learned that vigilance was vital. The government was determined that whenever the next health challenge arose, it wouldn’t be unprepared. In June 2004, Hong Kong set up the Center for Health Protection (CHP), using the Centers for Disease Control and Prevention in the United States as a model. Creation of the Center was recommended by the SARS Expert Committee appointed by Chief Executive Tung Chee-hwa. The government also earmarked a one-off grant of $500 million to support research into emerging infectious diseases. While $50 million was to support infectious disease research in the mainland, the bulk, that is, $450 million, was directed to support local investigator-initiated research and commissioned projects through the creation of the Research Fund for the Control of Infectious Diseases. The aim of the fund was to encourage, facilitate and support research on the prevention, treatment and control of infectious diseases. This was superseded in 2011 with the creation of the Health and Medical Research Fund, with the injection of an additional $1 billion.

On a down-to-earth level, the government took steps to ward off or at least mitigate the return of avian flu. Retail markets for live poultry came under close supervision. Rest days were introduced during which retail markets for live poultry were closed and thoroughly cleaned. Tests showed that viruses were dramatically reduced after a rest day. Live chickens were no longer imported from mainland China. Those taken to market came from local farms, and any chickens not sold at the end of the day were not returned to the farms but slaughtered, so that viruses could not be introduced—or reintroduced—onto farms from retail markets.

The University of Hong Kong, too, responded to the new situation. In 2004, it approved a proposal to establish a School of Public Health, which was formally inaugurated in 2009. The university was invited to submit proposals for research
related to basic laboratory, epidemiological and public health research in emerging infectious diseases. The university was asked to participate because of its pioneering work in discovering the SARS-coronavirus, its outstanding work on avian influenza A (H5N1) research and surveillance, and its track record of peer-reviewed publications, especially in journals with high impact factors. The university submitted a proposal, “Research preparedness for emerging and potentially reemerging infectious diseases in Hong Kong.” As a result, $30 million was approved for it to undertake a five-year portfolio of basic laboratory, epidemiology and public health research, as well as upgrade its bio-safety level 3 laboratory with enhancement for animal experimentation.

The H1N1 Pandemic of 2009

It was just as well that Hong Kong was consolidating its infectious disease and virology expertise and facilities after SARS because another storm was brewing. In March 2009, there was an outbreak of “flu” in a town called La Gloria in Veracruz, Mexico. It affected 60% of the town’s population and killed three children. It was believed to be the “common flu.” Between 14th and 17th April, specimens collected from two children with flu in California, U.S.A., were shown to have a strain of “swine flu” called H1N1. On April 24, the World Health Organization issued a disease outbreak notice confirming the infection of a number of people in Mexico and the United States by swine influenza A (H1N1) viruses not previously detected in pigs or humans. The 24th was a Friday and Malik heard the news Friday night. He gathered the “flu team” for a meeting the next day when they discussed what steps to take. A priority was to set up diagnostic tests for detecting the virus when it arrived in Hong Kong, as it inevitably would. They had the sequence of the virus provided by the U.S. CDC but for such molecular detection tests a positive control virus is needed to establish that the test is working properly. The new pandemic H1N1 virus was not available in Hong Kong. But a decade-long surveillance of swine influenza viruses provided a source within which to search and, indeed, a virus close enough to serve as the positive control was found. The next question was to understand the origins of the virus. It was decided to start genetic sequencing of the many hundreds of swine influenza viruses available from this surveillance effort.

By April 27, Jose Angel Cordova, the Minister of Health for Mexico, was reporting that 1,614 cases had been detected, 103 people had died and an additional 400 were in hospital. These were alarming statistics. On April 26, the U.S. declared a public health emergency and, the following day, the World Health Organization raised its pandemic alert to level 4, with 6 being the highest.

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100 “Research Fund for the Control of Infectious Diseases,” Hong Kong Medical Journal, 14, no, 1, Supplement, 1 February 2008.
**Metropark Hotel Quarantined**

On May 1, Hong Kong confirmed its first case of swine flu: a Mexican national who had arrived via Shanghai and stayed at the Metropark Hotel. It was the first reported case in Asia, and the Hong Kong government responded with the seriousness that it warranted. The alertness level was raised to “emergency.” With the example of Dr. Liu Jianlun—the Guangdong doctor who stayed overnight in the Metropole Hotel and infected more than a dozen other guests and visitors—seared into its collective memory, Hong Kong was not going to take any chances. While the 25-year-old Mexican patient was treated in isolation in hospital, the Metropark Hotel was quarantined and its roughly 200 guests kept in confinement for a week despite their protestations. Other interventionist measures learned during SARS included the closure of schools—primary schools, kindergartens and special schools, initially for two weeks and then extended to the summer holidays.

Historically speaking, Hong Kong had been identified with influenza research for decades. The 1968 pandemic, after all, was named Hong Kong Flu after having first been identified in the city. Then the bird flu saga of 1997 and SARS in 2003 put Hong Kong on the front lines of emerging disease outbreaks. “As a result, Hong Kong has invested heavily in infrastructure in preparation for future epidemics and pandemics,” explained one paper commenting on the territory’s public health research response to the 2009 outbreak. “There has also been substantial investment in research infrastructure, essential to guide evidence-based policy locally as well as internationally.” Thus prepared, even before the first case was reported in Hong Kong, it operated under containment efforts, including entry screening at airports, ports and border crossings, hospital isolation of cases, tracing and quarantine of contacts, and routine antiviral prophylaxis. On 26 April, Hong Kong raised its alertness level from “alert” to “serious,” just one step away from “emergency.” The next day, the World Health Organization, too, raised its alertness level. Dr. Keiji Fukuda, WHO’s Assistant Director-General, explained that the increase in pandemic alert level was in response to the outbreak of swine flu that had originated in Mexico, but that it did not mean that a pandemic was “inevitable.” Hong Kong also made swine flu a notifiable disease, a step it learned from its SARS experience.

“Actually, we had a number of research grants for pandemic preparedness,” recalls Professor Benjamin J. Cowling, Head of Epidemiology Biostatics in the School of Public Health. “This allowed us to scale up for research into the pandemic, so when the pandemic actually came here, we did a number of studies which were the envy of most other places in the world” (Fig. 14.13).

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101 P. Wu et al., “The Epidemiological and Public Health Research Response to 2009 Pandemic Influenza A(H1N1) Experiences from Hong Kong,” *Influenza and Other Respiratory Viruses* 7, no. 3 (2013):367–82.

102 “WHO Raises Pandemic Level: more Swine Flu Cases Feared,” CNN, April 27, 2009.

103 Interview with Benjamin J. Cowling, 22 February 2017.
A crucial question was how effective were these various measures at warding off the arrival of swine flu, verifying its severity and preventing or deterring its spread? Entry screening, Cowling and his colleagues determined, could delay local transmission for one to two weeks. “A delay of one to two weeks could be useful if the additional time permits more comprehensive planning and preparation for a local pandemic, or shortens the time required for other pandemic mitigation measures such as schools closures to be sustained,” they wrote. “However, the benefits of local screening should be balanced against the considerable resources required to implement screening.”

Still, when the virus reached Hong Kong, it spread rapidly. Within five months, 50% of children in Hong Kong were infected. Fortunately, it was not as severe as initially feared but the speed with which it spread was astounding. If it had been really virulent, there could have been a global catastrophe.

While the disease emerged first in North America, by May 11, it had spread to 30 countries, causing the World Health Organization to raise its pandemic alert to level 5 of 6. Hong Kong knew that it would not be spared. Only the previous year, the government had created the post of Under Secretary for Food and Health, with Professor Gabriel Leung as the first occupant of the post. When H1N1 emerged, he mobilized his former colleagues at the university to respond (Fig. 14.14).

In the U.S., the situation was worsening. A health alert was issued to doctors, who were warned of a new strain of swine flu that was a combination of swine, avian and human influenza that had not been seen before. The National Broadcasting Corporation (NBC), seeking expert views on the situation, was able to contact Professor Guan Yi, who was at that time in India, helping to set up a poultry influenza surveillance network. He was at the Bombay airport when NBC managed to reach him to ask for urgent comment on the spread of swine flu to humans. Guan Yi’s immediate response was that it was not easy to detect this kind of virus. After all, the H1N1 virus was already in humans, as a human virus.

Guan Yi went to work immediately after returning to Hong Kong. He told his team, “We need to find out how this virus was generated and where the virus came from.” They had an advantage in that Hong Kong was probably the only place in the world where there had been close surveillance and sampling of swine for over a decade as part of its anti-influenza program. Guan Yi, who had written his doctoral thesis on swine flu, had accumulated data on the subject while a student in the 1990s under Ken Shortridge, who himself had data going back to the 1970s. So while the rest of the world was short on information regarding swine, Hong Kong was data rich.

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104 B.J. Cowling, et al., “Entry Screening to Delay Local Transmission of 2009 Pandemic Influenza A (H1N1),” *BMC Infectious Diseases*, 10 (2012): 82.

105 J.S.M. Peiris, L.L.M. Poon and Y. Guan, “Surveillance of Animal Influenza for Pandemic Preparedness,” *Science*, 335, no. 6073 (2012): 1173–74.
In North America, Pigs with ‘Unsampled Ancestry’

Guan Yi and his associates set to work on the unique data available to them. According to Guan, the bulk of the analysis was done in one intensive week of work, from April 26 to May 2. With help from Andrew Rambaut, an evolution scientist with the Institute of Evolutionary Biology at the University of Edinburgh, they were able to “understand the evolutionary pathway of this virus.”106 “Here we use evolutionary analysis to estimate the timescale of the origins and the early development of the S-OIV epidemic,” the paper explains. “We show that it was derived from several viruses circulating in swine, and that the initial transmission to humans occurred several months before recognition of the outbreak.”

While surveillance and sampling had been taking place in Asia, this was not true of North America, and as a result there was “a long period of unsampled ancestry before the S-OIV outbreak, suggesting that the reassortment of swine lineages may have occurred years before emergence in humans.” Furthermore, it said, “the unsampled history of the epidemic means that the nature and location of the genetically closest swine viruses reveal little about the immediate origin of the epidemic…. Our results highlight the need for systematic surveillance of influenza in swine, and provide evidence that the mixing of new genetic elements in swine can result in the emergence of viruses with pandemic potential in humans.”107

The paper was submitted to the journal Nature for publication on 24 May 2009; it was accepted 4 June and was published online 11 June 2009. The timing was fortuitous. June 11 was the day when Dr. Margaret Chan, Director-General of the World Health Organization, announced the raising of the level of influenza pandemic alert from phase 5 to phase 6, the highest level. “The world is now at the start of the 2009 influenza pandemic,” she declared somberly.108 This means that on May 24, when the paper was submitted, “even before the world knew what was happening”—in the words of Guan Yi—“I provided critical information to the world with the University of Hong Kong catching the attention of the world.”

The university’s virologists were keen to study this novel virus, which was spread not by birds but by pigs. A study of the lineage of the H1N1/2009 viruses showed that three major lineages of swine H1 influenza viruses had been prevalent in pigs in surveys conducted in Hong Kong over the past 10 years. The H1N1 flu virus was a triple reassortant, combining the classical swine H1N1, the European “avian-like” H1N1 and triple-reassortant H1N2 (TRIG) viruses. And while the virus had jumped from pigs into humans, actually this had happened more than once. “After circulating in humans for some time they jumped back to pigs and tried to reassort with

106 Interview with Guan Yi, 14 March 2017.
107 G.J. Smith, et al., “Origins and Evolutionary Genomics of the 2009 Swine-Origin H1N1 Influenza A Epidemic,” Nature, 459, no. 7250 (2009), 1122–25.
108 Dr. Margaret Chan, “World Now at Start of 2009 Influenza Epidemic,” World Health Organization statement to the press, 11 June 2009.
other pig virus,” reported Professor Leo Poon, a diagnostic expert in identifying viruses. “That was quite interesting because it highlights the pig as a major reservoir, or intermediate host.”

**Pigs Don’t Fly: Or Do They?**

A paper published in the prestigious *Science* journal, co-authored by Leo Poon, Guan Yi, Malik Peiris and others concluded: “The 2009 pandemic, although mild and apparently contained at present, could undergo further reassortment in swine and gain virulence. It is therefore important that surveillance in swine is greatly heightened and that all eight gene segments are genetically characterized so that such reassortment events are rapidly identified.”

Observations made over 14 years of pigs in a Hong Kong abattoir were able to show that all major lineages of swine viruses of North American or European origin were present in Chinese pigs from different provinces shipped to Hong Kong for slaughter. Although pigs, unlike birds, don’t fly, they are exported from one country to another, often for breeding purposes. So, although the 2009 epidemic did not emerge in China but in Mexico, analysis of pigs in China was able to show how the mixing of viruses was occurring.

Peiris and his colleagues argued that similar events probably had also occurred, undetected, in Mexico. Indeed, they were right, but it took another 5 years to find these viruses in Mexico. So great was Hong Kong’s input that, in 2010–11, it contributed half of all the known swine influenza genetic data in the world. The diversity of genetic variants found in the studies by the Hong Kong group also allowed them to understand the genetic determinants that allowed a human transmissible virus to emerge from these precursor swine viruses.

According to Cowling, when there is a new influenza virus, the three immediate priorities of public health officials are to determine, first, how quickly it spreads between people, how severe the infections are, and what the options are for controlling it, that is, what can be done and the potential for success of such efforts. “The research that we did here covered all three of those important areas,” he said, whereas other research groups or government ministries are usually unable to do that.

Another project that Cowling and his team did was a comparison of the H1N1 virus and seasonal influenza viruses in community settings. Fortuitously, Cowling

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109 Interview with Leo Poon, 8 March 2017.
110 D. Vijaykrishna, et al., “Reassortment of Pandemic H1N1/2009 Influenza A Virus in Swine,” *Science*, 328, no. 5985 (2010): 1529.
111 D. Vijaykrishna, et al., “Long-term Evolution and Transmission Dynamics of Swine Influenza A Virus,” *Nature*, 473 (2011): 519–23.
112 H.L. Yen, et al., “Hemagglutinin-Neuraminidase Balance Confers Respiratory-Droplet Transmissibility of the Pandemic H1N1 Influenza Virus in Ferrets,” *Proceedings of the National Academy of Sciences of the United States of America*, 108, no. 34 (2011): 14264–69.
was in the midst of doing household transmission studies when H1N1 struck. He identified patients with flu in the clinics of general practitioners, then requested permission to test members of the household. When the epidemic arrived, he continued this work. The information that he was able to gather turned into a very important paper.\textsuperscript{113} For one thing, there is very little research data on the comparative epidemiology and virology of the pandemic 2009 influenza A (H1N1) virus and co-circulating seasonal influenza A viruses in community settings. Cowling and his team recruited 348 index patients with acute respiratory illness from 14 outpatient clinics in Hong Kong in July and August 2009. They then followed household members of 99 patients who tested positive for influenza A virus on rapid diagnostic testing and collected nasal and throat swabs from all household members at three home visits within 7 days for testing.

They were able to conclude that pandemic 2009 H1N1 virus has characteristics that are broadly similar to those of seasonal influenza A viruses in terms of rates of viral shedding, clinical illness and transmissibility in the household setting. “The household transmission studies allowed detailed inferences on the transmissibility of pH1N1 as well as the (mild) clinical profile of cases in the community,” a review of Hong Kong’s public health research response to the 2009 pandemic concluded. “Household studies have the unique advantage of a natural setting that allows comparisons of transmission characteristics and the effects of host, viral, and environmental factors on transmission.”\textsuperscript{114}

One study by Cowling and his team was to establish the transmissibility and virulence of the pandemic strain, information that was a priority for national and international health authorities in 2009.\textsuperscript{115} Patient data on all laboratory-confirmed pandemic H1N1 cases reported between May 1 and November 15, 2009 were collected by the Hospital Authority and the Center for Health Protection. During that period, H1N1 infection was a reportable disease, so the data collected was likely to be comprehensive. The information included demographic data on age and sex, clinical information including illness-onset date, laboratory-confirmation date and hospital-admission date. The researchers found that the estimated reproduction number of pandemic H1N1 appeared to be lower in Hong Kong than in other countries. The hospital admission rate in Hong Kong was high due to broader admission criteria, “with young children and pregnant women routinely admitted for testing and investigation.”\textsuperscript{116}

While the overall number of severe hospital cases was not high, Professor K.Y. Yuen found that for severe cases, the viral load in the respiratory tract didn’t decrease rapidly despite oseltamivir treatment. This led him and his associates to try another method: they selected mildly infected patients with a high level of neu-

\textsuperscript{113}B.J. Cowling, et al., “Comparative Epidemiology of Pandemic and Seasonal Influenza A in Households,” New England Journal of Medicine, 362 (2010): 2175–84.

\textsuperscript{114}Wu et al., “The epidemiological and Public Health Research Response to 2009 pandemic influenza A(H1N1): Experiences from Hong Kong,” 378 (2013).

\textsuperscript{115}B.J. Cowling, et al., “The Effective Reproduction Number of Pandemic Influenza: Prospective Estimation,” Epidemiology 21, no. 6 (2010): 842–46.

\textsuperscript{116}Ibid.
tralizing antibody and used the convalescent plasma of these patients to treat those severely ill. Yuen found that the treatment of severe A influenza (H1N1) within 5 days of symptom onset was associated with a lower viral load and reduced mortality. The mortality in severely ill patients treated by convalescent plasma was 20% whereas those treated by Tamiflu alone was 54.8%.

‘All of Us Should Subcontract Our Epidemiology Work to Hong Kong’

Dr. Joseph T. Wu of the School of Public Health led a study on the infection attack rate and the infection-hospitalization probability from data provided daily by the Hospital Authority and the Department of Health, from which he could construct an epidemic curve describing how fast the disease was spreading in Hong Kong. “The Hospital Authority gave us the number of confirmed infections and hospitalizations each day,” Dr. Wu explained, “and so data can easily be obtained on the severity of the H1N1 infections.” Wu also approached research on the infection attack rate and severity from a different angle. Working together with the Hong Kong Red Cross, researchers tested 14,766 blood samples from blood donors during the period when the virus was active. They discovered that almost half of all schoolage children in Hong Kong were infected during the first wave. However, because the symptoms were mild, few of them went to hospital. Paradoxically, a much smaller percentage of older adults aged 50–59 years were infected, but a much higher percentage went to hospital. If it wasn’t for the serological tests, such a phenomenon may have gone undetected and the disease may have been thought to be one that primarily attacked older people. Wu and his team also measured the impact of school closures on the mitigation of the H1N1 pandemic. They concluded that the closure of secondary schools for the summer vacation “was associated with substantially lower transmission across age groups,” and estimated that reporting of cases “declined to 5.2% of its initial rate through the second half of June.” By comparison, attack rates in previous epidemics have generally been highest in younger children, and this was true in Mexico and Chicago. This finding, they reported, “intuitively implies that closures were effective in preventing infections in this age group” (Fig. 14.15).

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117 I.F. Hung, et al., Hyperimmune IV Immunoglobulin Treatment: a Multicenter Double-Blind Randomized Controlled Trial for Patients with Severe 2009 Influenza A(H1N1) Infection" Chest, 144, no.2 (2013): 464–73.

118 I.F. Hung, et al., “Convalescent Plasma Treatment Reduced Mortality in Patients with Severe Pandemic Influenza A (H1N1) 2009 Virus Infection.” Clinical Infectious Diseases, 52, no. 4 (2011): 447–56.

119 Meeting with Dr. Joseph Wu, 8 March 2017.

120 J.T. Wu, et al., “The Infection Attack Rate and Severity of 2009 Pandemic H1N1 Influenza in Hong Kong,” Clinical Infectious Diseases, 51, no. 10(2010): 1184–91.

121 J.T. Wu, et al., “School Closure and Mitigation of Pandemic (H1N1) 2009, Hong Kong.” Emerging Infectious Diseases, 16, no. 3 (2010):538–41.
The data generated by the university was shared with the government and the WHO, giving them real-time situation awareness of the pandemic, even before the relevant papers were published. So impressive was Hong Kong’s performance that at the Second Global Influenza Seroepidemiology Expert Meeting sponsored by the European Center for Disease Prevention and Control in 2011 in Stockholm, the chairman, Angus Nicoll, speaking on Sustainability of Serological Surveillance, cited two options: “Routine Annual Surveys,” such as those conducted by Israel, Norway and Poland, or “Fast Ad Hoc Quality Research,” a la Hong Kong. At one point, he said, “In the next pandemic, maybe all of us should subcontract our epidemiology work to Hong Kong.”

H7N9: Another Avian Virus Jumps the Species Barrier

At the end of March 2013, a new virus was detected in China. First, a father in Shanghai became ill of severe pneumonia and died. Then two sons also developed quite severe pneumonia. This was scarily reminiscent of the SARS epidemic a decade previously. While they tested negative for SARS, it turned out that they had influenza, but a hitherto unknown kind of flu, H7N9. The Chinese authorities responded quickly by establishing a joint multi-sectoral coordination mechanism, initiating several investigations, notifying the World Health Organization, sharing viruses with WHO’s influenza collaborating centers and other laboratories and mounting effective counter measures such as closure of live poultry markets in some locations. Subsequently, WHO undertook a six-day joint mission to China.

Malik Peiris was part of the mission. Live bird markets were an immediate suspect. Even though some people refused to believe that the virus came from chickens, Shanghai closed all live bird markets and human infections disappeared. That made it quite clear that the retail poultry market was the cause. China CDC did a lot of work, but encountered opposition from those involved in the poultry trade and in agriculture. Because the poultry didn’t sicken, farmers weren’t too concerned about whether they were infected or not. And while closing live markets was effective in combating the virus, it was also extremely costly.

A joint assessment was made by experts from China and the WHO. “What we found is the virus is located in lots of different parts of China,” recalls Fukuda, who was Assistant Director-General for Health Security of the WHO at the time. “We also found that the risks of getting infected appeared to be similar to H5N1, some kind of contact with infected markets, with poultry markets. We also saw that when cities took control measures, close down markets, clean up markets, you could reduce the infection.” It was, Malik said, “like the H5 story all over again.”

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122 Recounted by Malik Peiris, who was present, as was Benjamin Cowling.
123 Mission Report of China-WHO Joint Mission on Human Infection with Avian Influenza A(H7N9) Virus, 2013.
124 Interview with Fukuda.
difference is that H7 is even more dangerous than H5 because it was able to infect humans more easily and because it caused no illness in birds—that is, it was a virus able to spread silently in poultry.

Since 2013, H7N9 has continued to be present in China and, in fact, there was an upsurge in 2017. However, according to Fukuda, “we don’t see major changes in the virus, or that it’s more transmissible; based on what we know both in 2013 and now, it is a reflection of an increase in infection in birds and increased contact between humans and infected birds.”

Fukuda is quick to compliment researchers in the School of Public Health, now his colleagues, such as “Malik, Guan Yi and Leo Poon, and Ben Cowling.” This group, he said, “has continued to operate at a very high level. The University here has such a strong research team, and they have collaborators in China.”

In 2009, when swine flu was first reported, Guan Yi was traveling in India. On March 31, 2013, when China reported to the World Health Organization the detection of three cases of human infection with a novel influenza A (H7N9) virus, he was again traveling. But this time, he was on holiday with his family in Guilin, China, the country where the outbreak was occurring. His immediate thought turned to the recent reports of thousands of dead pigs found floating in the Huangpu River in Shanghai, which had been dumped in the water by farmers. It crossed his mind that the dead pigs and sick humans might be connected.

Pigs Not Killed by Virus

After returning to Hong Kong, Guan tested samples of the virus on various animals, including pigs, and concluded that the H7N9 virus did not kill the pigs. That was one less thing to worry about. But the main concern was the infectivity and transmissibility of this new virus. A group of scholars from the University of Hong Kong and from Shantou University, plus international and mainland Chinese experts, published an article in *Science* magazine. These scholars conducted experiments on ferrets, which are considered the primary mammalian model for human influenza. While healthy ferrets inoculated with the virus displayed a brief fever one or two days after inoculation, with “robust sneezing and nasal discharge,” and three ferrets placed in direct contact with the inoculated group displayed similar symptoms, only one of three airborne-exposed ferrets displayed such symptoms, suggesting that transmission by air was much less efficient. Though the paper was formally published 12 July 2013, it was submitted April 30, accepted May 20 and published online May 23. “We were,” Guan Yi said, “the first team in the whole world to publish such a paper to define virus infectivity and transmissibility.”

Another paper in the *Lancet* showed that H7N9 was much more efficient at infecting the human

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125 Ibid.

126 H. Zhu, et al., “Infectivity, Transmission, and Pathology of Human-Isolated H7N9 Influenza Virus in Ferrets and Pigs,” *Science*, 341, no. 6142 (2013):183–86.

127 Interview with, Guan, 14 March 2017.
bronchus than H5N1 so that the chance of getting infected and potentially transmitting it to others was higher.\textsuperscript{128}

Still, the question was, where did this new virus come from? The answer, like that for H5N1, was poultry. “China has the largest poultry population in the world,” Guan Yi observes. “Domestic duck is the natural host of influenza virus, and 70% of domestic ducks in the world are in China. Likewise, 90% of domestic geese are in China.” At the time, it wasn’t clear which animal was the host to the virus, so Guan and his key associate Huachen Zhu, also known as Maria, sampled all major poultry from markets. “We pinpointed chicken as the source,” Guan said. Surprisingly, the virus was in the respiratory tract, not the digestive tract. Some people, Zhu and Guan said, offered the pigeon as a possible suspect, because the pigeon population is relatively small and the economic impact of its obliteration would be less damaging, but they showed beyond doubt that the chicken was the culprit. While the paper did not appear until the 10 October 2013 issue of \textit{Nature}—and even the online edition wasn’t published until 21 August, it was submitted on May 22, less than two months after the discovery of H7N9 and at a time when China’s ministry of agriculture was arguing strongly that chickens were not the source.

Again, a group of experts, including Guan Yi, was able to show how the H7N9 virus emerged from wild bird and chicken viruses. “Preliminary analyses suggest that the virus is a reassortant of H7, N9 and H9N2 avian influenza viruses, and carries some amino acids associated with mammalian receptor binding, raising concerns of a new pandemic,” they wrote in \textit{Nature}, in an article submitted on May 22, 2013. “However, neither the source populations of the H7N9 outbreak lineage nor the conditions for its genesis are fully known.”\textsuperscript{129} They went on: “Here we show that H7 viruses probably transferred from domestic duck to chicken populations in China on at least two independent occasions. We show that the H7 viruses subsequently reassorted with enzootic H9N2 viruses to generate the H7N9 outbreak lineage.”

Field Surveillance Conducted in Chinese Cities

Field surveillance was conducted in Wenzhou, in Zhejiang province, Rizhao, in Shandong province, and in Shenzhen, in Guangdong province. According to the authors, previous analyses suggested that the N9 gene of the H7N9 outbreak lineage was derived from wild bird viruses in Europe and Korea. However, their data showed that, for this gene, more closely related H11N9 and H2N9 viruses were found in migratory wild birds in Hong Kong in 2010–11. The authors concluded: “Domestic ducks seem to act as key intermediate hosts by acquiring and maintaining diverse

\textsuperscript{128} M.C.W. Chan, et al., “Tropism and Innate Host Responses of a Novel Avian Influenza A HN9 Virus: an Analysis of Ex-vivo and In-vitro Cultures of the Human Respiratory Tract,” \textit{Lancet Respiratory Medicine}, 1, no. 7 (2013): 534–42.

\textsuperscript{129} T.T. Lam, et al., “The Genesis and Source of the H7N9 Influenza Viruses Causing Human Infections in China,” \textit{Nature}, 502, (2013): 241–244.
influenza viruses from migratory birds, by facilitating the generation of different combinations of H7 and N9 or N7 subtype viruses, and by transmitting these viruses to chickens. After transmission, reassortment with enzootic H9N2 viruses formed the current H7N9 or H7N7 viruses seen in chickens. This probably led to outbreaks in chickens, resulting in the rapid spread of the novel reassortant H7N9 lineage through live poultry markets (LPMs), which then became the source of human infections. The cessation of human infections after the closure of LPMs, after a precedent set during the Hong Kong H5N1 ‘bird flu’ incident in 1997, strongly supports this proposition.” So the virus went from wild birds to domestic ducks to chickens, before infecting humans.

The authors reported the discovery of an H7N7 virus in chickens that has the ability to infect mammals experimentally. This, they said, suggests that H7 viruses may pose threats beyond the current outbreak. “The continuing prevalence of H7 viruses in poultry could lead to the generation of highly pathogenic variants and further sporadic human infections, with a continued risk of the virus acquiring human-to-human transmissibility,” they warned.

Another paper, produced with high input by Maria Zhu, appeared in June 2015 in *Nature* again. It was on the dissemination, divergence and establishment of H7N9 viruses in China. The authors showed that since H7N9 was first reported in March 2013, the virus had spread from eastern to southern China and had become persistent in chickens. Moreover, repeated introduction of viruses from Zhejiang to other provinces and the presence of H7N9 viruses at live poultry markets had fueled the recurrence of human infections. “The rapid expansion of the geographical distribution and genetic diversity of the H7N9 viruses poses a direct challenge to current disease control systems,” the authors reported. “Our results also suggest that H7N9 viruses have become enzootic in China and may spread beyond the region, following the pattern previously observed with H5N1 and H9N2 viruses.”

While the article appeared in print in June 2015, it was submitted more than eight months before, on 30 September 2014. Papers such as the *Nature* article marked a major advance in human knowledge of the H7N9 virus. His group, Guan said, had contributed at least 65% of the data on the H7N9 influenza virus in GenBank, the database produced and maintained by the National Center for Biotechnology Information as part of the International Nucleotide Sequence Database Collaboration.

It is certainly a tribute to Hong Kong, both to the government and to researchers in academia, that while H7N9 is now endemic in mainland China, there has to date not been a single local case in Hong Kong. How was Hong Kong able to keep H7N9 at bay? The answer lies in the interventions to reduce zoonotic and pandemic risks.131

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130 T.T. Lam, et al., “Dissemination, Divergence and Establishment of H7N9 Influenza Viruses in China,” *Nature*, 522, (2015): 102–05.

131 J.S.M. Peiris, et al., “Interventions to Reduce Zoonotic and Pandemic Risks from Avian Influenza in Asia,” *Lancet Infectious Diseases*, 16, no. 2 (2016): 252–58.
Steps to Counter Virus

One important step is the closure of live poultry markets. Such closures stopped H7N9 outbreaks in the mainland, but they were costly to the poultry industry. The closure of wholesale and retail markets in Shanghai, Hangzhou, Huzhou and Nanjing in 2013 is believed to have cost the poultry industry about US$8 billion. But there are also steps that can be taken short of shutting down the markets, steps that had proven effective in Hong Kong, such as rest days, when the markets are closed for a thorough cleaning, and banning of live poultry being kept overnight in live poultry markets. Separation of live ducks and geese from chickens can also reduce the risk of intermingling of different forms of viruses. One problem in countering the H7N9 virus is that the industry has little incentive to take any steps to detect its presence since the virus doesn’t sicken birds, only its human hosts.

Another measure taken by Hong Kong is a ban on holding poultry overnight in live poultry markets. This way, incoming chickens are not in the market for long enough to be newly infected and, in turn, infect other birds. Other steps include the removal of fecal matter, drinking water and poultry feed because viruses survive longer in water than on surfaces. Cages, too, need to be cleaned regularly and should be made of materials easily cleaned, such as plastic, not wood or bamboo. Such measures, proven to work in Hong Kong, can usefully be adopted elsewhere, such as in mainland China or Vietnam.

Because the scene of action of the H7N9 virus was initially not in Hong Kong, the Hong Kong research teams established collaborations in the “hot spots” in China. K.Y. Yuen and his collaborator, Professor Honglin Chen, flew to see their mainland collaborators to get clinical data from infected patients, the virus strain for full length sequencing, tissues from dead patients and, most importantly, virus strains from the wet market poultry. The first paper on H7N9 proving the link between human cases of H7N9 virus and poultry H7N9 virus in the markets was published in the Lancet. Yuen and his team, in another paper, showed that normal blood donors don’t have anti-H7N9 antibodies whereas more than 6% of 396 poultry workers were antibody positive to H7N9. This further confirmed the link between H7N9 in humans and H7N9 in poultry. A review article was published in the Lancet comparing H5N1 bird flu in Hong Kong in 1997 and H7N9 in Shanghai 16 years later. Crossing the species barrier from bird to human was previously unknown to medical history. The paper was called “The emergence of influenza A

132 H. Yu, et al., “Effect of Closure of Live Poultry Markets on Poultry-to-Person Transmission of Avian Influenza A H7N9 Virus: an Ecological Study,” Lancet, 383, no. 9916 (2014): 541–48.
133 Y. Chen, et al., “Human Infections with the Emerging Avian Influenza A H7N9 Virus from Wet Market Poultry: Clinical Analysis and Characterisation of Viral Genome,” Lancet, 381, no. 9881 (2013): 1916–25.
134 S. Yang, et al., “Avian-Origin Influenza A(H7N9) Infection in Influenza A(H7N9)-Affected Areas of China: a Serological Study,” The Journal of Infectious Diseases, 209, no. 2 (2014): 265–69.
H7N9 in human beings 16 years after influenza A H5N1: a tale of two cities.”135 As the authors noted, Hong Kong and Shanghai are located along the avian migratory route at the Pearl River delta and Yangtze River delta. They ended with the observation: “Why H7N9 seems to be more readily transmitted from poultry to people than H5N1 is still unclear.”

Malik Peiris and Hui-ling Yen went to Shanghai and worked with researchers there on studying patients with H7N9 disease. In a collaborative paper in Lancet, they reported the emergence of oseltamivir resistance in some patients that was associated with treatment failure and poor clinical outcome.136

**HKU Collaborates with China CDC**

The H7N9 outbreak also saw the beginning of much closer collaboration between The University of Hong Kong and the Chinese Center for Disease Control and Prevention (China CDC). Actually, the two institutions had collaborated previously, for example, on a study of hand, foot and mouth disease in China during the 2008–2012 period.137 Shortly after the Chinese government announced the emergence of the new H7N9 avian flu disease, Hongjie Yu, Director of the China CDC’s Division for Infectious Diseases, contacted Dean Gabriel Leung on his cell phone to discuss the situation. The dean immediately flew to Beijing with a group of about ten Hong Kong University specialists, including Ben Cowling and Joe Wu, and stayed there for about a month to take part in making an initial risk assessment on how easily the virus spread, its severity, control measures, the characteristics of the virus, and so on. After a month, the two sides published a series of papers led by Gabriel Leung as senior author, in which scholars from both sides participated. From 2013 to 2017, the H7N9 outbreaks came in annual waves, and specialists from the China CDC and HKU studied each one closely.

One article, published by the Lancet online on June 24, 2013 with Hongjie Yu as the lead writer, was an assessment of clinical severity of human infection with avian influenza A (H7N9) virus.138 It concluded that human infections with avian influenza A (H7N9) virus “seem to be less serious than has been previously reported.” It also said that “many mild cases may already have occurred,” thus lowering the mortality rate even more. Another article, published by Lancet online the same day, had Ben Cowling as the lead writer. It compared the epidemiology of human infec-

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135 K.K. To, et al., “The Emergence of Influenza A H7N9 in Human Beings 16 Years After Influenza A H5N1: A Tale of Two Cities,” Lancet Infectious Diseases, 13, no. 9 (2013): 809–21.

136 Y. Hu, et al., “Association Between Adverse Clinical Outcome in Human Disease Caused by Novel Influenza A H7N9 Virus and Sustained Viral Shedding and Emergence of Antiviral Resistance” Lancet, 381, no. 9885 (2013): 2273–79.

137 W. Xing, et al., “Hand, Foot, and Mouth Disease in China, 2008–12: An Epidemiological Study,” Lancet Infectious Diseases, 14, no. 4 (2014):308–18.

138 H. Yu, et al., “Human Infection with Avian Influenza A H7N9 Virus: An Assessment of Clinical Severity,” Lancet, 382, no. 9887 (2013): 138–46.
tions with H7N9 and H5N1 in China. The fatality rate on admission to hospital was 36% for H7N9 and 70% for H5N1, meaning that there was a lower death rate among the older H7N9 sufferers than for the younger victims of H5N1. The authors acknowledged that the difference in susceptibility to serious illness with the two different viruses remained unexplained.

They also collaborated anew on hand, foot and mouth disease, writing a joint paper that provided scientific evidence to support the Chinese government’s policy of vaccination. A later paper was on hepatitis A and hepatitis E in China.

The collaboration between HKU and China CDC went so well that a memorandum for cooperation by the two sides was signed on August 15, 2013, providing for such cooperation to continue for the next 5 years. The purpose was to “improve and enhance the capacity of understanding, surveillance and control of infectious diseases in China” as well as to develop training programs for people from both sides. The two parties agreed that their collaboration would include research projects on infectious diseases; reviewing and evaluation of the infectious disease surveillance in China and seasonal influenza and avian influenza H7N9 and H5N1.

Hongjie Yu, Director of China CDC’s Division for Infectious Diseases, confirmed that HKU experts, such as Gabriel Leung, Ben Cowling and Joseph Wu, were very helpful to China CDC in the study of emerging infectious diseases with potential pandemic threat and risk assessment. He said: “We have already set up a collaborative platform in this field and definitely will be working closely together to monitor the current outbreaks of Emerging Infectious Diseases (EIDs) like avian influenza H5N6, H7N9 etc. and to respond to future EIDs as well.”

What of the Future?

The Surgeon General of the United States, William Stewart, is frequently quoted as having said in 1967: “The time has come to close the book on infectious diseases. We have basically wiped out infections in the United States.” Whether he said it or not is now immaterial. The fact is that infectious diseases have not been wiped out, and the world needs to be ever alert to new threats.

139 B.J. Cowling, et al., “Comparative Epidemiology of Human Infections with Avian Influenza A H7N9 and H5N1 Viruses in China: A Population-Based Study of Laboratory-Confirmed Cases,” *Lancet*, 382, no. 9887 (2013): 129–37.

140 J.T. Wu, et al., “Routine Pediatric Enterovirus 71 Vaccination in China: a Cost-Effectiveness Analysis,” *PLOS Medicine*, 13, no. 3 (2016).

141 X. Ren, et al., “Changing Epidemiology of Hepatitis A and Hepatitis E Viruses in China, 1990–2014,” *Emerging Infectious Diseases*, 23, no. 2 (2017): 276–79.

142 “Cooperation Agreement between Division of Epidemiology and Biostatistics, School of Public Health, Li Ka Shing Faculty of Medicine, the University of Hong Kong, and Division of Infectious Diseases, the Chinese Center for Disease Control and Prevention in 2013–2018.”

143 Email from Hongjie Yu, 13 March 2017.
As for what constitutes modern outbreaks, Keiji Fukuda has an intriguing observation (Fig. 14.16). “Modern outbreaks are not disease,” he said. “In textbooks you read about disease. Modern outbreaks are combinations of disease and anxiety, disruption; when you have something like SARS, there is a huge amount of anxiety. In Beijing there was a day when there was virtually no car traffic at all, the entire city was at a standstill—that was not disease. That was fear of the disease.”

He continued: “I think if we look back in history, in the 1918 epidemic, we can see where fear and actual disease are commensurate; 40–50 million people died around the world, like Black Plague in the Middle Ages. But with SARS and bird flu, we’re not talking about millions of people dying and yet we’re talking about that level of fear, almost paralysis. Managing the disease aspect is relatively easier than managing the fear aspect.”

Despite books and movies about existential threats to the human species, experts are guardedly optimistic when speaking of whether future influenza pandemics are inevitable.

Dr. Peter Palese, a flu expert at the Mount Sinai School of Medicine, points out that human flus can infect people who inhale only one to ten virus particles, but it takes 100,000 to a million particles of an H5 bird flu to infect a human. “That’s why people who live under chickens in markets in Asia get it, and we don’t get it on Fifth Avenue,” Dr. Palese said.

More than a decade ago Ken Shortridge pointed out that Hong Kong had stopped the H5N1 virus in its tracks three times through surveillance, surveillance, surveillance. “I have no idea if H5N1 will cause a pandemic,” he said. “We can’t be certain at all.”

He did warn that H5N1 was in a “smoldering phase” of evolution, similar to that undergone by the 1918 virus before the influenza pandemic broke out. But he traced the root of the problem to people, not birds, saying: “The industrialization of poultry is the nub of this problem. We have unnaturally brought to our doorstep pandemic-capable viruses. We have given them the opportunity to infect and destroy huge numbers of birds and … jump into the human race.” He went on: “Something is not right. Human population has exploded, we are impinging on the realms of the animals more and more, taking their habitats for ourselves, forcing animals into ever more artificial environments and existences.”

So Hong Kong has a need to remain vigilant, not only for itself but for the world. Besides, infectious disease expertise has undergone a major transformation in the last two decades. When bird flu struck Hong Kong in 1997, the territory was dependent on external expertise to cope with that disease. Over the intervening years, researchers at Hong Kong University have become leading global experts in their own right. The lessons of bird flu and SARS have been well and truly learned. Hong Kong has grown and matured through those difficult days. Its research-based control efforts benefit the nation and the global community. As Angus Nicoll has observed, Hong Kong does fast as well as high quality research and does excellent epidemiological work, from which the rest of the world can benefit.

144 Interview with Fukuda.
145 Donald G. McNeil Jr., “A Flu Epidemic That Threatens Birds, not Humans,” The New York Times, 4 May 2015.
146 “(How to Stop) The Next Killer Flu,” Seed magazine, February/March 2006.
Fig. 14.1  Dr. Margaret Chan, Director of Public Health in Hong Kong, had to make tough decisions during the 1997 avian flu outbreak and SARS in 2003. Courtesy, Medical Faculty, HKU

Fig. 14.2  In 2001, the H5N1 virus was back and Lily Yam, Secretary for Environment and Food, held detailed discussions with K.Y. Yuen on measures to deal with the outbreak. Growing with Hong Kong—The University and Its Graduates: The First 90 Years. HKUA

Fig. 14.3  Health Secretary E.K. Yeoh told Margaret Chan to go directly to the Ministry of Health in Beijing for information rather than try to contact officials in Guangdong. Courtesy, Medical Faculty, HKU
Fig. 14.4 Guan Yi in 2003 proposed a trip to Guangzhou for an in-depth field investigation to ascertain the infectious agents responsible for an outbreak. Courtesy Medical Faculty, HKU

Fig. 14.5 B.J. Zheng went to Guangzhou to look for the SARS virus together with Guan Yi. Courtesy, Medical Faculty, HKU
Fig. 14.6 Zhong Nanshan, head of the Respiratory Research Center at the First Affiliated Hospital, Guangzhou Medical College, made samples available to HKU researchers. Courtesy Medical Faculty, HKU

Fig. 14.7 Dr. Kenneth Tsang, a respiratory physician, helped examine the Index patient at Kwong Wah Hospital. Courtesy, Medical Faculty, HKU
Fig. 14.8  Anthony J. Hedley, Chair Professor of Community Medicine, turned to Imperial College, London for help during the SARS outbreak. Courtesy Medical Faculty, HKU

Fig. 14.9  Members of the team in the small HKU lab had different assignments. Pathologist John Nicholls used electron microscopy to help identify viruses. Courtesy, Medical Faculty, HKU
Fig. 14.10  Malik Peiris said a ‘tricky virus’ was responsible for the SARS epidemic. Courtesy, Medical Faculty, HKU

Fig. 14.11  Prof. K.Y Yuen head of the Microbiology, Department during SARS, was honored after it successfully identified the SARS Virus, Medical Faculty, HKU
Dr. Leo Poon was listed in 2015 by Thomson Reuters as among the “world’s most influential scientific minds,” along with several other HKU professors. Courtesy Medical Faculty, HKU

Professor Benjamin Cowling of the School of Public Health and his colleagues found out that entry screening could delay local transmission of swine flu for 1 or 2 weeks. Courtesy, Medical Faculty, HKU
Fig. 14.14  Professor Gabriel Leung, the first Under Secretary for Food and Health, mobilized his former university colleagues to respond during the swine flu outbreak. Courtesy, Medical Faculty, HKU

Fig. 14.15  Dr. Joseph Wu was very helpful to China CDC in the study of emerging infectious diseases with potential pandemic threat and risk assessment. Courtesy, Medical Faculty, HKU
Keiji Fukuda observes that modern outbreaks are not disease but rather fear of the disease. Courtesy, Medical Faculty, HKU