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What have we learnt from SARS?

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With outbreaks of infectious disease emerging from animal sources, we have learnt to expect the unexpected. We were, and are, expecting a new influenza A pandemic, but no one predicted the emergence of an unknown coronavirus (CoV) as a deadly human pathogen. Thanks to the preparedness of the international network of influenza researchers and laboratories, the cause of severe acute respiratory syndrome (SARS) was rapidly identified, but there is no complacency over the global or local management of the epidemic in terms of public health logistics. The human population was lucky that only a small proportion of infected persons proved to be highly infectious to others, and that they did not become so before they felt ill. These were the features that helped to make the outbreak containable. The next outbreak of another kind of transmissible disease may well be quite different.

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In the year since SARS was first recognized as something new and threatening, we have learned a tremendous amount about the disease, the causative virus, its transmission dynamics, and the collateral damage to local life and economy arising out of the fear and stress that SARS engendered. In bringing together speakers from diverse disciplines who experienced the raw face of SARS as the story unfolded, this Discussion Meeting has enabled us to reflect upon the dangers and logistics of an unexpected, previously unknown infectious disease with high mortality. Happily, SARS remained an outbreak rather than maturing into a pandemic, although we acknowledge the estimated 8098 cases of illness and mourn the 774 people who have died from SARS.

In these concluding remarks, we consider that many of the lessons learned are specific to SARS, whereas others apply more generally to epidemic infectious diseases. So why did SARS appear where and when it did? Whereas avian influenza and SARS have a Chinese origin, we should recall that in recent history other disease outbreaks usually of zoonotic origin have occurred on all continents: AIDS came 'out of Africa', bovine spongiform encephalopathy/variant Creutzfeldt–Jakob disease is a truly British achievement, hantavirus pulmonary syndrome first appeared in the USA (as did Legionnaires' disease) and later in South America, and fruit bats (flying foxes) gave rise to hendravirus and nipahvirus in Australia and Malaysia, respectively. Rich or poor, north, south, east or west, the lesson is that novel infectious disease can appear anywhere (Weiss 2001).

As to why SARS arose in China at this time, the particular reasons discussed by Bell *et al.* (2004) relate to the increasing popularity of exotic foods, in this case civet cats (viverrids). We still do not know what the natural reservoir species of this CoV is, but the importation, holding together and rearing of so many species of viverrids and also one canid and one mustelid allowed its amplification and transfer to humans to occur. The rapidly expanding popularity of such animal foods in recent years, as the Guangzhong population became more urbanized and increased in wealth, may well explain why SARS is an early twenty-first century disease, although sporadic human cases may have occurred in earlier times. Although this interesting footnote of local culinary predilection to eat civet cats may explain this particular outbreak, the lesson of SARS for newly transmissible diseases in general was spelt out by McMichael (2004) in surveying the pace of ecological and environmental change that brings about new animal–human interfaces, often where humans live densely and hence may provide conditions for onward transmission.

Changing patterns of human ecology and behaviour affect two distinct steps in the development of a new transmissible disease. The first is altering the opportunity for animal to human transfer. Thus the more interspecies contacts there are, the greater is the risk of zoonotic infection. The relatively high proportion of civet cat handlers and exotic food restaurateurs who have serum antibodies that react or cross-react to the SARS-CoV indicates that the zoonotic transfer of a related, less virulent virus may occur far more frequently than the adaptation of such a virus to onward transmission among humans. The close phylogenetic relationship of SARS-CoV genomes described by Holmes & Rambaut (2004) further indicates that the outbreak that went on to spread internationally had a point source, whereas the viral genomes among the civet cats appear to be more diverse. However, evidence is emerging that non-symptomatic SARS-related CoV infection may have travelled as far as Hong Kong before the disease outbreak (Zheng *et al.* 2004).

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One contribution of 15 to a Discussion Meeting Issue 'Emerging infections: what have we learnt from SARS?'.

The second ecological factor is the opportunity for onward spread once a human has become infected. For every new pandemic such as AIDS and 1918–1919 influenza, there are probably thousands of 'failed' transfers. These zoonoses include those that are non-apparent, where infection does not result in pathogenesis, to those that may be fatal but are not usually transmissible between humans, such as rabies, or the 1997 H5N1 avian influenza outbreak in Hong Kong (for H5N1 in 2004 it is still too early to be definitive, but its spread among chickens is already far more widespread, and the case reports of human transmission more ominous). So far, local outbreaks of Ebola virus and Lassa disease in Africa have petered out. Like SARS, infection with Ebola carries a particular exposure hazard for family and professional health carers, although there is no evidence of respiratory transmission. SARS was more mobile across our global village, perhaps only because of the greater frequency of international air travel from southern China and Hong Kong than from central Africa.

Putting these two steps together generates a pathway to emergence in which new variants arise, occasionally infect individuals, and more infrequently still become capable of onward transmission from one person to another. Influenza is our best-understood example of this iterative probing of the opportunities for emergence. Bush (2004) showed us how understanding the recent evolution of influenza teaches us general lessons about the emergence of novel infections. Frightening though SARS has been, it transpired to be controllable through careful containment of cases. Peiris & Guan (2004) pointed out that this was possible only because SARS patients do not become highly infectious until after they are symptomatic. This is in direct contrast to influenza and many other infections where the burden of infectiousness largely precedes the onset of symptoms. By quantifying the relationships between time-to-infectiousness and time-to-disease, Anderson *et al*. (2004) were able to classify infections into those that can and those that cannot be controlled through the isolation of cases.

Thus, the differences between influenza and SARS may teach us more than their similarities. Influenza infections will tend to create other cases before the index case is symptomatic; the influenza pandemic that we fear will have higher transmission rates than were seen in the 2003 SARS epidemic. What they share is direct transmission and a short incubation period. Some of the most frightening emerging infections are those with long incubation periods, because for those, by the time the first cases are recognized, many infections have been generated and the logistics of control are correspondingly difficult (table 1). By the time AIDS was recognized as a novel disease, it was already spreading out of control in urban regions of the rich and poor world. By the time BSE was identified as more than just a few extra sick cows, it had spread across the UK and abroad. Thus there are several dimensions to the classification of emergent infections: more or less transmissible, early versus late infectiousness, short or long periods between infection and disease. Viewed in such a light, SARS might almost be classified as 'easy' to manage.

The rapidity with which a new epidemic disease can spread raises questions over the balance of freedom of action of the individual and freedom from infection of the community at large. O'Neill (2004) pointed out that it was easier to manage the SARS epidemic in a more controlled society with a strong sense of community, as in China, that in more individualistic, liberal democracies in the West. All the same, the early phases of the SARS epidemic in Guangzhong province were poorly controlled in public health terms. The reasons were partly as discussed by Zhong (2004), that SARS was not initially distinguished from a concurrent, more widespread influenza epidemic in Guangzhong; and partly the slowness of public health staff to realize that something new was afoot, and their initial reluctance to alert national authorities to the situation, thus abetting the spread of SARS to Beijing.

Table 1. Emerging infections classified by their infectiousness and incubation period.
(SARS was a frightening reminder of how quickly a novel infectious disease can emerge and spread. However, its short incubation period meant that the problem was recognized before infection had become widespread. Some of the difficulties of dealing with BSE and AIDS have been caused by the widespread dissemination of infection before the first cases were even recognized, a direct result of their long incubation periods. See Ferguson *et al.* 1999; Anderson *et al.* 2004.)

	incubation period from infection to disease	
infectiousness (R_0)	short (days or weeks)	long (years)
high	influenza A	BSE
low	SARS	HIV/AIDS

As Chen Zhu told us, an important lesson learnt in China, at the price of the resignations of the health minister and the mayor of Beijing, was the need for transparency and communication. Once it became aware of SARS, the World Health Organization swung into gear to manage what rapidly became an international outbreak as described by Heymann (2004). The WHO officer in Hanoi, Dr Carlo Urbani, sadly succumbed to SARS but not before he had alerted the world to the gravity of the situation. Even before the causative agent of SARS was identified, as Roy Anderson pointed out (Anderson *et al.* 2004), the pattern of transmission was being analysed, and models of best containment began to evolve. Harper (2004) described the UK Department of Health's proposed organization for SARS and other unexpected outbreaks. By contrast, Maunder (2004) analysed the psychological stress to exposed health care workers who did not know if they were incubating SARS and who wished to spare their families from infection. They became regarded by some not so much as heroes but as 'lepers' in their midst.

Perhaps the greatest achievement during the SARS outbreak was the rapid and magnificent effort of infectious disease laboratories to isolate and characterize the SARS-CoV (Lingappa 2004), resulting in three groups in Hong Kong, Germany and North America identifying the same agent. Peiris & Guan (2004) described how the virus came to light during the hectic days of the Hong Kong outbreak, Osterhaus *et al*. (2004) related how it was possible to use Koch's postulates to prove the CoV guilty of causing SARS, and Bermingham *et al*. (2004) illustrated how

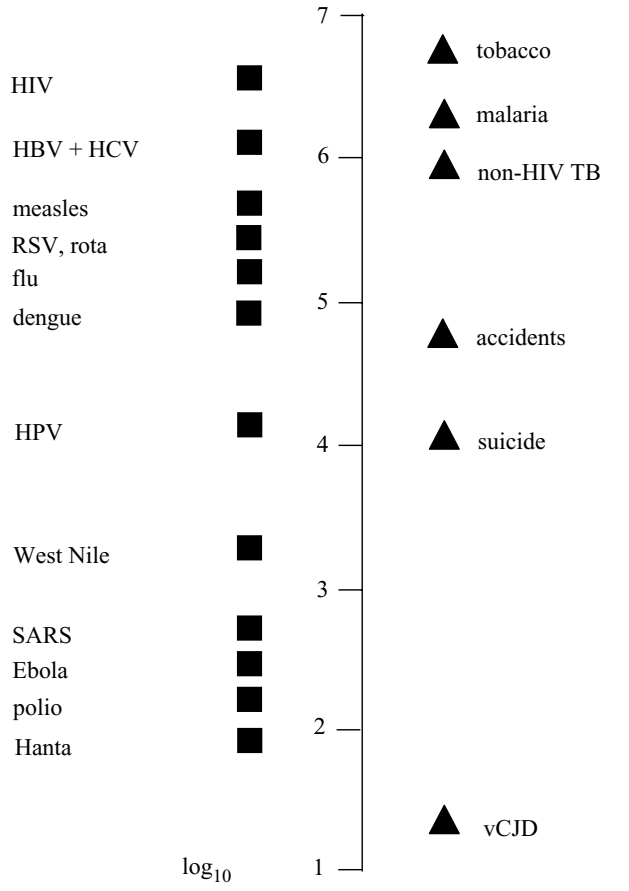

Figure 1. Natural weapons of mass destruction: a 'Richter' scale for global viral diseases measured as approximate numbers of deaths in 2003. This is a snapshot picture in time; for instance, the estimated yearly death toll of HIV has risen 10 000-fold in the past 20 years, whereas polio has fallen *ca*. 1000-fold thanks to successful vaccination policies. Vaccines—weapons of mass protection—led to the eradication or reduction of smallpox, yellow fever, polio and measles, mumps and rubella. HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RSV, respiratory syncytial virus; HPV, human papilloma virus; TB, tuberculosis; vCJD, variant Creutzfeldt–Jakob disease. (Adapted from Hale *et al.* 2001.)

quickly sensitive and specific diagnostic methods were devised to determine who was infected by the SARS-CoV. This combined effort would not have been possible if the investigators had waited to receive specific funds to tackle SARS; rather, they diverted influenza funding urgently to explore this new emergency. Moreover, they could not have made such excellent progress if there had not been a pre-existing network of influenza surveillance and reference laboratories, and a rapid and open means of exchange of information and materials between them, and above all, a sense of trust and mutual endeavour.

A lesson that requires to be continually taught is the need for novel means of surveillance, cooperation between the public health and academic sectors, and the provision of enough trained scientists with the time and curiosity to 'poke around' improving tests and keeping abreast of animal and human virology and microbiology in 'peacetime', to rise to the challenge in an emergency. For example, the dearth of professional clinical virologists in the UK parallels the erosion of state veterinary virologists highlighted after the 2001 epidemic of foot-and-mouth disease (The Royal Society 2002). When it comes to training and employing the next generation of infectious disease specialists, it would appear that the reproductive rate, R_0, is less than 1.

In the end, if it is the end, fewer than 1000 persons died from SARS, which makes it a minor cause of disease viewed on the global scale (figure 1). However, another lesson learned from SARS is how much greater the social and economic impact of the outbreak has been than one would have expected from calculating the actual number of deaths or days off work through sickness. Human society has had much reason to fear pestilence in the past (Weiss 2001), and in March 2003 it was not yet clear whether SARS was to be the 'big one'. Moreover, suppose that SARS arose when it did in the Middle East rather than the Far East. The inevitable conspiracy theories on deliberate release would have been rife and might have been used as a further excuse for war, though it might have deterred the advance of an occupying force.

Our main conclusion from this fascinating multidisciplinary Discussion Meeting on SARS is that humankind has had a lucky escape. Suppose that the SARS-CoV became readily transmissible from person to person some days before people became seriously ill with disease, as is the case with influenza A. Suppose that a much higher proportion of infected people served as 'superspreaders'. We do not yet know which human predispositions or genetic polymorphisms determine susceptibility to severe disease following SARS-CoV infection, or determine superspreader status, which is not synonymous with mortality. Perhaps it will prove to be related to the recently identified cell surface receptor for the virus (Li *et al.* 2003; Wang *et al.* 2004), or perhaps to the infected person's immune constitution. If the latter, suppose the virus had flown from Hong Kong to Durban instead of Toronto. It is a city of a similar size but without a similar health infrastructure, and with a significant proportion of its inhabitants immunocompromised owing to HIV-1 infection. Then Africa could have become endemic for SARS by now. Epidemiologists and public health experts sometimes frown upon us for indulging in such 'what if?' scenarios. However, modelling what has not yet happened, but might unfold next time, is surely part of contingency planning and preparedness.

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GLOSSARY

CoV: coronavirus

SARS: severe acute respiratory syndrome