EDITORIALS

Coronaviruses in animals and humans

Controlling outbreaks will require detailed knowledge of their biology and behaviour

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Coronaviruses have been around for many years and were first discovered in the 1960s. They include viruses contributing to the common cold (HCoV-229E) and a variety of animal and avian coronaviruses, such as infectious bronchitis virus (IBV), which infects poultry. Coronaviruses typically cause respiratory or gastrointestinal illness, but strains of IBV have been shown to target the oviduct in chickens, and others can cause severe kidney disease.

Animal and avian coronaviruses can have high mortality rates among infected animals and illustrate the difficulties in developing vaccines. Similar to influenza viruses, despite many decades of research there is no vaccine that protects against all strains of IBV coronavirus. This is due in part to the continuously shifting diversity in the virus spike glycoprotein, a major immunogenic target and hence a good vaccine candidate for animal and human infections.

During the mid-1990s these viruses were described as the backwater of virology, since none caused serious disease in humans. However, this changed in 2002-03 with the emergence of a coronavirus causing severe acute respiratory syndrome (SARS-CoV), and then in 2012 the Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia. The origin of both viruses was thought to be in bats, with civet cats and dromedary camels being the confirmed zoonotic reservoirs for SARS-CoV and MERS-CoV, respectively.

Covid-19

Despite rigorous control measures some isolated outbreaks of MERS-CoV are still occurring, illustrating the challenges of controlling an infectious disease with a zoonotic reservoir. Cases of SARS-CoV-2 infection (covid-19) 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 as long or even longer. The animal reservoir for SARS-CoV-2 has not been formally identified, but the genome sequence of the virus is most closely related to bat coronaviruses.

No licensed antiviral therapies or vaccines are available for treatment or prevention of coronavirus infection in humans. Several studies evaluating antivirals for MERS-CoV infection are under way. However, differences between animal models and humans may become apparent. For example, while the use of ribavirin and interferon therapy was effective against MERS-CoV[1] in an animal model, this did not translate into clinical effectiveness in humans.[2] 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 resistant strains. Targeting the host cellular proteins required for viral replication may hold more promise for rapid development of antivirals active against SARS-CoV-2. Such approaches reduce the risk of resistance and could substantially cut development time. They may also work across different coronaviruses, as the whole family shares a very similar but complex replication mechanism.

Prevention

Phase I human trials of a promising vaccine against MERS-CoV, based on ChAdOx1 (an adenovirus engineered to express genes encoding a protein/antigen) have occurred in the UK (clinical trial reference NCT03399578) and are about to start in Saudi Arabia (clinical trial reference NCT04170829). A DNA vaccine has already undergone successful phase I evaluation.[3] These approaches will almost certainly be appropriate for countermeasures against SARS-CoV-2.

Although SARS-CoV, MERS-CoV, and SARS-CoV-2 are in the same family, their properties appear subtly different, and understanding these differences will be key in controlling the spread of SARS-CoV-2 and in treating the clinical disease covid-19. For example, MERS-CoV has a case fatality rate of around 30%, while SARS-CoV is around 10%.

Data on asymptomatic infections are essential in modelling the risk posed by SARS-CoV-2. The importance of this became clear in the 2013-16 Ebola virus outbreak in west Africa, when later assessment of the incidence of asymptomatic infection

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resulted in a revision of the case fatality rate at the epicentre.[4] Accurate serology assays are essential to quantify the true incidence of infection, and this should be a research priority.

Comorbidities and coinfections

Comorbidities are likely to play a role in severity and outcome, including underlying health conditions and coinfections.[5] MERS-CoV has been found in combination with other respiratory pathogens including influenza viruses, respiratory syncytial virus, and *Klebsiella pneumoniae*. Genomic analysis of nasal aspirates to sequence any identified pathogens will be invaluable in establishing any correlation between coinfection and morbidity or mortality. The use of MinION sequencing (for example) provides rapid, portable identification of bacterial coinfection, to inform the use of antibiotics in real time.[5]

Studying the host response to SARS-CoV-2 will provide essential information on infection, immunity, and inflammation, and it will help identify biomarkers to define immune correlates of protection and disease severity.[6] This in turn can inform case management and the development of targeted treatments. In large outbreaks, and with limited resources, prognostic biomarkers can be instrumental in directing care resources according to clinical need.[7]

Perhaps the best hope for control of these outbreaks is open, honest, and accurate case reporting. Timely, comprehensive, and fully transparent reporting (including real time viral sequencing) is critical in shutting down transmission chains, targeting resources, and protecting populations.[8][9]

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