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Editorial

Severe Acute Respiratory Syndrome (SARS)

Typhoons are a regular occurrence in southern China, but they are usually a summer phenomenon. During the winter of 2002, a storm was brewing in the region, but in this case, one of a virological rather than meteorological nature. An unusual "atypical pneumonia" had been gathering force in Guangdong province, mainland China since November 2002, and by mid-February 2003, had reportedly led to 345 cases (Rosling and Rosling, 2003). An unusual characteristic of the disease was its predilection to affect health care workers. Some patients in Guangdong left a trail of infected health care workers in their wake as they were transferred from hospital to hospital, the so called "super-spreaders" or "super-spreading incidents" that subsequently became the hall mark of this disease (Zhao et al., 2003). At the time, a number of aetiological agents, including chlamydia and mycoplasma, were proposed as candidate pathogens, but none of these were confirmed. In adjacent Hong Kong, the Hospital Authority of Hong Kong instituted enhanced surveillance for severe community acquired pneumonia. However, being an international hub of business and travel, the arrival of the disease in Hong Kong rapidly led to its global dissemination, with outbreaks in Vietnam, Singapore and Toronto appearing around the same time as those in Hong Kong itself. These outbreaks led the World Health Organization (WHO) issue a global health alert about cases of severe atypical pneumonia on the 12th of March and a case definition for the disease, now named Severe Acute Respiratory Syndrome (SARS) was subsequently issued (World Health Organization, 2003a). By the end of June, the disease had affected over 8439 persons in 30 countries across five continents with 812 fatalities.

The last decade has seen the emergence of a series of novel pathogens, Nipah, BSE, Hantavirus pulmonary syndrome, H5N1 avian flu, to name a few. All of them are animal infections that have transmitted to man. However, SARS was the only one of these that had acquired the potential for efficient human–human transmission. Consequently, its global impact has been more dramatic than other emerging infections of the recent past. In the areas most severely affected, the impact on the health care system, the economy and society in general, was enormous. The economic impact of SARS on Hong Kong alone, during the few months of the outbreak is tentatively estimated to be HK$ 46 billion (viz US$ 5.9 billion), i.e. almost 4% of its GDP.

SARS is caused by a novel coronavirus (Peiris et al., 2003a; Drosten et al., 2003; Ksiazek et al., 2003). It is relevant to keep in mind that while novel molecular approaches (e.g. consensus PCR, random primer RT-PR, gene arrays, gene sequencing) played a role in characterising the virus, "conventional" virological methods such as virus culture, electron microscopy and serology using the novel virus isolate, were key in its initial identification and in establishing its aetiological role in the disease. This underscores the need for maintaining a full range of virological techniques in clinical virology laboratories and illustrates the synergies between the molecular and conventional technologies. The discovery of Nipah (Chua et al., 1999) and human metapneumoviruses (Van Den Hoogen et al., 2001) serves to reinforce this argument. The idea, driven in part by cost-containment and "managed-care" issues, that molecular techniques (PCR, gene arrays) make

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culture and electron microscopy redundant in the 21st century, has to be questioned.

The aetiological link between SARS CoV and the disease has been supported by the close epidemiological link between the virus and SARS (Peiris et al., 2003a,b) and by the reproduction of the disease in a macaque animal model (Fouchier et al., 2003; Kuiken et al., 2003). While other viruses such as the human metapneumovirus and chlamydia have been identified in addition to the SARS CoV in some patients (Poutanen et al., 2003; Kuiken et al., 2003), these are not consistently found in the majority of SARS patient cohorts. However, the role of co-factors, whether of viral, bacterial or non-microbial nature, that may contribute to disease severity or super-spreading events remains to be explored.

Coronaviruses are a group of single stranded RNA viruses that infect humans and animals. The two human coronaviruses 229E and OC43 known hitherto, are causes of the common cold, rarely anything more (Holmes, 2001). The SARS Coronavirus (SARS CoV) is genetically distinct from other human and animal coronaviruses and it appears not to have been endemic in the human population before. Thus the initial sequence information (Peiris et al., 2003a), subsequently confirmed by the full genomic analysis of the virus (Rota et al., 2003; Marra et al., 2003), indicated that this was a hitherto unrecognised animal virus that crossed to humans in the relatively recent past. Subsequently, the human SARS outbreak was maintained by a human-to-human transmission, presumably without need for continued reintroduction from the animal reservoir. Although not as transmissible as, for example influenza, the virus appears to have a particular propensity to transmit in a hospital setting. A significant proportion of the caseload has been caused by a relatively small number of sources and health care workers account for approximately 20% of all cases in most outbreaks (Lipsitch et al., 2003). The virus can be cultured from the respiratory tract, gastro-intestinal tract and urine, and thus, SARS is not exclusively a respiratory disease (Peiris et al., 2003a,b). A profuse watery diarrhoea, unrelated to antibiotics, was reported in a number of patients. Virus infection of multiple sites implies a viraemic phase, and it is of interest that in this issue of the Journal, Li and colleagues report preliminary evidence for virus replication within peripheral blood mononuclear cells (PBMC). Coronaviruses are positive strand viruses and Li and colleagues use RT-PCR to demonstrate both the genomic RNA and negative stranded RNA replicative intermediates in the first 6 days of the illness. Thereafter, the positive strand RNA was demonstrable for a further 6 days but the replicative intermediates could not. It would be desirable if the authors had controls where the RT-step is omitted, and also, if they describe whether the minus strand is still detectable if the cDNA is digested with RNAse prior to PCR. These would strengthen the argument that their minus strand signal comes exclusively from negative strand viral RNA. Attempts to culture virus from PBMC would be important confirmatory evidence, keeping in mind however, that SARS CoV is still not easy to culture from all body sites. As the authors state, the another key question is to define the cell sub-population with PBMC that the virus replicates in. Some of these questions may also be addressed through experiments in-vitro.

These findings have implications for blood safety as well as for diagnostics. We still do not know whether the virus can be detected in the peripheral blood during the late incubation period of the illness. If so, there is the possibility of a rare instance of blood-product associated transmission. There is also the question of how long the infectious virus persists in the PBMC although the data presented by Li et al. (2003) suggests that this should not be too long. The finding of virus in PBMC also provides an alternative clinical specimen for diagnosis. First generation diagnostic tests based on RT-PCR methods for virus detection in respiratory and faecal specimens showed that while diagnostic sensitivity was high later in the illness, diagnosis within the first 5 days of disease posed a problem (Peiris et al., 2003b; Poon et al., 2003). The second generation diagnostic assays have improved sensitivity in the early stage of the illness (Poon and Peiris, unpublished data) but virus detection in the blood is an option that needs to be further explored.

The World Health Organization announcement on July 5th that the human-to-human chain of transmission was interrupted world-wide, was a cause for collective global sigh of relief, especially so in those areas most affected by SARS (World Health Organization, 2003b). It represents a triumph for global public health and for the proactive role of WHO in particular. However, the question of whether SARS will return remains unanswered. The relative roles played by public health measures (intensive case detection and isolation) vs. seasonal factors in the interruption of SARS transmission is unclear. The virus still remains in its animal reservoir. How readily the animal virus transmits to humans and how often such inter-species transmission events can lead to establishing human-to-human transmission is not yet clear. Therefore it is recognised that intensive surveillance needs to be maintained, especially in the southern China region where the virus originated. In the meantime, the scientific community has a breathing space to get better diagnostics in place and to better understand the epidemiology, and options for infection control and treatment.

References

Chua KB, Goh KJ, Wong KT, et al. Fatal encephalitis due to Nipa virus among pig farmers in Malaysia. Lancet 1999;354:1257–9.

Drosten C, Gunther S, Preiser W, van der Werf S, Brodt H-R, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl J Med 2003;348:1967–76.

Fouchier RAM, Kuiken T, Schutten M, van Amerongen G, van Doornum J, van Den Hoogen B, et al. Koch's postulates fulfilled for SARS virus. Nature 2003;423:240.

Holmes KV. Coronaviruses. In: Knipe DM, Howley PM, editors. Field's Virology. vol. 1, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001; pp 1187–203.

Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel Coronavirus associated with Severe Acute Respiratory Syndrome. New Engl J Med 2003;348:1953–66.

Kuiken T, Fouchier RAM, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003; published on-line July 22.

Li L, Wo J, Shao J et al. SARS-Coronavirus replicates in mononuclear cells of peripheral blood ((PBMC) from SARS patients. J Clin Virol 2003; this issue.

Lipsitch M, Cohen T, Cooper B, Robins JM, Ma S, James L, et al. Transmission dynamics and control of severe acute respiratory syndrome. Science 2003;300:1966–70.

Marra MA, Jones SJ, Astell CR, et al. The genome sequence of the SARS-associated coronavirus. Science 2003;300:1399–404.

Peiris JSM, Lai ST, Poon LLM, Guan Y, Yam LYC, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003aa;361:1319–25.

Peiris JS, Chu CM, Cheng VCC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of a coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003bb;361:1767–72.

Poutanen SM, Low DE, Henry B, et al. Identification of Severe Acute Respiratory Syndrome in Canada. New Engl J Med 2003;348:1995–2005.

Poon LLM, Wong OK, Luk W, Yuen KY, Peiris JSM, Guan Y. Rapid diagnosis of a coronavirus associated with severe acute respiratory syndrome (SARS). Clin Chem 2003;49:953–5.

Rota PA, Obserste MS, Monroe SS, et al. Characterization of a novel coronavirus associated with Severe Acute Respiratory Syndrome. Science 2003;300:1394–9.

Van Den Hoogen BG, De Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24.

Rosling L, Rosling M. Pneumonia causes panic in Guangdong province. Br Med J 2003;326:416.

World Health Organization. Severe Acute Respiratory Syndrome (SARS): over 100 days into the outbreak. Weekly Epidemiol Record 2003a;78:217–28.

World Health Organization. SARS: Breaking the chains of transmission. 2003b; www.who.int/features/2003/07/en

Zhao Z, Zhang F, Xu M, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhaou, PR China. J Med Microbiol 2003;52:715–20.

J.S.M. Peiris
Department of Microbiology
The University of Hong Kong, Queen Mary Hospital, Pokfulam
Hong Kong
E-mail address: malik@hkucc.hku.hk