Preprint on Furin cleavage and European bat sequences

The search for the origin of the pandemic may have taken a new turn on the 17th of December, with the publication of a preprint by a group of scientists including Christian Drosten.1 Although on twitter Drosten called the paper “a modest contribution”, its implications are far from trivial. The fact that SARS like viruses are found in European bats is a well documented, but frequently overlooked element in the search for the origin of infectious SARS related coronaviruses.

To explain the relevance of the paper requires the addition of some technical details regarding viral ecology. Any host species that supports viral infections that could spill over and infect other species would be expected to show some distinct characteristics. They should contain a high diversity of viral sequences. They should harbour the virus continuously, if not in a single individual, then at least within social groups. Most critically, they should be naturally infected **beyond the geographic range of present social groups**.2 It is this last element that makes the emergence of the pandemic traceable to one single point source in China, whether it be a cave or a lab leak, rather problematic. Even if a single cave did contain a specific viral sequence, very similar sequences should be found throughout the range of the host species. Bat coronaviruses are not particularly fussy about which species they infect. At most, they can be specific to a genus. The caves in China contained not just populations of Chinese horseshoe bats. They also held greater horseshoe bats,3 which are familiar to anyone involved with conservation legislation in the UK.

Most RNA viruses, including coronaviruses, are maintained within a host population level by a high intrinsic error rate during replication.5 This results in high levels of antigenic variability which tends to cause waves of epidemic spread. Just such a pattern of spread, within bats, was found in a study in Germany.6

In short, viruses that spill over from wildlife such as bats into humans will be expected to be widespread and will also be expected to be highly variable. The main argument that has prevented researchers from looking for an origin for what became known as SARS-Cov-2 outside China has been finding the rather odd furin cleavage site. This is assumed to make the virus more likely to be able to infect humans, and other animals with the ACE2 receptor, although its precise role in enhancing transmission is not entirely clear.7 The ACE2 receptor is not found in bats in which SARS related viruses appear to cause acute self limiting infections8

This is where the preprint comes in. The group of researchers looked again at sequences they had taken from faecal matter collected from horseshoe bats in Italy, Bulgaria, Spain, and Slovenia back in 2008-2009. They noted that SARS-CoV and SARS-CoV-2 both belong to the same viral species,9 which they refer to as Severe acute respiratory syndrome–related coronavirus (SrC). Viral taxonomy is complex and the term “species” is used to provide a common vocabulary with which to refer to sequences which share characteristics, not necessarily with respect to virulence nor host specificity.10 They go on to state that the natural hosts of SrC are horseshoe bats, widely distributed in the Old World, and cite multiple studies that confirm this. The potential bombshell they found in their reanalysis was the existence of sequences that only differed from those coding for the furin cleavage site by one or two bases. To put this in context the code for the spike protein of the omicron variant is assumed to differ from that of the delta variant in at least 25 places.11

As RNA replication is intrinsically error prone it would appear to be highly likely that these bases could be accidentally replaced, so coding for the furin cleavage. This would not be of any advantage for the virus within a population of bats, but it could easily lead to a spillover into another species, including domestic cats which have a similar ACE2 receptor12 and frequently come into contact with young bats in maternal colonies. As endemic bat viruses including SrC must have been around for hundreds of years it would seem likely that this could have occurred at some point in Europe, not just in China.

The earliest PCR test was developed by members of the same research group and was based partly on European samples. When publishing the methodology they wrote “To show that the assays will detect other bat-associated SARS-related viruses, we tested bat-derived fecal samples available from13 and14 using the novel assays. All samples were successfully tested positive by the E gene assay. Detection of these relatively distant members of the SARS-related CoV clade suggests that all Asian viruses are likely to be detected.15” . There are also indications that SARS-CoV precursors existed in carnivores some time before the first SARS epidemic and have been transmitted from carnivores to humans again at least one additional time after the end of that epidemic.16 The assumption that all the viruses which are closely related to SARS must cause severe disease is questionable, particularly in light of the apparently mild nature of the Omicron variant. Conversely, other coronaviruses can be equally virulent. In 2003 an outbreak of what was eventually found to be OC43 was initially believed to be caused by SARS, when eight residents of a care home in Canada died, six with pneumonia.17

Drosten stated on Twitter that the paper was submitted months ago, but the journal cannot find adequate reviewers. This is strange, as the paper is short and well written The methodology appears sound, although it would need to be replicated independently in order to confirm the findings. The implications of this finding, if it can be confirmed, are profound. Journals could be rather reluctant to publish the article as it could be spun in the currently over heated political sphere as a finding that gets China off the hook. It could also be turned into a scare story by emphasising the risk of yet more novel coronaviruses emerging to cause pandemics in Europe. However, the most damaging suggestion for the currently accepted narrative could be that variants of what later became known as SARS-CoV-2 had already circulated in Europe prior to the pandemic, or that some variants emerged again around the time of the Wuhan outbreak. This would not be incompatible with either of the possible stories involving a Chinese origin. A lab leak or a wet market outbreak caused panic in Wuhan, but this does not rule out other sequences being detected throughout the world in the aftermath.

There is an urgent need for more studies to be conducted on samples taken from European, and non-European bats in order to fully understand the complexity of viral evolution that has unfortunately affected all our lives. The diversity of viruses that have not yet been sequenced far outweighs that of those that are known.19

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