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Outbreak of COVID-19 – an urgent need for good science to silence our fears?

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In the first two decades of the 21st century, we saw coronaviruses emerge across Asia, East and West. In 2002/3, severe acute respiratory syndrome (SARS) infected 238 and killed 33 in Singapore, including healthcare workers.[1] Ten years after that, the Middle East respiratory syndrome coronavirus (MERS or nCoV-2012) emerged in the Middle East and continues to appear with sporadic cases and localised outbreaks, including one in Korea.[2] Both these coronaviruses, thought to originate from bats, spilled over to civet cats and camels, respectively, and have caused significant human morbidity and mortality. While other human coronaviruses (HCoV) such as HCoV-NL63, HCoV-229E, HCoV-OC43 and HKU1 typically cause mild upper respiratory tract infections in immunocompetent patients, they can lead to pneumonia or cause exacerbations of chronic obstructive pulmonary disease or chronic heart failure, especially in older adults or the immunocompromised.[3] Animals are also not spared: swine acute diarrhoea syndrome coronavirus (i.e. SADS-CoV) and porcine epidemic diarrhoea virus (i.e. PEDV) have caused significant losses to the livestock industry in recent years.[3]

It is thus not unexpected that a novel coronavirus made its appearance at the end of 2019. These RNA viruses with crown-like spikes on its envelope have been predicted to be emerging pathogens with outbreak potential because of their inherent propensity for rapid mutation and recombination due to their large genomes. Towards the end of December 2019, the health commission of Wuhan in Hubei province, central China, declared an outbreak of clusters of pneumonia in people, many of whom had visited the local seafood wholesale market in Wuhan. Within days, genome sequencing had indicated that this disease (now officially called COVID-19, or coronavirus disease 2019) was caused by a novel coronavirus (named SARS CoV-2 by the International Committee on Taxonomy of Viruses) that was closely related to a SARS-like coronavirus in bats with an extraordinarily high (96%) identity.[4] This work was done at the Wuhan Institute of Virology, Chinese Academy of Sciences, China, which had done a lot of research on bat coronaviruses.[5] Infected patients mostly presented with fever, cough and dyspnoea within 7–14 days of exposure to the infection; few had upper respiratory signs such as rhinorrhoea or gastrointestinal symptoms such as diarrhoea. Around a quarter of those affected, mostly the elderly with comorbidities, required intensive care support for acute respiratory distress syndrome, multiorgan failure or co-infections.[6,7] The case fatality rate in the first published report of 99 cases from Wuhan was 11%,[7] while in contrast, the first comparable case series of patients with SARS from Hong Kong had a case fatality rate of only 2%. It is clearly too early to make comparisons between the two diseases in terms of case fatality. Differences in healthcare resources between the two cities may have had an impact on the outcomes.

Travel within the global village, compounded by the peak of the Lunar New Year season, rapidly introduced COVID-19 to other Chinese provinces as well as to the rest of the world. While the majority of these cases initially had a positive travel history to Wuhan, or contact with an individual with confirmed COVID-19, there was clear evidence of nosocomial spread in healthcare workers in Wuhan and elsewhere,[8] familial clustering outside Wuhan,[9] and local transmission in other countries in individuals who had not travelled to China. The reproductive number, R_0, was estimated to be 2.2 (95% confidence interval 1.4–3.9), which meant that every individual who was taken ill could potentially transmit the infection to two or three more people.[10] Following the exponential increase in cases, both in China and exported, and the death toll, the World Health Organization declared this an international public health emergency on 30 January 2020. As the epidemic spread beyond China, predictable events in other countries, such as the first local transmissions and the first fatality, followed weeks behind their first occurrence in China.

The indelible experiences of SARS and MERS, as well as concerns about avian and pandemic influenza, have fuelled pandemic preparedness efforts globally. Inevitably, imported cases of COVID-19 have reached the shores of Singapore and local transmission of COVID-19 has occurred. Fig. 1 illustrates a timeline of events since the outbreak began in China, globally and in Singapore. Singapore has adopted a proactive and multipronged approach, including broad entry restrictions for travellers from the entire mainland China; temperature screening at land, air and sea checkpoints; mandatory leave of absence for travellers within 14 days of their return from China; quarantine of contacts or those deemed to be in the incubation period; and public education on hand hygiene. The National Infection Prevention and Control Committee, National Public Health Laboratory, Ministry of Health Singapore and the brand-new, state-of-the-art National Centre for Infectious Diseases (NCID) provide the scientific expertise to support policy decisions. We

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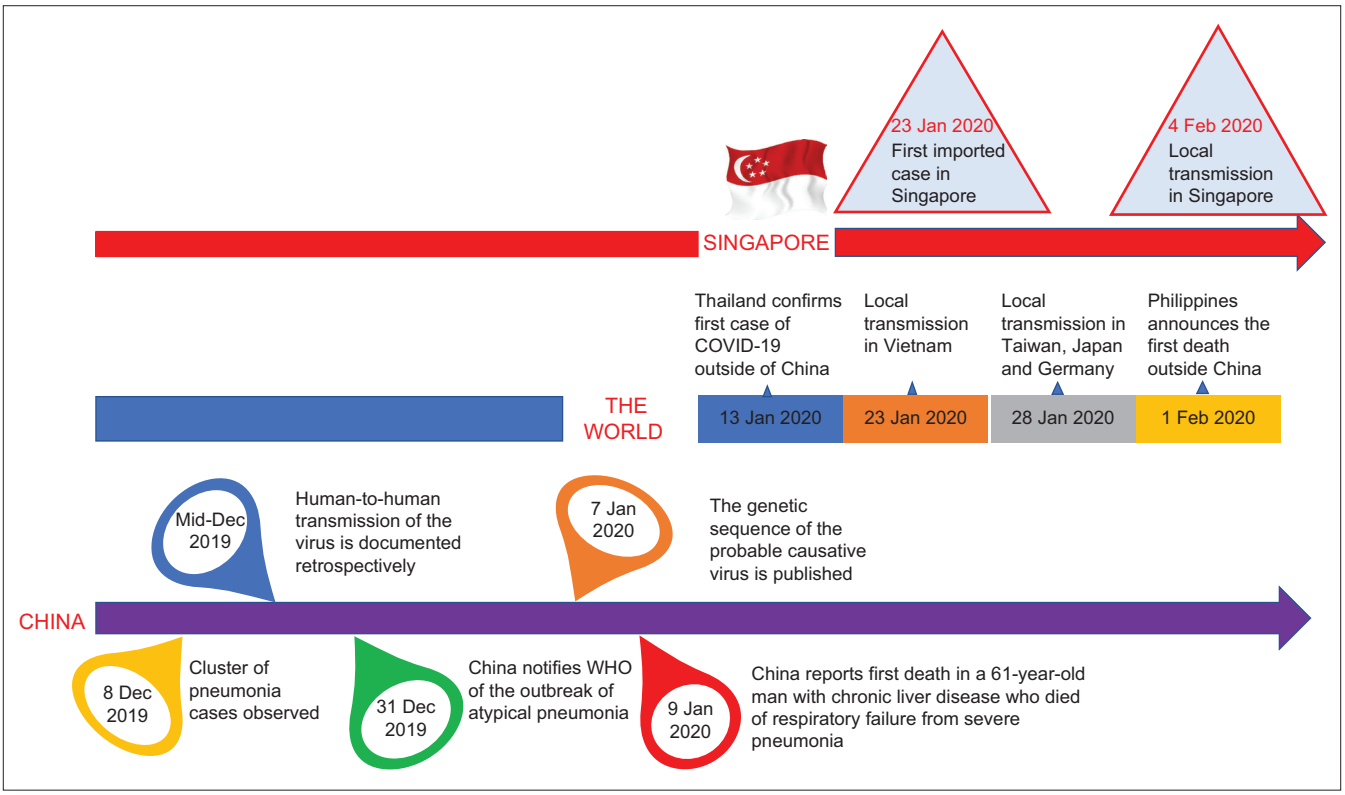

Fig. 1 Diagram shows the timeline of events in China, in Singapore and globally. COVID-19: coronavirus disease 2019; WHO: World Health Organization

have learnt some lessons from SARS, such as efficient contact tracing efforts and prompt use of isolation and quarantine; this time, we had a diagnostic test even before the first cases reached Singapore, unlike during the SARS outbreak where we had to wait for weeks.

There is, however, the danger of 'fighting the last war', as there do appear to be differences between this virus and SARS. Foremost among these is the probable transmission from individuals before the onset of symptoms or very early on with minimal symptoms, according to reports from China and Germany. This is unlike SARS, which was most infectious when patients were critically ill in hospital.[9,11] This makes COVID-19 much more difficult to control, as it is more similar to influenza than SARS. It also reduces the impact of temperature screening and highlights the critical need for accurate contact tracing starting from the day before the onset of symptoms (similar to chickenpox), as well as strict quarantine measures and monitoring, before more chains of contagion are established.

Although more publications are emerging that describe the clinical and virologic features of this outbreak, we still have many unanswered questions. We need to understand the source of this virus, especially identifying the putative animal host that would define it as a zoonosis. At the same time, case definitions may need constant refining as more is revealed about the epidemiologic characteristics and transmission dynamics. The relative contributions of 'super-spreaders' and pre-symptomatic spreaders also need to be better defined. Unlike during the SARS outbreak, Singapore now has a number of biosafety level 3 laboratories, including the one where scientists from Duke-NUS Medical School, SingHealth Duke-NUS Academic Medical Centre, Singapore General Hospital, NCID and Ministry of Health were able to culture COVID-19, making the virus available to researchers working on diagnostic tools and the development of effective vaccines and antiviral drugs. Outside Singapore, testing of antiviral agents such as ribavirin, remdesivir and lopinavir-ritonavir is already underway. In Singapore, we have also started treating some infected patients with lopinavir-ritonavir. Hopefully, this treatment will be validated in future clinical trials involving Singapore centres. While these are all positive steps, the epidemic of fear, perhaps partly fuelled by the drastic and unprecedented actions taken at the epicentre of the contagion, have led to high levels of anxiety among the public. The economic losses through disruption of travel and trade are already considerable, and the impact on a highly connected city such as Singapore is likely to be significant. The mobilisation of the community in Singapore during the SARS outbreak was a success; hopefully, that can be reproduced during this outbreak.

A global and concerted effort is required to break the chains of transmission of COVID-19. In a world with significant changes in climate, commerce and ecology as well as the proliferation of biomedical research in new settings, there is a constant risk of new diseases emerging. Despite this, the entire medical system seems to be built largely on commercial considerations. When SARS emerged, a lot of resources worldwide were devoted to vaccine and therapeutic development. The vast majority of these funds disappeared with the disease more than a decade ago. Scientists are now thawing old isolates from their freezers and rewriting grants that had been rejected repeatedly, before the attention of government agencies and funders worldwide is again lost when this epidemic inevitably comes to an end. We can only hope that with the better diagnostics, infrastructure and experience we

currently have in Singapore, the impact of this virus will not be as devastating for us locally and for the rest of the region, compared to where it first emerged. These outbreaks are constant reminders for us to remain vigilant and resilient, and to be advocates of the One Health approach to preserve life on this planet.

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