Anticipating a MERS-like coronavirus as a potential pandemic threat

The threat to global health security of yet another pandemic from a coronavirus remains likely because coronaviruses exhibit great genetic diversity, high rates of adaptive mutations, and readily cross species (figure A). While SARS-CoV and SARS-CoV-2 (subgenus sarbecoviruses) have been the recent focus of attention,[3] epidemic threats of the subgenus merbecoviruses, such as MERS-CoV, deserve serious consideration. MERS-CoV was first recognised as a cause of severe zoonotic disease in 2012, with dromedary camels being the proximate source of spillover. The virus continues to circulate in camels and cause disease in humans, sometimes associated with some human-to-human transmission.[4,5] As of March 21, 2024, there have been 2609 human cases of Middle East respiratory syndrome with 939 deaths reported to WHO since the virus was first recognised, most of which occurred in Saudi Arabia (36% case-fatality ratio).[6] Although MERS-CoV has not progressed to a large epidemic like SARS-CoV-2, its continued circulation in camels in the Middle East, Asia, and Africa, and ongoing zoonotic transmission are a reminder of its persistent threat to global health security.[2,5,7–9] MERS-CoV continues to evolve and the emergence of new lineages better adapted to human-to-human transmission is a cause for concern.[4,6–10] However, although MERS-CoV remains a source of major concern, more attention must be given to newly identified MERS-like coronaviruses isolated from bats, pangolins, and European hedgehogs, many with proven ability to infect human cells (figure B)[11,12] using the MERS-CoV host cell receptor, DPP4, or the SARS-CoV and SARS-CoV-2 receptor, ACE2. Just as SARS-CoV was, in essence, a warning signal for SARS-CoV-2, the potential pandemic threat posed by MERS-like coronaviruses needs to be recognised.
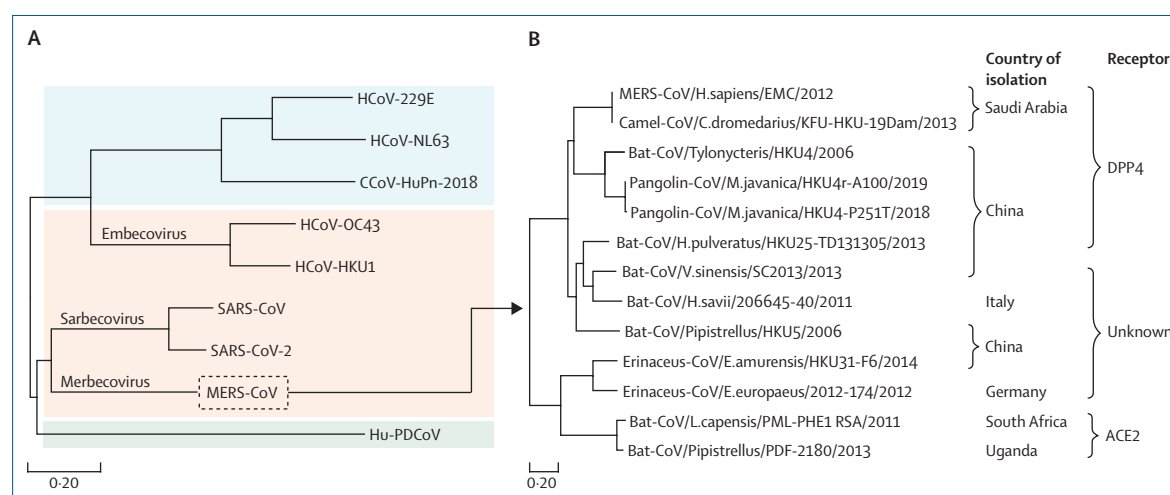

Figure: Phylogeny of merbecoviruses
(A) Location of merbecoviruses within the coronavirus family. Only the nine coronaviruses known to cause disease in humans are shown, with genera split by colour: *Alphacoronavirus* (blue), *Betacoronavirus* (pink), and *Deltacoronavirus* (green). Subgenera within *Betacoronavirus* are also shown. Four of these nine viruses cause the common cold (HCoV-229E, HcoV-NL63, HcoV-OC43, and HcoV-HKU1), while three cause severe pneumonia (SARS-CoV, SARS-CoV-2, and MERS-CoV). Two were recently identified in a few children with pneumonia (CCoV-HuPn-2018) or fever (Hu-PDCoV)[1,2] but whether these viruses will cause more widespread disease is not known. Phylogenetic analysis is based on whole-genome sequences from these disease-causing human coronaviruses. Sequences were retrieved from NCBI GenBank: SARS-CoV-2 (NC_045512.2), SARS-CoV (NC_004718.3), MERS-CoV (NC_019843.3), HCoV-OC43 (KU131570.1), HCoV-NL63 (JX504050.1), HCoV-229E (MT797634.1), HCoV-HKU1 (KF686346.1), CCoV-HuPn-2018 (MW591993.2), and Hu-PDCoV (MW685624.1). Sequences were aligned using MAFFT (version 7.511) and a maximum likelihood tree constructed using MEGA (version 11.0.13). (B) Phylogenetic analysis based on S₁ domain sequences from merbecovirus spike proteins. Sequences were retrieved from NCBI Protein: MERS-CoV/H.sapiens/EMC/2012 (YP_009047204.1), Camel-CoV/C.dromedarius/KFU-HKU-19Dam/2013 (AHX00721.1), Bat-CoV/Tylonycteris/HKU4/2006 (YP_001039953.1), Pangolin-CoV/M.javanica/HKU4r-A100/2019 (WFQ83171.1), Pangolin-CoV/M.javanica/HKU4-P251T/2018 (UJZ92542.1), Bat-CoV/H.pulveratus/HKU25-TD131305/2013 (ASL68953.1), Bat-CoV/V.sinensis/SC2013/2013 (AHY61337.1), Bat-CoV/H.savii/206645-40/2011 (AUM60014.1), Bat-CoV/Pipistrellus/HKU5/2006 (YP_001039962.1), Erinaceus-CoV/E.amurensis/HKU31-F6/2014 (QGA70692.1), Erinaceus-CoV/E.europaeus/2012-174/2012 (YP_009513010.1), Bat-CoV/L.capensis/PML-PHE1 RSA/2011 (AGY29650.2), and Bat-CoV/Pipistrellus/PDF-2180/2013 (YP_009361857.1). Sequences were aligned using the MUSCLE algorithm on MEGA and a maximum likelihood tree constructed on MEGA. Country of isolation and receptor usage are indicated. In both panels, the scale bar represents the number of nucleotide (A) or amino acid (B) substitutions per site. Panel B is adapted from figure 1B in Xiong and colleagues' article.[11]

And so, what does this mean in practice for public health priorities, research, and pandemic preparedness? First, continued surveillance of camelids, a potential intermediary species, and bats for merbecoviruses with potential to infect humans is crucial, with systematic risk assessment of such viruses that are identified. Key surveillance gaps include a paucity of MERS-like coronavirus sequence data and need for increased awareness and proactive surveillance for human infections in camel-herding regions. At present, although over 75% of MERS-CoV-infected dromedary camels are in Africa, and evidence of unsuspected zoonotic spillover exists,[13,14] there is insufficient awareness of, or surveillance for, zoonotic transmission.[3] Indeed, MERS-CoV is not on the priority list of zoonotic diseases for Africa.[15] This oversight is understandable, because zoonotic disease related to MERS-CoV has rarely been reported, in large part because it has not been actively sought.

Second, since merbecoviruses occur worldwide, increased attention and investments are needed for human, camel, and bat research to enable the rapid development of diagnostics, vaccines, and antivirals if a merbecovirus-mediated human disease is identified. Advancing preparedness and early warning systems for zoonotic coronaviruses requires improved quality of information flow at the science–policy–funder interface, enhanced early detection strategies, increased sequence analysis capacity, and rapid sharing of these data with prompt notification of human cases. It was only through extensive RNA sequencing that the global community learned the extent to which SARS-CoV-2 mutation and evasion of the immune response had occurred.

Third, improved understanding of why some coronaviruses robustly infect the human upper airway, facilitating transmission in pre-symptomatic and early symptomatic disease, whereas others (eg, SARS-CoV) that also use the ACE2 receptor do not will be important to identify merbecoviruses with pandemic potential. To our knowledge, detailed studies of differences in upper airway infection have not been done to date, and will be necessary to achieve this goal.

Awareness of the threat of MERS-CoV and MERS-like coronaviruses needs to be increased globally, beyond the Arabian Peninsula. Globally, there is little awareness of risk of Middle East respiratory syndrome beyond the Arabian Peninsula and there are no sequence data of MERS-CoV from central or south Asia, although the virus is enzootic in camels there. Despite being on the WHO Blueprint priority pathogen list,[16] global attention on MERS-CoV has decreased, overshadowed by the COVID-19 pandemic. The quadripartite Food and Agriculture Organization of the UN, UN Environment Programme, WHO, and World Organization for Animal Health global technical meeting on MERS-CoV and other emerging zoonotic coronaviruses, held in Riyadh, Saudi Arabia, in November, 2023,[17] involved a range of One Health stakeholders, including the newly formed Gulf Center for Disease Prevention and Control (Gulf CDC), and provided an opportunity for advancing research and development priority on coronaviruses. Predicting the future evolutionary trajectory of MERS-CoV, MERS-like coronaviruses, and other coronaviruses remains important for public health planning and will require substantial financial investments.

Since Saudi Arabia and Arabian Gulf countries have been grappling with Middle East respiratory syndrome for the past decade, they are in a strong position to take leadership of the portfolio of defined research and development priorities. The time is now right, not only for Middle Eastern governments, but also for the international community, to make available the required funding to refocus attention on strategic global public health goals and prioritise research activities needed in anticipation and preparedness to tackle future coronavirus pandemic threats. In ongoing discussions on the Pandemic Treaty, an important recommendation from the Independent Panel for Pandemic Preparedness and Response was the need to ensure that high-income countries and for-profit pharmaceutical companies avoid stockpiling vaccines and other products, and ensure equity of access and distribution—something that was not achieved during the COVID-19 pandemic.[18] Any collaborative efforts to develop new products and interventions for MERS-CoV or MERS-CoV-like coronaviruses should be based on obligations to provide equitable access.[19]

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