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Editorial

SARS-CoV: Lessons for global health

1. Living in a global community

On 16 November 2002, a man developed high fever and respiratory symptoms and was hospitalized and treated for pneumonia in Foshan, China (Zhao, 2007). After several weeks in intensive care and subsequent spread of the mysterious respiratory disease to his wife and several relatives, he recovered and was released on the 8th of January 2003. In early December, a restaurant chef in Shenzhen developed a fever with flu like symptoms and while suffering a severe disease course was hospitalized in Heyuan, infecting seven hospital staff and a patient between the 16th and 28th of December. In parallel, multiple cities around Guangzhou in Guangdong Province were reporting sporadic cases of an atypical pneumonia between the end of December 2002 and through early January 2003, oftentimes in chefs or dealers of exotic animals in wet markets and their close contacts.

While this scenario may have been repeated in earlier years given the low seroprevalence rates noted in archived serum samples (Zheng et al., 2004), it was the super spreader events that took place in the HZS-2 Hospital in Guangzhou that catalyzed the global severe acute respiratory syndrome (SARS) pandemic. Two brothers, working in restaurants and then a third individual were all hospitalized with severe acute respiratory symptoms (SARS) in HZS2 between the 18th and 30th of January, leading a pneumonia-related hospital outbreak on 31 January 2003. While each transmitted disease to family and health care workers, the third individual infected over 30 hospital members and patients during his 48 h stay in HZS2, 21 hospital staff after transfer to a second hospital HZS3 and about 23 relatives and friends. This key super spreader event allowed the epidemic to gain critical momentum. Another major turn of events occurred in Shanxi Province after a business woman traveled to Guangdong in late February. After returning home, she subsequently became sick. At the time, knowledge regarding the developing outbreak was not common, so she transmitted the disease to eight family members and five hospital staff in Shanxi. After being transfer to a Beijing Hospital on 1 March 2003 she became the index case for the outbreak in Beijing as well (Zhao, 2007).

Global spread of the outbreak began on the 21st of February 2003, when a physician from the HZS2 Hospital traveled to “Hotel M” in Hong Kong. Although he did not attend atypical pneumonia patients in HZS2, his health quickly deteriorated

and he was admitted to a hospital in Hong Kong on the 22nd. During his short stay at Hotel M, a super spreader event transmitted the disease to 16 guests who subsequently spread the disease to Toronto, Singapore, Vietnam and then beyond. The indication of a new global emerging virus respiratory threat was first reported by Dr. Carlo Urbani, MD in Vietnam to the WHO on February 28th, resulting in a global alert notification on March 12th. Tragically, Dr. Urbani became infected while treating patients and subsequently died from SARS infection, a fate shared by many other health care professionals who were engaged in treating patients suffering from this new disease. Importantly, Dr. Urbani’s sacrifice focused global resources on the new epidemic disease, resulting in the rapid implementation of public health measures, diagnostic criterion, and the scientific research community which undoubtedly saved countless of lives globally (Peiris et al., 2004).

Within a few weeks of the HZS2 super spreader event, atypical pneumonia had spread to 25 countries across five continents, infecting some 8000 people and resulting in 774 deaths before succumbing to aggressive public health measures in early July 2003. In addition to the large outbreaks widely recognized in cities in Singapore, Taiwan, China, and Canada, smaller communities were also affected. An individual visiting a sick relative in Canada contacted the disease during the second wave of the Toronto outbreak, returning to North Carolina in late May 2003. He developed symptomatic disease 1 day after working several days on a rural college campus in central North Carolina. After being confirmed as a SARS case, the University spent ~\$40–50k screening some 42 potentially exposed individuals. Amazingly, a mystery disease whose index case was identified 6 months earlier on the other side of the globe had arrived in rural North America. It is not surprising that the panic caused by the rapid spread of an unknown highly pathogenic, fatal respiratory virus is enormous and no community is exempt. Coupled with the current globalization of the world trade, it was inevitable that the economic impact would be extensive.

2. Economic impact

Between March and May of 2003, tourist arrivals in Asia dropped between 30 and 80%, with about half of all flights being canceled depending on the country and region. As word of the mystery illness spread, the Asian Equity Market Indices

declined by 15% over a 4-week period. Ultimately, the World Bank reported a ~2% loss of East Asian GDP in the second quarter of 2003 during the SARS outbreak. The Asian Development Bank placed the global economic loss at 59 billion USD with the bulk of these losses located from mainland China (17.9 billion) and Hong Kong (12 billion) while Canada suffered losses of more than 1 billion. Most financial losses were associated with disruptions of trade, travel, investment, interruption of product supply chains and behavior changes in consumers, rather than from medical costs or the loss of human life. For comparison sake, the bovine spongiform encephalopathy epidemic in the UK, the sporadic avian influenza virus cases, and the UK foot and mouth disease epidemic caused 10–13, 15–20 and 25–30 billion in economic losses, respectively.

The SARS-CoV has revealed a clear vulnerability in the global economy. As the world economy relies increasingly on manufacturing centered in Asia and elsewhere and the transport of those goods globally, pandemic outbreaks of disease have serious global consequences including the potential collapse of the Asian, European and US equity markets, interruptions of trade and travel, manufacturing stasis and decline and reduced availability of goods, foods and medicines. Given the current interconnection of the global marketplace and the speed of transcontinental travel, significant investments in basic and applied biomedical research are essential for maintaining the health of economies and the overall public health of the global community.

3. SARS-CoV: lessons in disease emergence

Emerging infectious diseases are clearly recognized as threats to human health and a significant public health problem. New emerging pathogens lists published prior to 2002 included HIV, influenza, the filoviruses, hantaviruses, and various arboviruses, recognizing that many emerging pathogens were zoonotic in origin. Despite the recognition that new emerging viruses are difficult if not impossible to predict, standardized lists were developed based primarily on epidemiologic trends over the past ~50 years. Another consistent theme was the near universal agreement that coronaviruses were not emerging pathogens, but rather were only associated with relatively benign upper respiratory tract infections in humans.

Because coronaviruses have relatively high mutation and RNA recombination rates and rapidly undergo cross species transmission events *in vitro* and *in vivo* (Baric *et al.*, 1999, 1997; Treshman *et al.*, 1996), we and others in the field have speculated that coronaviruses might be important emerging pathogens as early as 1996 (Baric *et al.*, 1996). Notably, several major coronavirus pandemics had been recorded over the past 25 years in economically important animal species. In 1978, porcine epidemic coronavirus (PEDV) emerged and has remained among the most important causes of severe gastroenteritis in swine in Europe and Asia. Sequence analysis suggested that PEDV likely evolved from human coronaviruses (Bridgen *et al.*, 1993; Duarte and Laude, 1994). In 1984, the less pathogenic porcine respiratory coronaviruses (PRCV) evolved from the highly virulent enteric strain, transmissible gastroenteritis virus (TGEV)

(Pensaert *et al.*, 1986). This was accomplished by either a single nucleotide mutation or deletion in the major surface glycoprotein gene, spike (Sanchez *et al.*, 1999; Wesley *et al.*, 1991). Currently, PRCV affords some level of cross protection against TGEV (van Nieuwstadt *et al.*, 1989; Wesley *et al.*, 1991), although more virulent forms of PRCV have recently emerged (Saif, 1999). A closely related arterivirus, the porcine respiratory and reproductive disease virus (PRRSV), emerged in the late 1980s in Canada and Europe, and is currently the most important swine pathogen worldwide, responsible for economic losses of \$200 million/year in the US alone (Blaha, 2000; Rossow, 1998). In 1992, a new respiratory pathogen was recognized that caused ‘shipping fever’ in cattle, a severe, oftentimes fatal, pneumonia. Sequence analysis suggests that “shipping fever” was caused by a respiratory bovine coronavirus (BCV-R), which likely evolved from an enteric bovine coronavirus by acquiring mutations in S and the replicase gene (Storz *et al.*, 2000). Concordant with this hypothesis, sequence comparisons have now indicated that host shifts, even between distant avian and mammalian species, are common events in coronavirus phylogeny (Rest and Mindell, 2003).

Coronaviruses have emerged rapidly by mutation or recombination of existing strains altering tissue tropisms and/or species specificity in animals and despite intensive management and vaccine efforts, these “new” coronaviruses are still major problems worldwide. The emergence of a new human coronavirus from zoonotic reservoirs is not surprising given the widespread activity noted in economically important animals. In reality, epidemiologic trends for many viral pathogens are based on relatively short (<60 years) timelines, with underreporting, of disease surveillance trends in human populations. The emergence of the SARS-CoV underscores the critical need for maintaining active basic science research not only on the medically relevant human pathogens, but also on virus families that are associated with limited or benign disease outcomes in humans. The limited investment in coronavirus research primarily in Europe and the US provided key investments necessary for the rapid identification and sequencing of the SARS-CoV genome, the prompt development of rapid PCR-based detection methods, the identification of the S gene as the likely candidate target for vaccine development, potential problems in vaccines and therapeutics development, and the development of reverse genetic systems; all within a few months of emergence.

4. SARS-CoV: a Chinese success story

The nation hardest hit by SARS was China and the SARS-CoV epidemic underscores the importance of local research infrastructure and governmental support in controlling new emerging diseases. In the end, the successful control of the SARS-CoV is a triumph for the Chinese basic, clinical and public health research infrastructure. The Chinese research community was among the first to successfully culture the virus, sequence the genome and develop rapid RT-PCR based detection strategies (Consortium, 2004). Despite an early belated response by governmental officials, aggressive quarantine and other public health measures demonstrated the effectiveness of classic

methods of tracking cases and their contacts as an effective means of curtailing disease spread. The Chinese research community rapidly demonstrated that SARS-CoV originated from animals and that the open markets were likely sources of future disease outbreaks (Guan et al., 2003). The closing of the animal markets has played a key role in tempering the scope and duration of SARS and will likely serve to temper the severity and scope of future outbreaks. Using epidemiology, molecular genetics and genome sequencing strategies, a detailed catalogue of the key genomic changes that contributed to disease emergence and spread have been identified and cataloged for future research (Consortium, 2004). Other key contributions include the development of animal models, vaccines and pathogenic studies. Perhaps most importantly, a local, well-funded basic scientific community is key not only for protecting global public health, but also in protecting the health of global economies.

5. Future directions and vulnerabilities

In many ways, we were lucky with SARS. Asymptomatic infections were rare and transmissibility was usually inefficient and typically occurred after disease onset, allowing for public health intervention strategies to control the outbreak (Peiris et al., 2004). SARS highlighted the importance of rapid reporting, infection control, tracing and quarantine of contacts in controlling new emerging diseases. However, if super spreader events were more common, the story may have been dramatically different. Importantly, the outbreak has underscored critical vulnerabilities in global public health intervention strategies. Highly pathogenic respiratory viruses are clearly capable of near instantaneous global transmission, and as such rapid approaches are needed to rapidly (a) detect, (b) sequence, and (c) develop and test candidate vaccines and therapeutics to protect human populations. Safe, universal, vaccine platforms are needed that can be tailored to new pathogens as they emerge, quickly tested for safety, and then strategically used to control new disease outbreaks in human populations. Basic investment into structure, replication, genetics and pathogenesis in each virus family is justified and among the first line of defense against future emerging threats. It is no longer sufficient that only the developed world be poised and able to protect itself from new emerging diseases threats. Rapid vaccination and therapeutic platforms are needed for the developing world as well, positioned to engage local research and public health communities in controlling local disease outbreaks at the source. If control measures can be implemented rapidly, then the scope, duration and suffering in epidemics will be minimized.

The number of laboratories engaged in SARS-CoV research was enormous at the height of the epidemic and many laboratories have made significant contributions to our current understanding of SARS epidemiology, replication, cross species transmission and pathogenesis. SARS highlighted the success of the basic research community and Public Health infrastructure as the principle determinants against new emerging diseases. This special issue of *Virus Research* reviews only a small subset of the enormous number of high quality scientific contributions made by the global research community.

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