

Severe Acute Respiratory Syndrome (SARS) — 150 Days On

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The Severe Acute Respiratory Syndrome (SARS) has been identified as a new clinical entity in the year 2003.^{1,2} It was on 12 March 2003 that the World Health Organization (WHO) issued a global health alert on the disease then known as atypical pneumonia. On 16 March 2003, the disease received its name SARS. Singapore entered the picture when the Ministry of Health issued its first circular on 13 March on SARS to all doctors and followed this up on 16 March 2003 with a second circular stating that Singapore had by then 20 patients with SARS.

History

SARS probably first arose in Guangdong in Southern China in November 2002. The Chinese authorities never revealed it to the world. The WHO only got wind of it when Dr Carlo Urbani (now deceased as a result of SARS) discovered the disease in Hanoi, Vietnam in February 2003. Those 3 months gave the disease a critical headstart. When China finally allowed a WHO team into Guangdong to study the SARS epidemic, they made little headway into tracing the origins of the disease. The leading theory is that SARS originated, like most influenza viruses, in aquatic birds (duck perhaps) and then made the jump to humans. SARS is due to a coronavirus, like the common cold and its origin in Southern China implies a zoonotic pathway similar to that of influenza. If SARS started as a waterborne bird virus, it might have passed via faecal droppings to a chicken or pig, or even directly to people. Along the way, the original virus probably mutated spontaneously and exchanged genes with viruses from other animals, acquiring new characteristics.³

On 1 February 2003 at the respiratory department of the Zhongshan No. 3 Hospital was a very ill patient, a seafood dealer, the first super spreader of what would be later identified as the SARS virus. He infected 90 people, including his doctor and health care workers from 3 different hospitals that treated him. He probably also infected a doctor who would travel to Hong Kong some 3 weeks later and check into the Metropole Hotel – thought to be the point where SARS first surfaced outside of China. The unknown disease had invaded the world.⁴

Usually in the fall in Southern China, there are deaths from pneumonia but in 2002, doctors in Guangdong reported some 300 cases of atypical pneumonia but the Chinese government downplayed the problem. So, as reported on 14 April 2003, this travelling killer had infected more than 2400 people leading to at least 89 deaths (this is an underestimate since China's contribution has been understated). With Asia as its epicentre, the number of cases/deaths is as follows: China 1220/49, Hong Kong 800/20, Taiwan 17/0, Vietnam 59/4, Thailand 7/2, Singapore 101/6, Malaysia 1/1. Elsewhere it is Australia 1/0, Canada 74/7, United States 115/0, Ireland 1/0, UK 4/0, Belgium 1/0, Germany 5/0, France 3/0, Spain 1/0, Italy 3/0, Switzerland 1/0 and Romania 1/0.⁵ Updated figures as of 22 May 2003 are China 5249/296, Hong Kong 1719/255, Taiwan 418/52, Singapore 206/29, Canada 149/24 and Vietnam 63/5.

In Hong Kong, the doctor from Southern China arrived on 21 February 2003 and stayed at the Metropole Hotel. He became seriously ill and died in Hong Kong, but not before infecting his brother-in-law, 2 nurses in the hospital and 7 guests who had stayed on the same floor of the hotel. Three of these guests were Singaporeans. The others went on to Hanoi and Toronto.

Singapore Hit

The 3 Singaporeans returned to Singapore and the first took ill with symptoms on 25 February 2003. She was eventually warded at Tan Tock Seng Hospital (TTSH) on 1 March 2003. The other two were also warded, one at TTSH and the other at the Singapore General Hospital (SGH). They recovered and were discharged. The first index imported case went on to spread the illness to others, many of whom were health care workers. Many of the patients in Singapore with SARS can be traced back to this index case.

As of 23 April 2003, some 7 weeks later, the SARS statistics were as follows: A total of 186 SARS cases, 87 suspect cases (including 5 below 18 years old), 14 deaths (2 more pending further post-mortem tests), 19 in intensive care and 110 discharged. Also the Prime Minister has written an open letter to all Singaporeans appealing for their help and cooperation in winning the battle against SARS. The letter was published in the local newspapers.

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The Disease

SARS is a form of atypical pneumonia that originated in Southern China and spread globally in a few weeks (November 2002 to February 2003). The agent responsible is probably a novel coronavirus. There are 2 case definitions used in making the clinical diagnosis, as there is no confirmatory laboratory test available to date.

A suspect case of SARS is a patient with high fever above 38°C and respiratory symptoms including cough, shortness of breath, or breathing difficulty AND close contact with a person diagnosed with SARS OR history of travel to areas reporting cases of SARS within 2 weeks of onset of symptoms. Close contact means having cared for, having lived with, or having had direct contact with the respiratory secretions and body fluids of a person with SARS. The SARS affected areas are Hong Kong, Hanoi, Guangdong, Shanxi, Taiwan and Toronto. On 20 March 2003, Singapore was added to this list of countries.

A probable case is a suspect case with chest X-ray findings of pneumonia or respiratory distress syndrome OR a person with an unexplained respiratory illness resulting in death, with an autopsy examination demonstrating the pathology of respiratory distress syndrome without an identifiable cause.

Cases from Hong Kong have been reviewed and published;⁶⁻⁸ likewise from Toronto.⁹ From Singapore, a single case report of the index case was reported in the Singapore Medical Journal.¹⁰

The Virus

It was first thought to be a paramyxovirus but is now confirmed to be a novel coronavirus. This was announced in Hong Kong and at the Centres for Disease Control and Prevention (CDC), Atlanta on 24 March 2003.¹¹ Further reports^{12,13} from Germany and the SARS working group (10 WHO collaborating laboratories) add to knowledge of this new virus. It has been proposed that it be named Urbani SARS – associated coronavirus in honour of Dr Carlo Urbani, the 46-year-old Italian WHO physician and infectious disease specialist whose work in Hanoi, Vietnam defined SARS. It is an RNA virus with 30,000 base sequences. Singapore scientists were the fourth group in the world to break the genetic code of the virus, after Canada, the United States and Hong Kong.¹⁴ Scientists from the Genome Institute of Singapore (GIS) unraveled the code and compared it with the other 3 genomes uncovered overseas a few days earlier. The code from specimens of a local SARS patient was found to be initially identical. A few small differences could either be due to national genetic variations of the virus or because of mutations.

The virus was recovered from a local patient, and isolated and grown in monkey cells to generate enough genetic material which was then sequenced using techniques developed to sequence the human genome. This was completed in 2½ weeks. Sequencing the genome is necessary for the design of new and precise molecular probes in diagnostic tests, as well as for looking at the life cycle of the virus and finding drugs to combat it.

Diagnostic Kits

At a WHO meeting in late April 2003, 3 Singaporean scientists (1 each from GIS, the Pathology Department at SGH and the Defence Medical Research Institute) joined an international network of 11 laboratories in 9 countries picked to help find the cause of SARS and develop diagnostic kits.¹⁵ Hopefully, a definitive test can be produced soon to assist in the diagnosis of SARS patients. The present clinical case definition of probable and suspect is the present classification used based on clinical features of the illness and epidemiological evidence of contact with SARS patients. What is needed is a confirmatory test for a patient with SARS.

A 3-hour diagnostic test made by GIS, using polymerase chain reaction technology, was promised by end-April.¹⁶

Mortality

The attack rate on health care workers (doctors and nurses who got sick after treating patients) was 56% in Hanoi. The death rate was under 4.9%, which is higher than the 1918 flu rate which was just under 4.%, reported CDC Director Julie Gerberding.¹⁷ Mortality rate is the number who died from SARS divided by the “population of interest” or the total number of cases with known outcomes, that is, those who either died or are discharged — not those still in hospital whose outcomes are yet unknown. By this definition then, on April 19, the mortality rates should read Singapore 13.8%, Hong Kong 18.2%, Canada 18.2% and Vietnam 9.8%. For Singapore, between 10 April and 19 April, the mortality rate fluctuated between a low of 10.7% and a high of 15.0%.¹⁸

Several autopsies have been performed in Singapore on patients who died from SARS. In addition to the usual features of adult respiratory distress syndrome with diffuse vascular damage and hyaline membrane formation, an interesting

observation not reported in other series of cases^{7,8} is the finding of significant thromboembolism, not only in peripheral veins but also in the pulmonary vasculature. In the paper of 138 cases from Hong Kong,⁷ the authors instead reported a prolonged activated partial thromboplastin time in 42.8% of the patients.

Management

This new coronavirus has no known treatment at present. Many centres have tried ribavirin (intravenous, aerosol and oral) together with methylprednisolone but the results are inconclusive. In the publication in the *New England Journal of Medicine* earlier referred to are details of how patients were treated in Hong Kong^{6,7} Canada⁹ and Germany.¹³ In the paper reporting 685 cases in Hong Kong, the largest series so far in the literature, the authors state their empirical treatment protocol. Three groups of drugs were used – a broad-spectrum antiviral agent (ribavirin), hydrocortisone and methylprednisolone, and antibacterial coverage for typical and atypical agents.⁸

As the most likely route of transmission is by droplets and direct inoculation of secretions onto mucus membranes, all health care workers are suitably protected with N95 masks, gown and gloves, as well as goggles or visors for eye protection when caring for these patients. Daily disinfection with hypochlorite solution (1000 ppm) of bed, handrails, bedside tables, floor and equipment has to be thorough. Careful and frequent handwashing becomes a necessary and critical routine. In Singapore, because of the venous thromboembolism detected at autopsies of SARS patients, those who are ill with SARS have regular frequent imaging of their peripheral and central veins for thrombi; and based on the findings, aggressive heparin therapy is instituted.

Fast Backward

China has, in recent days, become more open to WHO sending teams to Guangdong and Beijing and other parts of the country to investigate. It has also dismissed its Health Minister and the Mayor of Beijing. Nonetheless, the virus has had a headstart of some 3 to 4 months. On 12 March 2003, WHO issued a global alert about SARS. It could have done this in November or December 2002. On 14 March 2003, the CDC in Atlanta activated its emergency operations centre to support the response of the WHO to this global threat. Singapore received WHO support through its representative sent to MOH headquarters. Later in April 2003, another doctor arrived from CDC Atlanta to help MOH. On 24 March 2003, scientists announced that a new coronavirus had been isolated from patients with SARS. Since then, its 30,000 base sequence has been decoded and different primers made for use in diagnostic kits. The GIS is also in this quest for a quick, efficient and reliable diagnostic kit. This would greatly help in the clinical management of patients with suspected and probable SARS as well as to rule out the disease in others with fever not due to the virus of SARS.

Meanwhile, the disease has gone global. In the ASEAN region alone, fewer and fewer countries have been spared. In China, there may be 10 times more cases than previously reported and Shanghai, in addition to Beijing, has cases too.

Fast Forward

What lies ahead? There could be 3 possible scenarios: the situation could get worse, stay the same or get better.

With globalisation and easier, faster air travel, disease spread is facilitated. By issuing travel advisories, WHO has tried to prevent people visiting SARS affected countries. In these countries, steps are being taken to prevent the import and export of cases with health declaration forms, body temperature monitoring, quarantine of the sick and certifications by doctors of passenger's fitness to travel.

Airline companies are suffering as fewer people are flying. Entry and exit points have become bottlenecks. However, borders remain porous.

Within a country, the disease could become endemic. Spread could become community-wide when it becomes impossible to relate back to an index patient as the source of the illness. Quarantine and stay-home orders with drastic penalties for those who defy them, means a large enforcement agency is essential. The use of technology to help in this policing function means better use of resources but nonetheless, manpower resources are still necessary.

Until the diagnosis can be better other than clinical alone, we are handicapped in managing the crisis. This new disease, with many unknowns, leaves us with assumptions which may be wrong, logic which is faulty and therefore strategies and plans which do not succeed in combating the disease. In a sense, we are flying blind.

The coronavirus is probably the SARS virus. RNA viruses mutate a million times faster than human cells and therefore compared to DNA viruses, there is little proofreading and repair of RNA after duplication. So this is an error-prone process. Coronaviruses have the largest RNA genomes. Their potential for mutation is so large that no 2 coronavirus particles are

genomically identical.¹⁸ So far, all the SARS viruses that have been sequenced (1 each from Toronto, Hanoi, Bangkok and Singapore and 2 from Hong Kong) already show some differences. This has serious negative implications for the diagnostic test kits, as well as pathogenesis and transmissibility in the community.

So based on these reasonings, it is not surprising that WHO said in mid-April 2003 that SARS could become a global epidemic. The situation in China is a wild card and its earlier lack of transparency has compounded the matter.

Could the situation stay the same? We in Singapore have been told to be prepared for the long haul in the battle against SARS. At the same time, we are advised to return to normalcy after having instituted precautionary measures. Just as life after 9/11 has changed, so too has life in Singapore after SARS. Until we learn more about SARS and its aetiological agents, it seems what we in Singapore are doing are practical and pragmatic, though inconvenient to many. Expatriates polled in a regional survey by the Hong Kong-based Political and Economic Risk Consultancy (Perc) gave Singapore health care top marks despite the severe stress on the medical system. A far second behind Singapore was Japan, then Hong Kong. The scores given, based on 0 to 10 with zero the best and 10 the worst grade, was 2.33 for Singapore and 4 for Japan. However, the score for the United States was 0.86, Britain 2.08 and Australia 2.14.¹⁹ So maybe SARS is here to stay. It may take its place with tuberculosis and malaria as just another human affliction.

And finally, could the situation get better? What role has GIS in this? Sequencing the genome of the virus has been achieved at GIS. Its first priority is to obtain a reliable diagnostic kit to aid in diagnosis for early treatment. A 3-hour diagnostic test that could detect virus 10 to 100 times faster? On a mass scale? We will know by the end of May 2003. Next, if proteins can be extracted from the virus, some form of therapy may be forthcoming. And in the longer term, a vaccine could be produced. According to WHO, there are 13 laboratories in 9 countries devoted to studying SARS. Hopefully, there will be fruit — fast.

Conclusion

China's Guangdong province could be a Petri dish for bugs even deadlier than the mysterious SARS.³ On the positive side, within a period of 6 weeks, researchers collaborating worldwide to crack down on SARS have identified the disease, the virus and its genetic code — a remarkable international scientific accomplishment. Yes — fast, faster and faster yet. But fast enough?

“This is a much more serious illness than many people, including some health officials, appreciate.” — Dr Scott Dowell, Director of Programs to detect new diseases in Asia, CDC, Atlanta.

On 28 April 2003, WHO declared Vietnam SARS-free. There were no new cases in Hanoi since 8 April. WHO also said the SARS outbreak is over for Singapore, Hong Kong and Canada. Is this the good news we expected or is it too good to be true?

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