Role Of Receptor Binding Domain Conformation on Spillover Potential of Cambodian Sarbecovirus

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In recent years, spillover of viruses from their animal reservoirs into humans has occurred with increasing frequency. In late 2019, the emergence of SARS-CoV-2 demonstrated for a third time in recent history the potential impact of coronavirus spillover. Since then, global scientific community has made unprecedented advances in the rapid development of treatments and vaccines. However, other sarbecoviruses with zoonotic potential are circulating in nature. The spillover potential and the effectiveness of current vaccines, antibodies and other treatments is unknown for these viruses. One such virus, RshTT200, collected in 2010 in Cambodia, may pose such a threat. Despite the capacity of the RshTT200 S glycoprotein to bind human ACE2, it fails to facilitate human ACE2 dependent entry. Through structural determination of the RshTT200 S, we identified regions of conservation and divergence that inform not only the likely effectiveness of vaccines and monoclonal antibody treatments but also inform on receptor usage both in the natural reservoir of these viruses, Rhinolophus bats but also within humans. Through an examination of receptor binding and cellular entry of non-replicating pseudovirus, we reveal the role of conformational accessibility of the RshTT200 receptor binding domain, RBD, in the spill over potential of this virus. Conformational accessibility of the RshTT200 RBD appears to be a major barrier to human infectivity potential of RshTT200. Together this structural and biophysical approach demonstrates multiple avenues by which RshTT200 may spread and evolve and identifies tools that could be used as a first response should this occur in the future.