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SARS-CoV-2 and zoonotic preparedness: unknown knowns?

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Emerging infectious diseases (EIDs) with pandemic potential are a major threat to global health security and the global economy. Prevention, preparedness and response to EIDs within hotspots for EIDs is considered a global public service. In December 2019, coronavirus disease 2019 (COVID-19) came under the spotlight; caused by a novel ssRNA coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapidity at which the virus spread worldwide has been remarkable and the global response to the pandemic unprecedented.

The rate of emergence of infectious diseases of zoonotic origin is increasing. Multiple new pathogens have emerged or re-emerged over the past few decades, many of viral origin, of which 75% are considered to have originated in animals.[1] Before SARS-CoV-2, globally, around 1 billion zoonotic infections occurred in humans each year of which around 0.1% resulted in death.[1] Prominent examples of EIDs include acquired immunodeficiency syndrome (AIDS), Ebola and Marburg hemorrhagic fevers, *Escherichia coli* O157 infection, Middle East respiratory syndrome (MERS), and severe acute respiratory syndrome (SARS).

The pandemic potential of coronaviruses (CoVs) is a major global public health concern. The SARS and MERS CoVs both jumped into humans from animals. The SARS (2003) and MERS (2012) outbreaks spread rapidly but were swiftly halted by intensive public health interventions (fast clinical diagnosis, isolation, contact tracing and partially effective treatment). In total, 8096 SARS cases and 774 deaths were reported (mostly in China) from SARS, but by 2004 SARS was no longer a public health problem. SARS-like viruses still persist in reservoir animal populations but there has been no reported spread to humans since the initial outbreak.

SARS-CoV-2 can spread before obvious symptoms develop and infection will continue to spread from infected to susceptible individuals in the population. Interventions, such as isolation of the infected, together with acquired immunity from exposure or vaccination and public health interventions are expected to bring the pandemic under control. SARS-CoV-2 will likely continue circulating within susceptible populations much like other common seasonal viruses, eg, influenza. H1N1, a new strain of flu that emerged in 2009, swiftly became a pandemic, but eventually became part of the normal seasonal flu architecture. SARS-CoV-2 will likely become another one of the 4 CoV strains that commonly infect humans every year.

CoVs are a broad and diverse group of viruses found across multiple animal and human hosts. While most CoVs exist in animals, SARS-CoV-2 is one of seven CoVs known to actively infect humans, all having likely derived from animal hosts.[2,3] The majority of CoV infections result in mild infection (eg, 229E) though MERS-CoV, SARS-CoV and SARS-CoV-2 may result in severe morbidity and mortality.

SARS-CoV and SARS-CoV-2, 79.6% identical at the nucleic acid level, belong to the Sarbecoviridae β-coronavirus group of SARS-like CoVs.[4] Bats are the likely ancestral host for SARS-CoV.[4] The closest known relative of SARS-CoV-2, RaTG13, with 96.2% nucleic acid identity, is a bat SARS-like CoV discovered in a *Rhinolophus affinnis* horseshoe bat in Yunnan in 2013. A closely related virus from horseshoe bats, RmYN02, is 93.3% identical, but shares higher homology across the ORF1ab region. This suggests SARS-CoV-2 may be

derived by recombination events from several closely related β-CoVs.[5] How bat ecology, relation to other intermediate hosts and spillover events, impact on CoV prevalence and/or how unique traits of bat metabolic and immune systems are implicated in viral maintenance and transmission, remain largely unknown.[6-9]

An intermediate species responsible for introduction of SARS-CoV-2 into humans has not been identified and remains unknown.[10] Several closely related Pangolin-CoVs, identified in confiscated Malayan pangolins in China, show up to 97.5% homology to the S1-portion of the SARS-CoV-2 Spike protein, but the overall homology of these viruses to SARS-CoV-2 is far lower than for the bat SARS-like CoVs.[11-13] That the pangolins exhibited signs of illness and respiratory distress suggests they are not a suitable reservoir species.[14] A recent study on wild or recently captured Malayan pangolins has shown no presence of CoVs.[15] Palm civets infected with SARS-CoV[16] similarly showed signs of illness and respiratory distress, suggestive as a role as an intermediate host but unlikely to be a natural reservoir.

A study in Africa indicated co-roosting behavior of pangolins and bats but how common this is, and whether this occurs in Asia, remains speculative.[17] An increasing prevalence of SARS-related CoVs was observed along the wildlife trade route in Vietnam, particularly in rodents[18] and clearly trade in wildlife is a risk factor for SARS-CoV transmission between species. Whether stressed pangolins can acquire CoVs along trade routes, from co-housing with other species or from humans is unknown.

Viral surveillance of bats in China is showing a far wider geographical distribution of SARS-related CoVs than previously thought[19] with closely related viruses identified in Yunnan, Guangxi, and Guangdong provinces, geographically distant from Wuhan, Hubei. This may be suggestive of human interference, potentially via wildlife trafficking in zoonotic progression of this virus. As more SARS-CoV-2-like sequences emerge, a greater understanding of potential risk will be revealed.

There remain more unknowns than known about the natural ecology of SARS-related CoVs and this only serves to highlight the importance of investigating a range of natural intermediate hosts that may have played a role in the progression of SARS-CoV-2, or its parental variant, into humans.[20] Further understanding of their biology, the interconnectedness of bats, domestic and wild animals, and their relations to humans, specific to zoonotic spillover, in each region is a necessity. Small mammals are largely under sampled; there is evidence of sex bias in the sampling of bats[17]; sampling has been skewed towards sampling of horseshoe bats due to the known high prevalence of viral genotypes in these populations; and few studies on potential intermediate hosts are published to date. The limited information on suitable intermediate hosts, their geographic distribution, levels of artificial interference from humans and prevalence of CoVs in other mammals in China and surrounding countries should all be prioritized in terms of future research needs. A deeper understanding of basic bat biology may additionally reveal unique factors influencing potential for spillover, not present in other animals.

The combination of identifying potential pathogens, potential hosts, minimizing zoonotic risk factors, effective containment of positive patients, effective control measures and

development of effective vaccines are all equally essential to increasing our preparedness and preventing future pandemics.

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