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Emergent human coronaviruses – History informs the future

1. Control of COVID-19 pandemic

This pandemic has caused immense health and economic disasters globally, with the attendant negative impacts on social activities. The WHO has received more than 62.2 million reports of this infection, with a fatality of 1.5 million (November 30, 2020) ([WHO situation report, 2020](#)). The principles and practice for control of infectious disease outbreaks in humans, animals or agriculture have been widely studied and much are reported in the literature. These include prompt identification, isolation, monitor, surveillance as well as virus-host pathogenesis and immune response studies to inform anti-infective and vaccine developments.

2. Prompt identification and public health measures

Prompt virus identification indeed is one of the successful hallmarks of this dramatic pandemic with the PCR and genomic/next generation sequence analysis providing the mainstay of diagnostics and molecular epidemiology (Z. Chen, 2021; JVM - March, Vol 289). These methods facilitated early and timely reports on identification and genotyping of this novel coronavirus (Lu et al., 2020; Zhu et al., 2020). For those diagnostic laboratories offering round-the-clock work, real-time/quantitative reverse transcription PCR test for the genomic SARS-CoV-2 RNA, results are generally available within 24 h, which facilitate prompt epidemiological tracing/monitor of contacts of individuals who were tested positive as well as public health and patient management. The use of specific molecular probes viz. FAM, Taqman, FRET with the qPCR or other nucleic acid amplification approaches e.g. loop-mediated isothermal amplification are widely reported in the literature. The enormous demands, globally, for PCR reagents have presented supply issues to laboratories which have prompted them to develop other PCR formats with SybrGreen dye, instead of probes with the RT PCR for SARS-CoV-2 RNA detection (Marianoel Pereira-Gomez et al. 2021: JVM - March, Vol 289).

Like typical serious respiratory disease outbreaks, the minimization of COVID-19 cases has been reasonably successful with strong encouragement of mask wearing (J. W-T. Tang 2021; JVM - March, Vol 289), social distancing, improved hygiene standards with public awareness and cooperation. Such practices are low costs and simple to implement. Indeed, these practices have already been encouraged more than a thousand years prior, perhaps not in official scientific reports then, but in biblical works (K.L. Hon et al. 2021; JVM - April, Vol 290).

Local transmissions (and aided by air travels prior to border restrictions) of SARS-CoV-2 have indeed accelerated the spread of this novel bat-associated virus in nearly all countries. However, other bat-

associated CoV infections viz. SARS-CoV-1, MERS and related bat CoVs have not all led to major local human-human transmissions (D. Smith 2021; JVM - March, Vol 289). The latter report may offer helpful perspectives on the complex range of bat-associated zoonotic viral infections.

3. Pathogenesis studies informing the road ahead

Unlike the current extensive literature on diagnostics, epidemiology and public health measures, further studies on the biology, pathogenesis and emergence of the more pathogenic CoVs viz. SARS-Cov-1, SARS-CoV-2, MERS are needed to fully understand each of these viruses (compared to the less pathogenic HKU1 and NL43 CoVs) with their different infection and transmission manifestations (Weiss, 2020). Indeed, post-SARS-CoV-1 epidemic (2003), there has been no report on this virus being detected and its classification as select agent (security sensitive, ([Department of Health - Australia, 2016](#))) may have discouraged research on pathogenesis studies, unlike the HIV/AIDS epidemic or the seasonal influenza. The lack of small animal models and requirement for laboratories with BSL3 and BSL4 biosafety facilities to study the more pathogenic CoV may limit the number of laboratories that can pursue this research (Munoz-Fontela et al., 2020). The biology, immunology, pathogenesis and transmission studies of these emergent CoVs in bats, as well as in other mammals and humans, are clearly important and helpful to advance disease understanding and control (Olival et al., 2020; Wang and Anderson, 2019). The large size of CoV genomic RNA (27–29 kb), their characteristic, nested subgenomic mRNAs produced during replication with high frequency of recombination (e.g. 25 % for the Mouse Hepatitis virus (Banner et al., 1990; Baric et al., 1990) have been suggested to facilitate genetic diversity with resultant emergent viruses (also see I. Davidson 2021; JVM - March, Vol 289). Vaccines and anti-infectives, together with prompt public health management and quarantine measures, would be needed to work in concert to control this pandemic. Currently, there are 212 SARS-CoV-2 candidate vaccines (48 in clinical trials and 164 preclinical evaluation) ranging from inactivated virus, protein subunits, non-replicating & replicating viral vectors and virus-like-particles to DNA and mRNA ([CoVid-19 candidate vaccines, 2020](#)). In addition to the aim of eliciting neutralizing antibodies and T cell responses (Burton and Topol, 2020), how do we determine which of these vaccines may unintentionally induce possible heightened disease or unwanted serious side effects in vaccinees who may be subsequently infected with the same or mutated strains of the virus (Haynes et al., 2020)? Host-pathogen and immune studies are important and necessary to fully inform development of safe and efficacious vaccines and anti-infectives.

<https://doi.org/10.1016/j.jviromet.2021.114095>

Available online 2 February 2021

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4. Emergent human pathogenic coronaviruses

A synopsis, in reverse chronological order, of significant human coronavirus infections that have caused large outbreaks or pandemics are included below. To date, there are seven human CoVs that cause mild to fatal respiratory infections with SARS-CoV-1, SARS-CoV-2 and MERS being three of the highly pathogenic serotypes. The remaining four CoVs viz. 229E, OC43, HKU1 and NL43 cause less severe respiratory tract infection or mainly common cold.

5. SARS-CoV-2 pandemic (2019)

An unusually high number of severe viral-like pneumonia cases were recognized in the city of Wuhan, Hubei Province, China (December 2019). The aetiology of this infection was shortly identified as a novel coronavirus and genotyped as a member of the beta-CoV group (Lu et al., 2020; Zhu et al., 2020). Within a few weeks, more than 2000 similar cases were reported, including evidence of human-human transmission in China, Germany, Japan, USA and Vietnam (WHO CoVid19 timeline, 2020). This led the WHO Director-General to declare the outbreak a public health emergency of international concern (January 30, 2020). The WHO named the new disease as COVID-19 (February 11, 2020) and the International Committee on Taxonomy of Viruses named the novel virus as "Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2)". The new virus shares 79 % genetic homology with the previous SARS-CoV-1 virus and about 50 % with MERS virus. The genetic similarity between this novel CoV and the previous SARS-CoV-1 suggest that SARS-CoV-2 has zoonotic origins from bats, although this awaits confirmation.

6. MERS (2012)

In April 2012, a similar severe respiratory syndrome emerged in Saudi Arabia. The causative agent was subsequently identified as the Middle East Respiratory Syndrome coronavirus (MERS). Since then, there has been 2468 laboratory-confirmed reports of this virus in 27 countries (with 12/27 in the Eastern Mediterranean) with a fatality ratio of 851/2468 (34.5 %); although this may be an overestimate due to unconfirmed number of asymptomatic cases (EMROPub-MERS, 2019). The MERS CoV is a member of the beta-CoV lineage C group. It has been reported that 55 % of MERS CoV infection is a result of direct contact with dromedary camels or its products, however, the remaining 45 % of cases have no known contacts with camels or patients. Expectedly, bats, as well as the camels, have been strongly implicated as potential reservoirs for MERS CoV (Banerjee et al., 2019; Conzade et al., 2018).

7. SARS-CoV-1 (2003)

On March 15, 2003 with the recognition of a mysterious and severe respiratory illness reported initially in China which then spread to a number of countries, the WHO named this infection as severe acute respiratory syndrome (SARS) and declared a worldwide health threat (SARS-CoV-1 Chronology, 2003) The causative agent was identified as a newly emerged coronavirus (Ksiazek et al., 2003; Peiris et al., 2003; Zhong et al., 2003) and subsequently genotyped as a member of the beta-CoV lineage B group. The first case of SARS was traced back to November 16, 2002 in Foshan City, Guangdong Province, China. A total of 8096 cases were reported in 27 countries with the more significant numbers in China 87.5 % (7083/8096), Taiwan 4.3 % (346), Canada 3.1 % (251) and Singapore 3% (238). The overall fatality case ratio was 9.6 % (774/8096). With the last locally transmitted case in Taiwan, the WHO declared that SARS was contained worldwide on July 5, 2003 (SARS-CoV-1 cases, 2015) Two years later, research groups in Australia led by L. Wang (Li et al., 2005; Wang et al., 2006) and by K.Y.Yuen in Hong Kong (Lau et al., 2005) reported their findings that horseshoe bats are the natural reservoirs of SARS coronavirus. The dramatic emergence

of SARS-CoV-1 and association with bats stimulated the hunt for other CoVs. This led to the identification of two new human CoVs viz. HCoV-HKU1, beta-CoV lineage A (Woo et al., 2005, 2006) and HCoV-NL63, alpha-CoV (van der Hoek et al., 2005). The HKU1 was reported to be associated with community-acquired pneumonia (2.4 %) and the NL63 with bronchiolitis and croup.

8. Human coronavirus prototypes 229E and OC43 (1960s)

Human coronaviruses (HCoVs - B814 and 229E strains) were first isolated during the mid-1960s from adults with signs and symptoms of common colds - upper respiratory tract infections. B814 was isolated with embryonic organ cultures in England (Tyrrell and Bynoe, 1965) and 229E in the US using tissue cultures (Hamre and Procknow, 1966). The HCoV 229E (and related OC38 and OC43 strains) was initially reported to cause mainly upper respiratory tract infection (McIntosh et al., 1970) but later studies reported 8–19 % incidence of lower respiratory tract infection in infants under 18 months of age (McIntosh et al., 1974). In a study with HCoV OC43, Kaye and colleagues showed antibody seroconversion by haemagglutination inhibition in 44/93 (47 %) in children with respiratory illness and 49/93 (53 %) without illness. The symptoms and signs of infection were pharyngitis, cough, coryza, fever and cervical adenitis (Kaye et al., 1971). The HCoV 229E and OC43 became the prototype human coronaviruses.

There are also emerging animal CoVs that cause major outbreaks that lead to extensive economic loss e.g. avian infectious bronchitis virus (AIB), bovine CoV, porcine transmissible gastroenteritis and porcine epidemic diarrhoea viruses amongst other CoVs. Indeed, there has been extensive research on animal CoVs including vaccine studies in particular with AIB (Franzo et al., 2019; OIE, 2018) that may inform different perspectives for vaccine development with human CoVs.

On behalf of the editorial board, we would like to express our sincere gratitude to all authors who have contributed manuscripts to this special issue on human coronaviruses during the current challenging period. Precise, high quality research, testing and development of virological methods are indispensable in controlling the current COVID19 pandemic, as well as other human, animal and plant emerging viral infections.

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