Severe coronavirus infection in animals and humans – lessons learnt to aid COVID-19

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Coronaviruses have been around for many years and were first discovered in the 1960s. Typically, these included viruses that contributed to the common cold (HCoV-229E) and a variety of animal and avian coronaviruses, such as infectious bronchitis virus (IBV). Common features included respiratory but also gastrointestinal illness. Strains of IBV have been shown to target the oviduct and others to cause severe kidney disease. These animal and avian coronaviruses can have high mortality rates and illustrate the difficulty of developing vaccines. Similar to the story with influenza virus, despite many decades of research, there is no pan-IBV vaccine that protects against all strains of this coronavirus. This in part is due to the continuous diversity in the virus spike glycoprotein, a major immunogenic target and hence good vaccine candidate.

During our PhDs on coronaviruses in the mid-1990s, these viruses were described as the backwater of virology with no identified coronaviruses that caused serious disease in humans. However, this changed in 2002/2003 with the advent of the severe acute respiratory syndrome coronavirus (SARS-CoV). Fast forward to 2012 and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) emerged in the Kingdom of Saudi Arabia. Despite rigorous control measures, isolated outbreaks are still ongoing, and illustrate the problems in controlling infectious diseases with a zoonotic reservoir. Cases of SARS-CoV-2 have overtaken the number of cases we saw with SARS-CoV, yet it took over a year to halt the spread of SARS-CoV. This suggests that controlling SARS-CoV-2 may take a similar period of time or longer.

There are no licenced antiviral therapies or vaccines for the treatment of coronavirus infection in humans. Several studies are ongoing evaluating antivirals for MERS-coronavirus infection. However, differences between animal models and humans may become apparent. For example, whilst the use of ribavirin and interferon therapy was effective in an animal model for MERS-coronavirus1, this was not reflected in the clinic2. The purpose of an antiviral is to reduce viral load, thus improving outcome and reducing clinical symptoms. However, one of the persistent threats with this approach is the emergence of resistance strains. Transiently targeting the function of host cellular proteins required for virus biology may hold one of the best promises for rapid antiviral development for SARS-CoV-2. Such approaches reduce the risk of resistance and potentially dramatically reduce development time. They may also be pan-corona as the virus family has a very conserved replication mechanism. However, a promising vaccine for MERS-CoV, based on ChAdOx1, is about to undergo Phase 1 clinical trials in humans in Saudi Arabia to assess safety and tolerability. A DNA vaccine has previously undergone successful Phase 1 evaluation3. These vehicles will almost certainly be appropriate for SARS-CoV-2.

Despite SARS-CoV, MERS-CoV and SARS-CoV-2 being in the same family, their properties appear subtly different, and understanding these will be key in the ultimate control of SARS-CoV-2 and treating COVID-19. For example, MERS-CoV has a case fatality rate (CFR) of approximately 30%, whereas for SARS-CoV this was around 10%. Of course, we also need to take into account potential asymptomatic infections, and such data is essential in modelling the risk posed by SARS-CoV-2. The importance of this was demonstrated in the 2013-2016 West African Ebola virus outbreak. Subsequent accurate assessment of asymptomatic patients resulted in a revision of the CFR at the epicentre of the outbreak4. This underscores the need for the development of robust serology assays and how they are used to assess the true picture of infection.

Co-morbidities are likely to play a role in severity and outcome. Apart from underlying health conditions, the presence of co-infections will certainty contribute5. For example, MERS-CoV has been found in combination with other respiratory pathogens including influenza virus, respiratory syncytial virus and Klebsiella pneumoniae. Metagenomic analysis of nasal aspirates using sequencing-based approaches will prove invaluable in establishing any correlation between co-infection and morbidity/mortality. The use of MinION sequencing, which provides a rapid, portable and within a day capability will be useful in defining bacterial co-infection and point to appropriate and specific antibiotic care packages in real time5.

Similar to SARS-CoV6, studying the host response in SARS-CoV-2 infections will be essential in providing information on infection and immunity, inflammation, and identifying biomarkers to define immune-correlates of protection, and/or severity. This will tie into both clinical case management and the development of targeted therapeutics. In large outbreak situations and limited resources, the use of prognostic biomarkers will be instrumental in the allocation appropriate medical care to the right patient, rather than a one size fits all strategy7.

Perhaps the best lesson we can learn in the control of these outbreaks is open, honest and accurate reporting of cases. This is critical in shutting down transmission chains and real time virus sequencing can support field based epidemiological investigations8 9. Lessons can be learnt at a governmental level by how both Saudi Arabia and Singapore respond to severe coronavirus cases, with information being immediately available.

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