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Title:

The persistent threat of new respiratory tract infectious diseases to global health security

- The explosive outbreak of COVID-19 (Novel Coronavirus Disease 2019)

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Respiratory tract infections remain the top cause of morbidity and mortality from infectious diseases worldwide (1). The emergence of new pathogens which cause lethal human respiratory illnesses with pandemic potential (2,3) pose major challenges and rapidly focus the attention of global public health authorities and healthcare workers. Two zoonotic coronaviruses which cause lethal respiratory tract infections in humans feature on the WHO Blueprint list of priority pathogens for research and development (4) due to their pandemic potential, The Severe Acute Respiratory Syndrome (SARS-CoV) which was first identified in Guangdon province China (5) the Middle East Respiratory Syndrome (MERS-CoV) which was first identified in Jeddah, Saudi Arabia in 2012.

In January 2020, another novel zoonotic coronavirus that causes lethal human disease, SARS-CoV, was included on the WHO priority Blueprint list (4). This followed the appearance in December 2019 of a case cluster of patients with pneumonia of unknown origin in Wuhan, China (6,7,8). The Chinese Center for Disease Control and Prevention (China CDC) epidemiological investigations implicated the source as Wuhan's Huanan Seafood Wholesale Market (6). They took prompt action instituting public health measures including intensive surveillance, epidemiological investigations, and closure of the market on 1 Jan 2020. A novel coronavirus was identified from patients' samples using whole genome sequencing (8,9) and was provisionally named 2019-nCoV, now renamed as SARS-CoV-2 (10). The disease caused by SARS-CoV-2 is abbreviated as **COVID-19** (**CO**rona**VI**rus **D**isease-20**19**).

The World Health Organization International Health Regulations Emergency Committee declared COIVD-19 outbreak a Global emergency (11) since SARS-CoV has spread rapidly within and outside China at an alarming pace and has caused considerable consternation and panic among the national, regional and international public and political communities compounded by news media and social hype media hype (12) . A specific molecular test for SARS-CoV-2 was developed (13) and a flurry of investigations and research on COVID-19 outbreak rapidly defined the epidemiological, virological and clinical features and provided evidence of human-to-human transmission in community, household, and hospital settings (6,8-10,14-19). These have guided the development of numerous WHO guidelines and recommendation documents related to case definitions, reporting of cases, diagnosis, management, prevention and control guideline documents. (10) The rapid spread occurring within China despite a lock down of Wuhan, resulted in numerous chains of transmission

(6,10, 14-19), and spread of the virus was facilitated by national and international travel during the January New Year holiday period (20).

The appearance of novel zoonotic diseases is never without controversies (21,22,23). Reports of conspiracy theories for the source and sudden appearance of the virus have been negated by phylogenetic studies using sequences of SARS-CoV2-19 obtained from early cases (8,9) which indicate that the novel virus may have been introduced to human populations from the animal kingdom in November or December, 2019 (21). As with SARS-CoV (24) and MERS-CoV (25), defining the actual zoonotic source and mode of primary transmission of SARS-CoV-2 to humans remains an enigma, and requires further stud (23).

The clinical and virologic features of SARS-CoV-2 have been defined by several studies (6,10,14-19) and whilst there are similarities to SARS-CoV and MERS-CoV some differences have also been observed. COVID-19 appears replicates efficiently in the upper respiratory tract (14) and appears to cause less abrupt onset of symptoms, which are similar to conventional human coronaviruses that are a major cause of common colds and URTIs in the winter seasons. Furthermore, during the prodrome and early phase of disease, the upper respiratory tract appears to have large quantity of virus and may be responsible the rapid person to person spread. In SARS-CoV and MERS-CoV, whilst accurate data are unavailable highest viral loads were seen in seriously ill patients. This has implications on infection control measures. COVID-19 also has affinity for cells in the entire respiratory tract. As with SARS and MERS, data for COVID-19 available to date (14-19) indicates a spectrum of clinical manifestations occur, from asymptotic sub-clinical infection, or mild upper respiratory tract illness to non-life-threatening pneumonia to severe pneumonia progressing to acute respiratory distress syndrome (ARDS) requiting intensive care, mechanical ventilation and extracorporeal membrane oxygenation (ECMO). A study of 138 hospitalized patients with COVID-19 (Wang et al, 2020, the median age was 56 years (interquartile range, 42-68; range, 22-92 years) and 75 (54.3%) were men. Several studies (14-19) show that symptoms of COVID-19 patients are similar to MERS and SARS with fever (92-98%), dry cough (75-82%), fatigue (69-75%) and gastrointestinal symptoms (20-40%) were the most common clinical manifestations. A wide spectrum of clinical disease is being seen- from asymptomatic, sub clinical, mild and self-limiting disease, to severe disease and Acute Respiratory Distress Syndrome (ARDS) among older people or those with other comorbid diseases such as diabetes, chronic respiratory disease and hypertension, with men are more likely to die than women. Several of these

patients have negative rtPCR tests. Bilateral ground glass or patchy opacity are the most common signs of radiological finding and CT changes (26) have been included as a case definition of COVID-19 by China CDC.

Whilst COVID-19 appears from currently available data to have a low lower death rate (6), it has caused more deaths than SARS and MERS combined. The SARS outbreak in 2003 had rapidly spread from southern China in 2003 and infected more than 3000 people, killing 774 by 2004 before it ended. For Covid-19 outbreak, the China CDC recently reported epidemiological features of 44,672 COVID-19 cases across all of China (6) which showed the overall death rate at 2.3 %. In China's provinces the death is 2.9% compared with 0.4% in the rest of the country. At least 80% of the cases have been mild, with the sick and elderly most at risk. Worryingly 3,019 healthcare workers have been identified with COVID-19.

The WHO has and established a global surveillance system to collect information to describe and monitor COVID-19. Case classifications are based on WHO case definitions for COVID-19 (27). Active surveillance is taking place globally for possible infections in all countries using the WHO-recommended surveillance case definitions. Since its first discovery in December 2019, the COVID-19 epidemic has progressed relentlessly and there are no indications that the epidemic is slowing down (6, 28). As of 21st February 2020, there were 75,748 confirmed cases of COVID-19 reported to the WHO (28). Of these 74,675 were from China with 2121 deaths, and 1,073 cases from 26 countries outside China with 8 deaths. Continued intensive source control is ongoing at the epicentre in China with contact tracing and strict health facility infection prevention and control.

With ease of travel the world has become increasingly susceptible to outbreaks of new and reemerging infectious diseases that can spread quickly due to ease of transportation and rapid movement of people within regions and continents. The virus has spread beyond mainland China to countries around the globe and two cruise ships are now confirmed to have been affected. WHO has recommended that countries with frequent air travel exchange with Wuhan should take precautionary public health measures and undertake screening and infection control activities? The lock-down of Wuhan City seems to have slowed international spread of COVID-19 but many challenges remain before it can be brought under control (29).

A recent Conference (11th and 12th February 2020) held in Geneva hosted by WHO in Geneva delineated priorities for intensified research for development of point of care diagnostic tests, new vaccines, treatments, improved collaborations with the animal and environmental sectors, and community engagement. Whilst the world awaits the development of new vaccines, anti-SARS-CoV-2 specific drugs, antibody and/or other host-directed interventions (30,31), public health infection control measures remain prime importance in limiting human-to-human transmission, especially among close contacts and health care workers, and minimizing risk of international spread by identifying and isolating patients early. Although China had cancelled all mass gathering events at the start of the outbreak in Wuhan, mass gathering religious, sporting and other events continue to attract people from across all continents including China, increasing the risk of spread globally. In this edition of COPM, Petersen and colleagues (32) review recent literature on viral and bacterial infections diseases with special focus on the Hajj, the largest annually recurring religious pilgrimage in the world attracting 3 million people from 182 countries. Recurring mass gathering religious, sporting and other events attract people from across all continents increasing the risk of spread of aerosol transmissible respiratory tract infections, and for this year's events, event organizers should be on alert for both lethal coronaviruses, SARS-CoV-2 and MERS-CoV-2 (Petersen et al, 2020, COPM).

It may be that COVID-19 may follow the path of SARS and die out within the next 12 months or it will pan out to be like seasonal influenza or other respiratory tract viral illnesses, manifesting as self-limiting disease and severe disease among older people or those with comorbidities. It is thus critical that whilst COVID-19 requires intense attention currently, the current global focus and media hype on the novel COVID-19 outbreak should not detract the attention of physicians and health services from other respiratory tract infections which cause over 5 million deaths globally annually.

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