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# Zoonotic coronavirus infections

**Coronaviruses have long been known as important pathogens in the veterinary field that can cause severe diseases in livestock and companion animals. In humans, however, coronaviruses have essentially been neglected for a long time since they were known to cause mainly mild respiratory symptoms (common cold), except for rare cases in elderly and immune-compromised people [1]. This changed dramatically when SARS emerged.**

In 2002, a new zoonotic coronavirus emerged causing severe acute respiratory syndrome (SARS) in humans [2]. Up to this date only two human coronaviruses were known, namely HCoV-229E and HCoV-OC43. But in the aftermath of the SARS-CoV outbreak two new human coronaviruses, HCoV-NL63 and HCoV-HKU1, were identified, and surprisingly they have already been for long time in the human population but have not been discovered until researchers specifically looked for coronaviruses. In 2012 the sixth human coronavirus, Middle East respiratory syndrome (MERS-)CoV, emerged in the Arabian Peninsula, and like SARS-CoV, MERS-CoV can cause severe respiratory disease in humans [3]. Interestingly, the phenomenon of emerging coronaviruses has also been observed in the veterinary field, for example in pigs with the recent emergence of the high pathogenic swine acute diarrhea syndrome (SADS-)CoV [4].

## Zoonotic transmission – SARS coronavirus

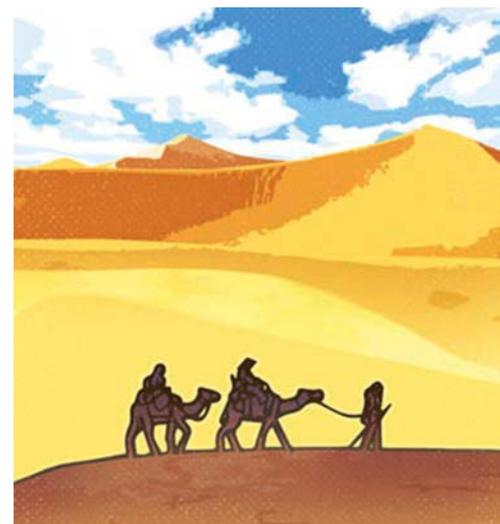
One hallmark of the two highly pathogenic viruses, SARS-CoV and MERS-CoV is that they arose through zoonotic transmissions. In the case of SARS-CoV, transmission to the human population was facilitated by an intermediate host, the civet cats from live animal markets in Guangdong, China in 2002. However, the actual viral res-

ervoir has later been traced back to horseshoe bats [1]. A sustained human-to-human transmission was the primary cause for the human epidemic, which led to a total of 8,098 infected people and 774 SARS-related deaths worldwide. However, immediate and effective public health measures contained the outbreak by 2003 and as of today the virus has been declared eradicated in the human population [5].

An intriguing characteristic of SARS-CoV is the condition under which the virus has been transmitted to a high number of people. Superspreading events occurred for example as an infected patient from Hong Kong caused virus transmission in several other countries while travelling. The possibility of superspreading a virus is most probably influenced by viral, host and environmental factors [6]. Epidemiologic investigation of this phenomenon is crucial in order to apply corresponding actions in case of future highly pathogenic coronavirus outbreaks. Furthermore, one of the major determinants of overcoming species-barriers is the defined interaction between the coronavirus spike protein and the host cell receptor. Angiotensin-converting enzyme 2 (ACE2) has been identified as SARS-CoV receptor, and for the emergence from civet-to-human towards human-to-human transmission, a mutation in the SARS-CoV spike (Lys479Asn) causing a higher affinity to ACE2 receptor is suspected to have played a major role in the animal-to-human jump. Such mechanisms underline the possibility of the emergence of novel zoonotic coronavirus in the future that could pose a threat to the human population [7].

## MERS coronavirus: from bats to camels to humans

MERS-CoV emerged in the Middle East in 2012 and has so far caused 2,428 infections with a fatality rate of approximately 35% of reported patients [8]. Dromedary camels are the reservoir and the primary source of transmission to humans. However, viruses related to MERS-CoV have been identified in bats and are speculated as the ancestral MERS-like coronaviruses. MERS-CoV spillover from dromedary camels to humans is still ongoing as the virus is circulating in this camelid population. In contrast to SARS-CoV, human-to-human transmission is still inefficient and has mainly been observed in hospital settings upon close contact. Nonetheless,



Camels have been identified as a reservoir and source of current (MERS-CoV) and past (Camel229E-CoV) coronavirus transmission to humans. The zoonotic transmission from camels to humans also explains the current geographical location of MERS-CoV.

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upon established human-to-human transmission the virus would be at a major risk of becoming epidemic.

### Bats: the major coronavirus reservoir with high virus diversity

It is speculated that many human and animal coronaviruses originate from bat coronaviruses. With regard to the six known human coronaviruses, a zoonotic origin from rodents has been speculated for HCoV-HKU1 and HCoV-OC43, whereas SARS-CoV, MERS-CoV, HCoV-NL63 and HCoV-229E are considered to have ancestral viruses in bats. Actually, a SARS-like coronavirus has been discovered from fecal samples in horseshoe bats (*Rhinolophus pearsoni*) [1]. This virus has 92% sequence identity with SARS-CoV Tor2, which was isolated during the epidemic [9]. Similarly, several strains genetically related to MERS-CoV have been discovered in a variety of bats, which supports the notion that bats are the ancestral reservoir host [10]. The emergence of novel coronavirus species that are capable of adapting to new hosts is the result of environmental, viral, and host factors that favor interspecies transmission. The increasing expansion of human and animal populations living in close proximity favors interspecies transmission events. Besides, coronaviruses display a high estimated mutation rate. This combined with a large RNA genome,

which allows for extra plasticity in accommodating and modifying genes without too much loss of fitness, facilitates the transmission of coronaviruses across species barriers [11].

### The emergence of common cold viruses – evolutionary parallels between coronaviruses?

HCoV-229E causes common cold in humans and has been circulating in the human population for a long time with only slight variations in its sequence [12]. Interestingly, variants of HCoV-229E have been found in bats and moreover in dromedary camels, proposing the ancestral emergence of HCoV-229E from these bat- and dromedary camel-associated viruses [13]. Genetic analyses revealed that several deletions in the genome occurred on the way from bats to camels to humans [14]. Camel-229E variants may have jumped to humans several hundred years ago, and contemporary camel-229E coronaviruses can still infect human cells through the same receptor. However, they lost the ability to replicate in the human airway epithelium [13]. Similarly, replication of HCoV-229E is not anymore possible in camelid cells, indicating that HCoV-229E is now well adapted to the human host. Considering MERS-CoV with an established reservoir in dromedary camels and ancestral relation to viruses in bats, the findings of bat- and

## Zoonotische Coronavirus-Infektionen

Das plötzliche Auftreten des SARS-Coronavirus im Jahr 2002 hat gezeigt, dass ein Coronavirus nicht nur im Tier, sondern auch im Menschen schwere Erkrankungen hervorrufen kann. Mit dem Auftreten des MERS-Coronavirus im Jahr 2012 hat sich dies nun bestätigt. Die evolutionären «Eltern» der SARS- und MERS-Coronaviren finden wir in Fledermäusen, die wohl das wichtigste Reservoir für viele Coronaviren darstellen. Wir finden dort sogar Viren, die den uns heute bekannten Schnupfenviren verwandt sind. Interessanterweise gibt es zwischen Schnupfenviren, zum Beispiel dem humanen Coronavirus 229E, und dem MERS-Coronavirus auffällige evolutionäre Parallelen. Beide Viren haben ihren Ursprung in Fledermäusen und sind über Dromedare auf den Menschen übergesprungen. Die zoonotische Übertragung des MERS-Coronavirus vom Kamel zum Menschen, die wir heute sehen, hat sich wohl vor mehreren hundert Jahren beim uns heute bekannten Schnupfenvirus HCoV-229E in ähnlicher Weise abgespielt.

camel-229E viruses suggest evolutionary parallels between a human common cold virus and the highly pathogenic MERS-CoV. If MERS-CoV could establish replication in the human host, we will maybe see adaptation to the new host along with loss of pathogenicity, and possibly a new common cold virus in the future.

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