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MINI-SYMPOSIUM: SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

Epidemiology of severe acute respiratory syndrome (SARS): adults and children

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Summary Severe acute respiratory syndrome (SARS) is a newly described respiratory infection with pandemic potential. The causative agent is a new strain of coronavirus most likely originating from wild animals. This disease first emerged in November 2002 in Guangdong Province, China. Early in the outbreak the infection had been transmitted primarily via household contacts and healthcare settings. In late February 2003 the infection was transmitted to Hong Kong when an infected doctor from the mainland visited there. During his stay in Hong Kong at least 17 guests and visitors were infected at the hotel at which he stayed. By modern day air travel, the infection was rapidly spread to other countries including Vietnam, Singapore and Canada by these infected guests. With the implementation of effective control strategies including early isolation of suspected cases, strict infection control measures in the hospital setting, meticulous contact tracing and quarantine, the outbreak was finally brought under control by July 2003. In addition, there were another two events of SARS in China between the end of December 2003 and January 2004 and from March to May 2004; both were readily controlled without significant patient spread.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is a newly described and highly contagious respiratory infection. This infection is frequently associated with rapid deterioration in infected patients and the mortality rate is very high, especially in elderly patients. The global epidemic of this infection emerged in Guangdong Province in Southern China in November 2002. The disease was transmitted to Hong Kong when an infected physician from the mainland visited there in late February 2003. Subsequently, the disease quickly spread to many parts of the world with help of the international air travel. With increasing recognition of this unusual infection, the World Health Organization (WHO) termed this condition severe acute respiratory syndrome (SARS).[1] In this review we summarise the history of the outbreak and describe the epidemiological features of this devastating disease.

THE ORIGIN OF AN EMERGING INFECTION

The global epidemic began in the Guangdong Province in Southern China in mid-November 2002. The first case of SARS that fulfilled the WHO criteria was reported in Foshan, a city about 20 km from the capital city of the Guangdong Province.[2] In December 2002 the second case was reported to be a chef who had regular contact with live caged animals used as game food. In the initial stage of the outbreak the disease was confined to household contacts and healthcare workers who looked after patients with an unusual type of atypical pneumonia of unknown aetiology,[3] subsequently known as SARS.[4] The World Health Organization (WHO) was first informed on February 11th, 2003,

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by the Chinese Ministry of Health, of an outbreak of atypical pneumonia of unknown aetiology involving 305 cases and five deaths in the Guangdong Province.[5] On March 26, 2003 the Chinese government provided an update of the outbreak in the Guangdong Province. From November 2002 to 28th February, 2003 there were a total of 792 cases with 31 deaths. In the meantime, SARS quickly spread across the country and Beijing was severely affected with an increasing number of new cases. The pattern of spread was fairly consistent. Initially, the infection was confined to household contacts and healthcare workers who had looked after the infected patients without the proper protective equipment. Subsequently, the infected health workers and visitors to the hospital wards brought the infection out of the hospital system, resulting in a massive community outbreak across the country. The rapid spread and exponential increase in the number of cases at the end of January and in early February 2003 was most likely related to movement of people during the Chinese New Year holiday season.[2]

With increasing understanding of the condition and the recognition of the magnitude of the problem by the central Chinese government, effective control measures including proper isolation of infected cases, meticulous contact tracing, appropriate quarantine and stringent infection control measures in the healthcare facilities, were introduced. Special designated hospitals in various regions of China were assigned to treat patients with SARS only. The outbreak came under control and the number of new cases gradually declined. On June 24th, 2003 Beijing was removed from the WHO list of areas with recent local transmission of the disease. In the period between November 2002 and June 2003 there were a total of 5327 cases resulting in 348 deaths in mainland China. The crucial incident that led to the pandemic happened in mid-February when an infected doctor travelled to Hong Kong and spread the infection to the other guests and visitors at the hotel where he had stayed for just one night.[6]

THE EPIDEMIC IN HONG KONG

The epidemic of SARS in Hong Kong began when an infected doctor from Guangzhou came to Hong Kong in mid-February 2003.[2] At least 17 visitors and guests at the hotel where he stayed came down with the illness. These infected individuals in turn spread the disease to other cities including Toronto, Singapore and Hanoi.[7,8] One of the infected visitors was admitted to the Prince of Wales Hospital in early March with pneumonia. In just two weeks, 138 healthcare workers, medical students, other patients and visitors to the index ward contracted the disease. The exact reason causing such an extensive outbreak was not clear. It was postulated that the use of the jet nebuliser in the index patient might have generated large amounts of infective droplets in the environment. The infected visitors and patients who had been in the same ward then brought the disease out of the hospital and it spread to the community.

Another major community outbreak in Hong Kong occurred in the Amoy Garden Apartment complex where over 300 residents were infected. The index case of this outbreak was a chronic renal patient who acquired the infection while staying at the index ward at the Prince of Wales Hospital. He had visited his relatives living at Amoy Gardens a few times. There were several hypotheses that tried to explain the extent of the outbreak. Early environmental investigations suggested that the likely route of spread was via leaky sewage pipes, resulting in an aerosol contaminated with infectious fecal material which escaped into the narrow light well between the buildings. Furthermore, a team of investigators from WHO found that the traps of floor drains in many units were dry, resulting in an open connection to the vertical sewage drainage pipes. As there were exhaust fans in the kitchens and bathrooms, backflow of infectious aerosol might occur when the exhaust fans were running, resulting in spread of the infection into the other units in the same apartment block. Further analyses with the use of airflow-dynamics and computational fluid-dynamics revealed evidence of airborne transmission from the index apartment block to the other apartment blocks.[9] The infected residents in turn spread the disease at work or via other social contacts resulting in a territory wide outbreak in Hong Kong. During the outbreak of SARS in 2003, a total of 1755 patients came down with the disease and it claimed 300 lives. At the height of the outbreak, schools and hospitals were closed. Furthermore, the residents of Block E at Amoy Gardens were put under quarantine. With these effective measures along with meticulous infection control in the hospitals, proper isolation of infected cases and contact tracing, the outbreak finally came under control and Hong Kong was removed from the WHO list of areas with local transmission in June 2003.

THE GLOBAL EPIDEMIC

Among the infected guests at the index hotel in Hong Kong was a Chinese-American businessman who had stayed in a room across the hall from the infected Guangdong doctor. He travelled to Hanoi and became ill while in Vietnam. Dr Carlo Urbani was the first to recognise this new infectious disease and he instituted stringent infection control measures early on in the outbreak in Hanoi. There were only 63 cases with five deaths in Vietnam and it was the first country to be removed from the list of countries with local transmission by the WHO. Unfortunately, Dr Urbani contracted the disease and subsequently died in Thailand where he planned to deliver a scientific presentation.[10]

The outbreak in Singapore started in late February when two infected guests who had stayed in the index hotel in Hong Kong returned home.[8] Following the typical pattern

Table 1 Cumulative number of cases of SARS in affected countries.

Area	Cases (n)	Median age	Number of deaths	Case fatality ratio (%)
Australia	6	15	0	0
Brazil	1	4	0	0
Canada	251	49	38	15
China (Mainland)	5327	–	349	7
Hong Kong (China)	1755	40	300	17
Macau (China)	1	28	0	0
Taiwan (China)	665	46	180	27
Colombia	1	28	0	0
Finland	1	24	0	0
France	7	49	1	14
Germany	9	44	0	0
India	3	25	0	0
Indonesia	2	56	0	0
Italy	4	30.5	0	0
Kuwait	1	50	0	0
Malaysia	5	30	2	40
Mongolia	9	32	0	0
New Zealand	1	67	0	0
Philippines	14	41	2	14
Ireland	1	56	0	0
Korea	3	40	0	0
Romania	1	52	0	0
Russian Federation	1	25	0	0
Singapore	238	35	33	14
South Africa	1	62	1	100
Spain	1	33	0	0
Sweden	3	33	0	0
Switzerland	1	35	0	0
Thailand	9	42	2	22
United Kingdom	4	59	0	0
United State of America	33	36	0	0
Vietnam	63	43	5	8
Total	8422	–	916	11

of spread within hospitals, the infection spread out to the community. In contrast to the situation in Hong Kong, the health authorities instituted very stringent measures of isolation, contact tracing, home quarantine and closure of schools fairly early on in the outbreak. Therefore, the magnitude of the outbreak was relatively small with a total of only 238 cases. Similarly in Taiwan, SARS was transmitted into the region by travellers who had visited Southern China or Hong Kong. Despite the knowledge of the infection accumulated in Hong Kong and the Mainland, initial control measures were sub-optimal resulting in a major community outbreak. There were a total of 346 cases resulting in 37 deaths and Taiwan was the last region to be removed from the list with recent local transmission. The largest outbreak outside of Asia was in Toronto, Canada when one of the infected guests from the index hotel in Hong Kong returned home in late February 2003.[7] The pattern of spread was similar to that in Singapore and Hong Kong. The total toll in Canada was 251 cases and the outbreak finally came under control in early July 2003. Other than the outbreaks mentioned above, 23 other countries have reported cases in people who had recently travelled to the affected regions (Table 1).[11] Because of the heightened index of suspicion and implementation of proper infection control measures, very few cases in these countries were healthcare workers and the disease did not spread into the communities.

DEMOGRAPHY

The demography of the patients from different parts of the world showed several consistent features. As a large proportion of the patients were healthcare workers, most of them were relatively young. The reported median age of the patients was mostly under 50 years.[12] There was a slight female predominance as many of the infected healthcare workers were nurses. In Hong Kong and Singapore, 22% and 41% of the patients were healthcare workers respectively. Infection among children and adolescents was relatively uncommon. Only 6% of all SARS cases from Hong

Kong were under 18 years of age. Almost all infected children had close contact with an infected adult in the same household. It is interesting to note that many children were attending schools up until they were admitted to hospital with respiratory symptoms or fever, there has not been any case of spread in the school setting in Hong Kong. For the initial cohort of infected adults admitted to the Prince of Wales hospital, only 5% of close family contacts were infected. This suggests that patients are non-infectious while they are incubating the disease. In Hong Kong the majority of the infected children were associated with the outbreaks at the Prince of Wales Hospital or Amoy Gardens Apartments complex.

Among areas with larger outbreaks, Hong Kong and Canada had the highest case-fatality rate of 17%.[13] Mortality is increased in those with pre-existing illness and those in the older age group. Young children had much milder disease and they usually recovered uneventfully. A small proportion of adolescent patients, however, may develop more severe disease similar to the disease in adults. In Hong Kong there were five pregnant women infected with SARS but none of the neonates was found to have evidence of infection after the delivery despite extensive investigations.[14]

MOLECULAR EPIDEMIOLOGY OF SARS

With the advance of modern molecular biological techniques, scientists are able to trace the possible origin of the virus and the spread of infection. Early in the outbreak of SARS the WHO quickly established a laboratory network around the world to facilitate the collaboration in search of the responsible infectious agent.[15] The causative agent of SARS was identified as a newly described strain of coronavirus.[16,17] Within just 2 months of the outbreak in Hong Kong, the genome of the virus was completely sequenced and it has very low homologies to all known coronaviruses.[18] Subsequent investigations of wild animals and animal traders suggested that the virus originated from wild animals such as the palm civet and raccoon dog that have been hunted for consumption as a delicacy.[19] Therefore, the SARS coronavirus most likely represents a new virus introduced to humans by interspecies transmission. From the genomic sequential analysis of 61 SARS coronavirus derived from the early, middle and late phase of the SARS epidemic in the mainland of China, it was again found that the earliest genotypes were similar to the animal SARS-like coronavirus. Major deletions were observed in the open reading frame 8 (Orf8) region of the genome, both at the start and the end of the epidemic. The neutral mutation rate of the viral genome was constant but the amino acid substitution rate of the coding sequences slowed down during the course of the epidemic. The spike protein showed the strongest initial responses to positive selection pressures, followed by subsequent purifying selection and eventual stabilisation. These changes may be related to the increasing virulence of the virus strains, leading to more severe symptoms and higher infectivity of patients in the middle and late stage of the epidemic.[20]

Detailed phylogenetic analyses of nucleotide acid sequences of various strains of SARS coronavirus isolated from Hong Kong, Guangdong, Singapore and other countries showed that several strains of the virus were introduced into Hong Kong by residents who had recently traveled to Southern China.[18] However, only one isolate was responsible for most of the cases in Hong Kong and the subsequent spread to other countries by the infected guests at the index hotel. SARS-CoV isolated from an oropharyngeal swab of this patient demonstrated a mutation which caused an aspartic acid to glycine switch and the G:G:C:T:C motif was genotypically the closest sequence to that of the index hotel outbreak.[20] The clinical characteristics of the patients appeared to be more severe with higher mortality and frequency of diarrhoea in the cluster of patients from Amoy Gardens and it has been suggested that it might have been due to mutation of the virus. However, molecular analyses of the isolates from the patients from Amoy Gardens showed very minor differences from the isolate causing the outbreak at the Prince of Wales Hospital.[21] Alternations in the genome are unlikely to be the reason for the distinctive features of the patients from Amoy Gardens. Further studies are necessary to determine the factors responsible for the differences in the clinical features among the patients from different outbreaks.

SARS EVENTS IN 2004

There were two events of SARS in the mainland of China following the first outbreak in 2003. Four new cases of SARS emerged from the end of December 2003 to January 2004. The S-gene sequence analysis of the coronavirus from the throat specimen isolated from the first case again showed high homology with that from the civet cat (Guan Y, personal communication). The second case was a waitress working at a restaurant where wildlife animals were processed as game food. A close linkage of SARS-CoV between human beings and small wild mammals, in particular civet cats, was suspected. In addition, as game foods are considered to enhance the vitality of the body, the Cantonese consumed them in substantial amounts and wildlife markets blossom each year during the cold weather, facilitating more possible cross infection of SARS from wildlife to humans. Early in 2004 the Guangdong government and the Department of Public Health took strong actions to control the wildlife market, including cessation of rearing, sales, transport, slaughter and food processing of small wild mammals, civet cats in particular. Seventeen rearing farms were closed within 5 days. All suspected cases of infection were isolated immediately and all close contacts were put under quarantine. This control strategy seems to be working and there have not been any new cases since Jan 30, 2004 in Guangdong.

With regards to the second SARS event, a young postgraduate working at an institute of virology in Beijing from March 7 to March 22, 2004 developed symptoms of pneumonia on March 25. When she returned home to Hefei, the capital city of Anhui Province, she was diagnosed as having SARS and transmitted the disease to another seven people including her parents and healthcare workers both in Beijing and Hefei. Twenty-three days later another person working at the same institute presented with the same symptoms, who was also diagnosed as having SARS. It has been confirmed that these two separate cases arose from the same contaminated lab. The institute was shut down immediately. In addition to the isolation of nine SARS cases, more than 200 contacts were put in quarantine. Fortunately, there were no further outbreaks from the third event of SARS.

CONCLUSIONS

Severe acute respiratory syndrome (SARS) is the first new infection identified in the new millennium with a pandemic potential. This disease frequently leads to rapid deterioration, with a high case-fatality rate, especially in the elderly. For reasons that are still unclear, children tend to develop very mild disease and the majority recover uneventfully. Epidemiological studies revealed that the most likely route of transmission is by respiratory droplets. However, given the right environmental conditions, airborne transmission may be possible as illustrated by the outbreak at Amoy Gardens in Hong Kong. Similar to epidemics caused by new strains of influenza, SARS coronavirus is most likely to originate from animal species. Health authorities will have to evaluate the risk of allowing sales of wild animals for human consumption as well as the operations of wet markets in China and other Asian countries. As illustrated by the recent cases of transmission from the laboratory, appropriate control measures in the laboratory are necessary to prevent the spread of SARS or similar infections into the community.[22,23]

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