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Review

Severe acute respiratory syndrome (SARS): breath-taking progress

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Reports of a new severe respiratory disease, now defined as severe acute respiratory syndrome (SARS), began to emerge from Guangdong, in southern China, in late 2002. The condition came to international attention through an explosive outbreak in Hong Kong in March 2003. Cases appeared throughout South-East Asia and in Toronto, the spread of SARS being accelerated by international air travel. A global emergency was declared by the World Health Organization, bringing together an international team of epidemiologists, public health physicians and microbiologists to study and contain the disease. This response has enabled the nature of the infectious agent to be identified, its mode of transmission to be established and diagnostic tests to be created rapidly.

Introduction

Reports of a new severe respiratory disease began to emerge from Guangdong, in southern China, in late 2002. It burst upon international attention through an explosive outbreak in Hong Kong of what was soon to be defined as severe acute respiratory syndrome (SARS) in March 2003 (Lee *et al.*, 2003). The appearance of cases throughout South-East Asia and in Toronto was accelerated by international air travel (Poutanen *et al.*, 2003). The World Health Organization declared a global emergency, bringing together an international team of epidemiologists, public health physicians and microbiologists to study and contain the disease. The co-ordinated response to SARS by the medical and scientific community has enabled the nature of the infectious agent to be identified, the mode of transmission established and diagnostic tests to be created rapidly (Drosten *et al.*, 2003; Ksiazek *et al.*, 2003). Furious efforts are being made to determine the optimal treatment regimen and to develop therapeutic agents and vaccines. Nonetheless, it is a paradox that, despite these technological achievements, we remain as vulnerable to this new agent as our ancestors were to previous plagues.

Early phase

SARS initially appeared as a small cluster of cases of viral pneumonia in rural Guangdong province in the People's Republic of China, which, although out of the ordinary, was not considered exceptional. As far as can be ascertained, the first recognized case of SARS occurred in Fushan City and was reported on 16 October 2002. Three members of the index case's family were also affected, but no medical staff. Small clusters of cases were noted over the next 3 months. The event that was to lead to the current global alert was the admission of a patient to a tertiary referral hospital in Guangzhou with presumed viral pneumonia who had been referred from Zhongshan city outside Guangzhou. He was admitted to the 2nd Affiliated Hospital of Sun Yet-San Medical University for 2 days, then transferred to another hospital. Following his admission at the 2nd Affiliated Hospital, 28 medical and nursing staff fell ill with SARS, as well as the ambulance driver who transferred him. SARS then spread rapidly to five different hospitals and this has just been documented (Zhao *Zhao et al.*, 2003). The early and high attack rate amongst hospital staff was to become a constant feature in all further outbreaks in different countries. The spread of SARS outside Guangdong province occurred when a nephrologist from Guangzhou travelled to Hong Kong on 21 February 2003. He had a 5-day history of respiratory symptoms and was admitted to hospital on the second day of his stay in Hong Kong. Unfortunately, while staying at a hotel in Hong Kong, he is presumed to have infected a couple from Toronto, Canada, a businessman who travelled to Hanoi, Vietnam, three people who travelled to Singapore and a number of Hong Kong residents. All of these people went on to initiate large outbreaks (Poutanen *et al.*, 2003; Lee *et al.*, 2003).

The SARS coronavirus

It has now been firmly established that the cause of SARS is a

Abbreviations: HCW, health-care worker; SARS, severe acute respiratory syndrome.

coronavirus (Drosten *et al.*, 2003; Ksiazek *et al.*, 2003), and Koch's postulates were fulfilled fully when experimental infection was achieved in macaques (Fouchier *et al.*, 2003). The sequence contains nine novel viral proteins for which sequence analysis has predicted functions. Coronaviruses typically have narrow host ranges and are significant veterinary pathogens, causing severe bronchitis, peritonitis and gastroenteritis in different animal species. Human coronaviruses fall into groups 1 and 2 and are responsible for about one-third of upper-respiratory-tract infections (Rota *et al.* 2003). At least two examples of this virus have been fully sequenced, and this work demonstrates that the SARS agent is not related to any of the three previously described coronavirus groups (Rota *et al.*, 2003; Marra *et al.*, 2003).

It should not be a surprise that the SARS coronavirus is different from previous members of this genus, as the behaviour of the pathogen differs markedly from human coronaviruses described previously. The virus may have acquired a conserved motif, s2m, from avian infectious bronchitis virus but, apart from this, there is no evidence of any exchange of genetic material with non-Coronaviridae (Marra *et al.*, 2003; Rota *et al.*, 2003). This is consistent with the hypothesis that a previously unknown animal coronavirus has recently mutated, developing the ability to productively infect humans. There are some indications that the civet cat, eaten as a delicacy in southern China, was the source animal.

Not only did this virus differ genetically from other coronaviruses isolated in humans, but it behaves differently from other human coronaviruses and most other respiratory pathogens. The mortality rate appears to be very high (Tsang *et al.*, 2003; Lee *et al.*, 2003). Elderly patients with pre-existing respiratory complaints are especially vulnerable. This must be compared with acute community-acquired pneumonia, which has an approximate case fatality rate of 5 % for those patients admitted to hospital, but this represents the tip of a substantial iceberg of clinical disease managed in the community with negligible mortality. It is not yet known whether some patients may be infected with the SARS agent and develop few or no symptoms. Only when these data are available will it be possible to calculate an accurate case mortality rate. However, it is likely that the mortality rate of this infection is over 10 % (Booth *et al.*, 2003). In view of its ability to spread in the hospital environment to health-care workers (HCW), it is likely that SARS will alter medical practice in many ways.

Virus transmission

Some patients, like the index patient at the hotel in Hong Kong, appear to shed large amounts of virus, resulting in a very large number of secondary cases. These patients have been described in other viral infections such as Ebola haemorrhagic fever (Khan *et al.*, 1999) and are termed 'super-spreaders'. This epidemiological model assumes that there is no asymptomatic carrier state and, although there is no evidence of such a state, it has been noted that, in some outbreaks, there are mild cases of infection (Poutanen *et al.*, 2003). This difference has been ascribed to age, genetic predisposition, smoking, previous immunity and co-infection with another pathogen. Should it be found that asymptomatic carriage occurs, control of the SARS coronavirus is going to be extremely difficult.

The route of transmission seems to be via aerosolized droplets. The portal of entry is thought to be inhalation or contact with mucous membranes and/or conjunctiva. Virus is also present in faeces, and about 25 % of patients complain of diarrhoea (Zhao *et al.*, 2003; Lee *et al.*, 2003; Poutanen *et al.*, 2003). The high attack rate in medical staff is probably a function of the stage at which patients present and the production of virus-containing aerosol when medical procedures (such as suction and intubation) are undertaken without adequate protection (Donnelly *et al.*, 2003).

Transmission to health-care workers (HCW)

One of the biggest concerns around the spread of SARS has been the high rate of infections amongst HCW and in health-care settings. In the Greater Toronto area, 111 of the 144 cases admitted to hospital had exposure to SARS in a hospital, and 73 (51 %) were HCWs (Booth *et al.*, 2003). In Hong Kong, among 138 cases of secondary and tertiary spread, 85 (62 %) involved HCWs (Lee *et al.*, 2003). Most of this spread was prior to the recognition of the aerosol, environmental and fomite spread of the virus. This has led to specific recommendations of nursing of suspected cases in negative-pressure isolation or a single side room. Protocols have been set up for patients meeting the clinical case-definitions to be recognized early and isolated appropriately. HCWs in contact with patients have adopted specific infection-control measures, including the use of face masks with filter efficiencies of 95 % or above, use of gloves and eye and head protection (Seto *et al.*, 2003) and careful attention to hand-washing. Not since the advent of HIV have such stringent infection-control procedures been adopted so universally by HCWs. However, despite these measures, there have been reports of transmission to HCWs in the intensive-care setting (Hong Kong Department of Health, 2003). This is thought to be as a result of aerosol-generating procedures like non-invasive ventilation, endotracheal intubation, open tracheal suction, use of nebulizers and bronchoscopy. The recognition that there is a significant increase in viraemia in the second week of the illness (Peiris *et al.*, 2003) and that patients requiring intensive care may therefore have high levels of circulating virus support this increased risk. Moreover, it is now apparent that the virus can survive for over 24 h outside the body on environmental surfaces (WHO, 2003a). This has led to many treatment centres minimizing or avoiding certain high-risk procedures and adopting protocols that include the use of hood respirators with a filtered air-supply for unavoidable procedures. Such equipment is expensive and requires extensive training to gown and de-gown safely and, unless teams are comfortable with and fully versed in their use, this may lead to increased risk of contamination. A recent report of the investigation of one

series of such transmission in Canada highlights the need for appropriate training in the execution of existing infection-control procedures (Health Canada, 2003).

Clinical features

Infection

Incubation period ranges from 2 to 10 days and early symptoms are fever, myalgia and headache. Fever appears to be almost universal and is often the presenting feature, although some patients present with mild respiratory symptoms (Booth *et al.* 2003). The respiratory phase starts after 3–7 days, with a dry cough and dyspnoea. In some patients, hypoxia develops and progressive pulmonary infiltrates appear on the chest X-ray. In China, this has been called the 'blossoming flower' lesion. The infiltrates are typically peripheral and a study using thin-section CT has shown this, together with a characteristic 'crazy-paving' appearance due to thickening of interlobular septa (Wong *et al.*, 2003). Some patients develop respiratory failure and require ventilation. This presents considerable cross-infection control problems (see above). There is some evidence that non-invasive methods of ventilation may be associated with a better outcome, but there are concerns that this approach to ventilation may be associated with the generation of aerosols and an increased risk of viral transmission (Zhao *et al.*, 2003).

In some patients, the illness is biphasic in that, 4–7 days after defervescence of pyrexia, new infiltrates appear on X-ray and respiratory failure worsens; these patients often do badly. Consistent laboratory findings are a thrombocytopenia and leucopenia, which particularly affects lymphocytes. Consistent with virus replication in organs other than lung is the elevation of creatine kinase, lactate dehydrogenase and liver transaminases (Tsang *et al.*, 2003; Booth *et al.*, 2003). In a multivariate analysis, the independent predictors of an adverse outcome were advanced age (odds ratio per decade of life, 1·80; 95 % confidence interval, 1·16–2·81; $P = 0{\cdot}009$), a high peak lactate dehydrogenase level (odds ratio per 100 U l^{-1}, 2·09; 95 % confidence interval, 1·28–3·42; $P = 0{\cdot}003$) and an absolute neutrophil count that exceeded the upper limit of the normal range on presentation (odds ratio, 1·60; 95 % confidence interval, 1·03–2·50; $P = 0{\cdot}04$) (Lee *et al.*, 2003).

Diagnosis

The laboratory tests that can be applied for routine diagnosis are PCR and immunofluorescent ELISA detection of serum antibodies using SARS coronavirus from Vero cell culture. Early efforts at the University of Hong Kong using random RT-PCR provided 646 bp of genomic sequence, from which a diagnostic PCR was developed (Peiris *et al.*, 2003). Parallel efforts in Hamburg yielded three fragments that, when sequenced, did not overlap with a 400 bp fragment reported the day before (24 March 2003) by the CDC (Drosten *et al.*, 2003). Nested primers were designed by the Hamburg group within the orflab region, which encodes the viral replicase 1B (Marra *et al.*, 2003). The Hamburg group found five of the patients with probable SARS studied to be positive with all of their primers, both nested and non-nested. Only three of 13 suspected patients were positive. The group also developed a real-time quantitative PCR that showed that the concentration of viral RNA was highest in sputum and low in nose and throat swabs, suggesting that sputum is the best diagnostic sample. The index patient had very high viral loads [$8{\cdot}3 \times 10^6$ virus copies (ml sputum)$^{-1}$]. This fits with the highly infectious nature of patients at presentation. Low levels of virus were found on day 9 in serum, suggesting a long viraemic phase and replication of the virus outside the respiratory tract (exemplified by deranged liver function tests). Viral RNA was also found in the faeces of patients late in convalescence, a feature of other coronaviruses (Cho *et al.*, 2001). Extended testing of patients and contacts for antibody to SARS coronavirus will be important in the future to delineate spread and to identify asymptomatic carriage. The CDC group also developed RT-PCR and an ELISA as well as IFA for antibody detection (Ksiazek *et al.*, 2003). Through the efforts of the WHO, a standardized PCR protocol is now available in participating national reference laboratories.

Outcome

One study has determined a more accurate estimate of the case fatality rate than initial work early in the epidemic. Depending on the statistical method used, mortality in $<$ 60-year-old patients was 13·2 or 6·8 % and, for $>$ 60 years, 43·3 or 55·0 % (Donnelly *et al.*, 2003). This rate was higher than the cumulative rates given previously by the WHO and local authorities. One of the explanations is that the study was able to allow for new patients that had been added to the denominator but that had not yet experienced mortality.

Global control

In an effort to co-ordinate a global public health effort to curb the spread of SARS, early recognition and isolation of cases remain key elements in formulating local, national or international strategies. Epidemiological monitoring of the outbreak in terms of numbers of cases, clustering of cases and documenting exposures has been crucial in identifying modes of transmission and incubation period (Donnelly *et al.*, 2003). The WHO devised case-definitions based on close contact with a suspected case or travel to an area reporting local transmission associated with symptoms of a respiratory tract infection and radiological changes. Now that the first-generation tests for the SARS coronavirus have been developed, these have been incorporated into the case-definitions (CDC, 2003). However, viral cultures and viral detection in patient secretions and excretions by RT-PCR remain relatively insensitive for a reliable early diagnosis. Serological diagnosis is likely to provide definitive diagnosis based on acute and convalescent specimens. Detailed clinical features and prognostic markers for disease progression have been characterized (Booth *et al.*, 2003; Hsu *et al.*, 2003; Lee *et al.*,

2003) and continue to be analysed and, should the epidemic become widespread and contact histories difficult to assess, these features may be useful in identifying cases.

In order for the case-definitions to remain a valid tool, daily reporting of probable cases and areas reporting community transmission have been collated by WHO and disseminated via their website (http://www.who.ch). After early spread of the disease to Hong Kong, Singapore, Vietnam and Canada, travel warnings restricting travel to affected areas were issued by the WHO and exit screening was introduced for travellers from these areas (WHO, 2003b). Although the incubation period of the illness is short (Donnelly *et al.* 2003) and transmission is only believed to occur after the onset of symptoms, the effectiveness of such measures is yet to be determined.

At national and local levels, strenuous control measures, in addition to infection control around known cases, have been adopted. In areas where community transmission has been reported, vigorous public education in reporting symptoms, early isolation of possible cases, exhaustive contact tracing and isolation and quarantine measures were introduced, often requiring emergency legislation. As the epidemic has evolved, the possibility of an environmental source of transmission of SARS coronavirus has become apparent. At the end of March 2003, 320 cases of SARS were reported amongst the residents of Amoy Gardens, a block of apartments in Hong Kong, where sewage contamination was the likely source of infection. Closures of buildings, hospitals and schools and markets have been required. The economic impact of such measures will be enormous, but there have been successes. Vietnam was the first affected country to terminate community and hospital transmission successfully. Canada and the Philippines were next to declare control of the infection (but see below), since followed by Singapore. Unfortunately, in China and Taiwan, the epidemic continues to grow.

The situation in the UK

In the UK, the Health Protection Agency, via the SARS coordinating committee, has been instrumental in formulating and implementing a public health strategy for protecting the population from SARS. This includes reporting of suspected cases, contact tracing and surveillance of cases and contacts. As of May 2003, up to eight probable cases and more than 150 suspected cases had been reported in the UK. Apart from one, all the probable cases have had contacts abroad. Four of these cases have subsequently been discarded on the basis of an alternative diagnosis and only one of the remaining probable cases has had a coronavirus infection confirmed by serology (Health Protection Agency, 2003).

Treatment

The influence of treatment regimens intuitively has an effect on mortality and, in such a fast-evolving epidemic, it is hard to undertake tightly designed trials. However, the experience of the first major outbreak in the world in Guangzhou shows some important trends (Zhao *et al.*, 2003). Some 190 patients were randomized to four different treatment regimens. It was found that very-high-dose steroids given early with non-invasive ventilation offered the best outcome; there was no convincing evidence that ribavirin helped. Recently, a very small study has supported these findings (So *et al.*, 2003). The Guangzhou group went on to treat a further 160 patients with the optimal regimen, with only three deaths. At the time this study was undertaken, no diagnostic tests were available, so only clinical case-definitions could be used. This means there may be an excess of suspect cases, leading to a lower mortality.

The clinical features of SARS are now well recognized. Many of the characteristic features were described in early reports (Tsang *et al.*, 2003; Booth *et al.*, 2003). Treatment remains supportive; early hopes that ribavirin would be effective (Koren *et al.*, 2003) have not been borne out by experience (Zhao *et al.*, 2003). The use of corticosteroids, particularly at high doses, is important and two studies, one with 31 patients and the other with 190, support this action (So *et al.*, 2003; Zhao *et al.*, 2003). Much effort will doubtless be expended in developing antiviral agents in the future. The major protease of SARS coronavirus is a potential target and has been expressed in *Escherichia coli* (Anand *et al.*, 2003). Preliminary characterization shows that it retains many of the structural motifs found in other coronavirus proteases. Molecular modelling suggests that inhibitors such as AG7088 would serve as good lead compounds for development of specific antivirals.

The fate of the epidemic

China was the source of SARS coronavirus and remains the worst affected country, with 5013 of the world's 7447 cases on 12 May 2003. Almost half (252) of the total deaths (552) have also been there. Spread of SARS from the developed cities of the eastern coastal region to inland rural areas may make control and eradication much harder. Reports that SARS has been identified in Hebei, Anhui, Guangxi and Henan (Parry, 2003) are worrying. The latter province is estimated to have 1 million HIV carriers, and the interaction of this virus with individuals with an attenuated immune system is another great unknown in the rapidly unfolding SARS story. There are encouraging reports that the epidemic is being controlled, but the difficulties experienced in Toronto (WHO, 2003a), with a new outbreak after the epidemic was declared over, mean that we cannot be complacent about controlling this new threat to public health.

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