

Assessment of SARS-CoV-2 replication in the context of other respiratory viruses



There is a wide diversity of respiratory pathogens associated with human infection and disease. To better understand the emergence of zoonotic viruses and the threat that these viruses pose to human health, it is often valuable to investigate newly identified viruses not in isolation, but rather in comparison, and in concert, with other related viruses. When assessing a newly identified virus, studies using genetically related strains, or viruses that share a similar cellular tropism, can facilitate identification of commonalities in numerous properties, such as binding, infectivity, and replication capacities. Comparative studies that identify how novel pathogens interact with host cells in ways that might contribute to viral pathogenicity, transmissibility, or tropism, are as valuable.

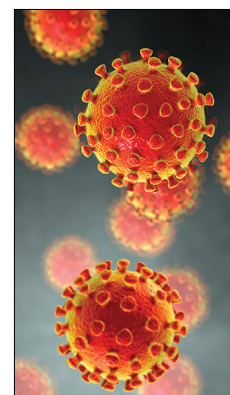
During the early months of 2020, many studies have been initiated to better characterise severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus that causes coronavirus disease 2019 (COVID-19). Some of the most valuable studies resulting from these research efforts are those that have evaluated this novel coronavirus alongside other contemporary coronaviruses associated with human infection (eg, severe acute respiratory syndrome coronavirus [SARS-CoV] and Middle East respiratory syndrome coronavirus [MERS-CoV]), and viruses from other families that have jumped species barriers to cause pandemics, or are considered to have pandemic potential (eg, the 2009 pandemic influenza H1N1 virus [H1N1pdm], or the highly pathogenic avian influenza H5N1 virus [H5N1]). Kenrie Hui and colleagues,¹ in *The Lancet Respiratory Medicine*, use exactly this approach, including all these viruses, to do a comparative analysis of virus tropism and induction of host responses in relevant human cell types and ex vivo explant cultures.

The well characterised infection model developed by this group has aided past assessments of novel and emerging viruses, including A(H7N9) influenza viruses associated with human infection in 2013² and A(H1N1) swine influenza viruses.³ Hui and colleagues¹ show that SARS-CoV-2 binds to and replicates efficiently in ex vivo cultures of human bronchus and the lung, identifying cell type-specific parallels in virus replication compared

with other transmissible viruses. Additionally, they show diminished induction of proinflammatory cytokines in human alveolar epithelial cells and peripheral blood monocyte-derived macrophages infected with SARS-CoV-2 and other coronaviruses compared with human and avian influenza viruses.

Considering the wide clinical presentation of COVID-19 in humans,⁴ inclusion of non-respiratory tissues in this study is especially valuable. Hui and colleagues show the **susceptibility of human conjunctival explant cultures to SARS-CoV-2 infection (with higher levels of virus replication than SARS-CoV),** a notable finding considering reports of ocular manifestations **in some patients with confirmed COVID-19 infection, and detection of viral RNA in ocular swabs.**⁵ These observations support current recommendations by the US Centers for Disease Control and Prevention (US CDC) for personal protective equipment worn by health-care personnel to include both respiratory and eye protection.⁶ Human colorectal carcinoma epithelial cells were also found to support virus replication with SARS-CoV-2, consistent with reports of detection of viral RNA in faecal samples and other tissues from the gastrointestinal tracts of patients with confirmed COVID-19, even in the absence of gastrointestinal symptoms.⁷

Most traditional risk assessments of emerging viruses study virus infection in previously uninfected cells, tissues, or serologically naive animal models, to investigate virus pathogenicity specifically attributable to the virus strain under evaluation. However, it is important to consider that humans are constantly exposed to a variety of viruses, with the potential for concurrent or subsequent infection with multiple pathogens. Interestingly, Hui and colleagues present preliminary data demonstrating that angiotensin-converting enzyme 2 (a receptor for SARS-CoV-2) mRNA was upregulated in human alveolar epithelial cells early after infection with human or avian influenza viruses. Although this finding will require additional evaluation, further study is warranted to better understand the dynamics of host susceptibility to SARS-CoV-2 in the context of infection with other pathogens, especially



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Lancet Respir Med 2020

Published Online

May 7, 2020

[https://doi.org/10.1016/S2213-2600\(20\)30227-7](https://doi.org/10.1016/S2213-2600(20)30227-7)

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[https://doi.org/10.1016/S2213-2600\(20\)30193-4](https://doi.org/10.1016/S2213-2600(20)30193-4)

because coinfection with SARS-CoV-2 and influenza A virus has been reported.⁸

With a diversity of viruses in zoonotic reservoirs potentially capable of overcoming host range restrictions and acquiring the ability to spread in an immunologically naive population, the possible emergence of a new pandemic virus in humans is always on the horizon. There is a need for studies like those done by Hui and colleagues, which are inclusive of diverse viruses previously associated with human pandemics, and viruses believed to have the potential to do so, that use a range of relevant respiratory and non-respiratory tissue and cell types that might support virus replication following multiple exposure routes. These laboratory studies provide crucial context for interpretation of what makes each virus unique and how best to develop medical countermeasures to improve human health.

I declare no competing interests. The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the US CDC or the Agency for Toxic Substances and Disease Registry.

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