Title:

Lethal Zoonotic Coronavirus Infections of Humans - Comparative Phylogenetics, Epidemiology, Transmission, and Clinical features of COVID-19, MERS and SARS

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Purpose of review

SARS-CoV2, the cause of COVID-19, emerged as a new zoonotic pathogen of humans at the end of 2019 and rapidly developed into a global pandemic. Over 106 million COVID-19 cases including 2.3 million deaths have been reported to the WHO as of February 9th 2021. This review examines the epidemiology, transmission, clinical features and phylogenetics of three lethal zoonotic coronavirus infections of humans: SARS-CoV1, SARS-CoV2 and MERS-COV.

Recent findings

Bats appear to be the common natural source of SARS-like CoV including SARS-CoV1 but their role in SARS-CoV2 and MERS-CoV remains unclear. Civet cats and dromedary camels are the intermediary animal sources for SARS-CoV1 and MERS-CoV infection respectively while that of SARS-CoV2 remains unclear. SARS-CoV2 viral loads peak early on day 2-4 of symptom onset and thus high transmission occurs in the community, and asymptomatic and pre-symptomatic transmission occurs commonly. Nosocomial outbreaks are hallmarks of SARS-CoV1 and MERS-CoV infections while these are less common in COVID-19. Several COVID-19 vaccines are now available.

Summary

Of the three lethal zoonotic coronavirus infections of humans, SARS-CoV2 has caused a devastating global pandemic with over a million deaths. The emergence of genetic variants, such as D614G, N501Y (variants 1 and 2), has led to an increase in transmissibility and raises concern about the possibility of re-infection and impaired vaccine response.Continued global surveillance is essential for both SARS-CoV2 and MERS-CoV, to monitor changing epidemiology due to viral variants.

Keywords: SARS-CoV, MERS-CoV, COVID-19, epidemiology, transmission.

Key points:

- Civet cats and dromedary camels are the intermediary animal sources for SARS-CoV1 and MERS-CoV infection respectively. The animal source of SARS-CoV2 remains unclear.
- Bats are the natural reservoirs of CoV1 but their role in SARS-CoV2 and MERS-CoV is less clear.
- SARS, MERS and COVID-19 present a spectrum of clinical manifestations from asymptomatic. mild, moderate to fulminant disease.
- Patients with co-morbidities who have MERS-CoV infection progress to respiratory failure much more rapidly and have high case fatality rates than those with SARS-CoV1 or SARS-COV2 infection.
- Nosocomial outbreaks are hallmarks of SARS-CoV1 and MERS-CoV infections while SARS-CoV2 has the highest community transmission potential due to peaking of viral load in the first week of illness.

Introduction

Coronaviruses (CoV) were first identified as human pathogens in the 1960s. Over the past two decades, three lethal zoonotic coronaviruses have jumped the species barrier and cause lethal disease in humans: SARS coronavirus (SARS-CoV) emerged in China in November 2002 and caused the severe acute respiratory syndrome (SARS) epidemic and disappeared by 2004; The Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) causing MERS, first identified in September 2012 in Jeddah, Saudi Arabia, 2012 and continues to cause sporadic and localized outbreaks; and SARS-CoV-2, the cause of the ongoing global COVID-19 pandemic. In this article, we review the phylogenetics, epidemiology, transmission, and comparative clinical features of SARS-CoV2, SARS-CoV1 and MERS-CoV.

Classification and phylogenetics

Coronaviruses (CoVs; order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*) are a group of enveloped, positive-sense, highly diverse, single-stranded, RNA viruses that may cause respiratory and diseases of other systems of varying severity in many animal species, including humans. There are four genera of CoVs including αCoV, βCoV, γCoV and δCoV [1]. Prior to the Severe acute respiratory syndrome (SARS) epidemic, the main coronaviruses causing respiratory tract infection in humans were HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. A novel group 2b βCoV (SARS-CoV1) was discovered in March 2003 as the causative agent responsible for SARS outbreaks [2]. SARS-CoV2 emerged at the end of 2019 in Wuhan, China [3] and led to a pandemic since March 2020. SARS-CoV1 and SARS-CoV2 and Middle East

Respiratory Syndrome coronavirus (MERS-CoV) are βCoV. SARS-CoV1 and SARS-CoV2 belong to lineage B while MERS-CoV belongs to lineage C (**Figure 1**) [4].

COVID-19

Epidemiology

On 31 Dec 2019, unusual cases of pneumonia in Wuhan, China were reported to the World Health Organization (WHO) and the outbreak was associated with a seafood market where game meat was also sold. A novel coronavirus, later named as SARS-CoV2, was identified as the cause of this outbreak on 7 Jan 2020. There was 79.6% similarity of SARS-CoV2 in genetic sequence to SARS-CoV1 and 96% similarity at the whole genome level to a bat CoV [5]. SARS-CoV-2 appears to be a mutated version of bat CoV-RaTG13, detected and isolated in bats from the species *Rhinolophus affinis* in Yunnan Province in China, between 2015 and 2017 [5,6]. Lu et al.[7] analyzed the genome from nine patients (eight of whom had visited the Huanan seafood market in Wuhan) and showed that SARS-CoV-2 was more related to two SARS-like bat CoV from Zhoushan in eastern China: bat-SL-CoVZC45 (with 87.99% identity) and bat-SL-CoVZXC21 (with 87.23% identity), and more distant from SARS-CoV (about 79%) and MERS-CoV (50%) The data suggest that bat SARS-like CoVs and human SARS-CoV-2 might share the same ancestor [8]. Pangolins were implicated as a potential intermediary source but there was only 91.02% similarity between pangolin-CoV and SARS-CoV-2 at the whole-genome level [9]. Minks were the first farm animals to experience COVID-19 outbreaks in Europe and appear to be a highly susceptible species to SARS-CoV-2 [10]. Therefore, it is plausible that the widespread infection on the mink farms is due to human-to-animal transmission. Nonetheless, evidence of mink-to-human transmission is

limited to one worker, according to the preliminary sequencing data [10]. While dogs and cats can be infected, it does not necessarily mean that they are potential reservoirs of the original virus and most of these animals had mild to no symptoms[10,11].

Despite lockdown of Wuhan city on 23 Jan 2020, the outbreak quickly spread throughout China and many other countries by travelers from Wuhan. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020 and the WHO announced a name on 11 Feb 2020 for the new coronavirus disease as COVID-19. On 11 March 2020, the WHO announced the extent and evolution of the global outbreak of COVID-19 as reaching a pandemic [12].

As of 9th February 2021, more than 106 million cases of COVID-19 have been confirmed worldwide with over 2.3 million deaths [13]. Common presenting symptoms of COVID-19 include fever (44% on admission and then increased to 89% during hospitalization), cough mainly non-productive (67.8%) while diarrhoea is uncommon (3.8%). The median incubation period is 4 days (interquartile range, 2 to 7). Absence of fever in a high proportion of patients makes it difficult to detect these cases in the community in the early stage of infection [14].

According to the WHO, people aged ≥60 years, and those with underlying medical comorbidity (such as hypertension, cardiac and pulmonary problems, diabetes mellitus, obesity or cancer) are at higher risk of developing serious illness from COVID-19 [15]. In the USA, the prevalence of reported severe outcomes increased with age; the percentages of hospitalization, intensive care admissions and deaths were highest among persons aged ≥70 years, regardless of underlying conditions, and lowest among those aged ≤19 years [16]. Age is an independent risk factor for severe illness, while the risk in older adults is also partly related to the increased likelihood that older adults have other

underlying medical conditions [17].

Transmission

Human to human transmission has been documented in the Wuhan seafood market outbreak [3]. There is evidence that patients in the pre-symptomatic stage and those with mild disease may transmit infection to others [18]. At least 50% of community transmission may be related to asymptomatic infection [19]. Laxminarayan et al have shown that 5% of infected individuals account for spreading of 80% of cases [20]. Transplacental transmission of SARS-CoV2 infection has been documented [21].

Viral kinetic studies have shown that the viral load peaks on day 2 to 3 of the patient's illness [22] and this explains the high potential of SARS-CoV2 in causing community transmission among close contacts. Serology response starts on day 7 of illness while PCR positivity in deep throat saliva could last for at least 3 weeks in one third of patients [23].

There have been increasing reports of COVID-19 outbreaks in long-term care facilities (LTCF) from countries in Europe and in the UK. High community prevalence of COVID-19 increases the risk of importation of the virus to institutions, possibly through asymptomatic visitors and staff with COVID-19. With the increased vulnerability of LTCF residents, COVID-19 outbreaks in these settings could have devastating effects. Increased morbidity and mortality have been reported in LTCF even with implementation of specific control measures in these settings. The overall risk related to COVID-19 infection is assessed as being very high [24]. Short range airborne transmission is possible in the presence of poor environmental ventilation [25].

The emergence of genetic mutants such as D614G, N501Y and the related South African (501Y.V2), Brazilian (B.1.1.28: K417N/E484K/N501Y) and UK (VOC-202012/01)

variants has led to an increase in transmissibility in the community without increase in severity (**Figure 1**) [26]. How wide these new variants have spread and how they may affect existing treatments and vaccines remain to be defined.

SARS

Epidemiology

SARS-CoV1 first emerged in Guangdong in the southern part of China in November 2002 before spreading to Singapore, Canada, Vietnam and other countries by travelers through Hong Kong (HK) in February and March 2003 [27,28]. In November 2002, there was an unusual outbreak of "atypical pneumonia" in Foshan, Guangdong Province in China, with a very high rate of nosocomial transmission to healthcare workers (HCWs) [29,30]. A retrospective study of 55 patients hospitalized with "atypical pneumonia" in Guangzhou between January and February 2003 revealed positive SARS-CoV1 in their nasopharyngeal aspirates (NPA) while 48 (87%) patients had positive antibody to SARS-CoV1 in their convalescent sera. Genetic analysis subsequently showed that the SARS-CoV1 isolates from Guangzhou shared the same origin with those in other countries, with a phylogenetic pathway that matched the spread of SARS-CoV1 to other parts of the world [31].

In March 2003, a novel CoV was confirmed as the causative agent for SARS, and recently referred to as SARS-CoV1. A retrospective serologic survey suggested that cross-species transmission of SARS-CoV1 or its variants from animal species to humans might have occurred frequently in the wet market where a high sero-prevalence of 16.7% was detected among asymptomatic animal handlers [32]. It was once thought that masked palm civets might have been responsible for transmission of SARS-CoV1 to humans

following detection of a close variant of SARS-CoV1 in 2003 from palm civets in Dongmen market, Shenzhen [33]. During the small-scale SARS-CoV1 infection outbreaks in late 2003 and early 2004 in China, three of the four patients had direct or indirect contact with palm civets [34,35]. However, viral genomic sequence analysis revealed that the SARS-CoV-like virus had not been present among masked civets in markets for that long. CoVs highly similar to SARS-CoV1 were isolated in horseshoe bats in 2005 [36,37]. These bat SARS-like CoVs shared 88-92% sequence homology with human or civet isolates and the data suggest that bats could be a natural reservoir of a close ancestor of SARS-CoV1 [38].

A 64-year old nephrologist who came from southern China to HK on 21 Feb 2003 was the index case causing subsequent outbreaks of SARS-CoV infection in HK, Singapore and Toronto [27,28,39,40]. Sixteen hotel guests/visitors were infected by the renal physician while staying or visiting friends on the same floor of the hotel M, where the physician had briefly stayed. Through international air travel, these visitors spread the infection to 29 countries/regions with a total of 8098 cases and a mortality rate of 774 (9.6%) by the end of the epidemic in July 2003 [41].

Transmission

SARS-CoV1 appears to have spread by close person-to-person contact via droplet transmission or contact with fomite [42]. Super-spreading event was a hallmark of SARS-CoV1 infection, as reflected by the nosocomial outbreak at a major teaching hospital in HK where 138 subjects (many being HCWs and previously healthy) were infected within a fortnight following exposure to one patient (a visitor of Hotel M), who was hospitalized with community acquired pneumonia to a general medical ward [27,43]. This super-spreading event was likely caused by several factors including the use of a jet

nebulizer for delivering bronchodilator to the index case, overcrowding, and poor ventilation in the hospital ward [27,43]. In addition, the temporal-spatial spread of SARS-CoV1 among inpatients in the index medical ward of the hospital in HK was consistent with airborne transmission [44].

In addition, SARS-CoV1 might have spread by opportunistic airborne transmission in a major community outbreak involving over 300 residents in a private residential complex, Amoy Gardens, in HK [45,46]. Drying up of 'U-shaped' bathroom floor drains and backflow of contaminated sewage (from a SARS-CoV1 patient with renal failure and diarrhoea) related to negative pressure generated by the toilet exhaust fans might have created infectious aerosols that moved upward through the warm airshaft of the building. Based on analysis of the distribution of all confirmed cases, airborne spread was the most likely explanation in the Amoy Gardens outbreak and the SARS-CoV1 could have spread over 200 meters to nearby residential complexes [47]. Air samples obtained from a hospital room in Toronto occupied by a SARS patient and swab samples taken from frequently touched surfaces in rooms and in a nurses' station in Toronto were positive by PCR testing [48]. These data suggest the possibility of airborne transmission and stress the importance of taking appropriate respiratory protection apart from implementing strict surface hygiene practices.

Asymptomatic SARS-CoV1 infection appears uncommon as a meta-analysis has shown overall sero-prevalence rates of 0.1% for the general population and 0.23% for HCWs although the true incidence of asymptomatic infection remains unknown [49]. A case control study involving 124 medical wards in 26 hospitals in HK and Guangzhou has identified six independent factors of super-spreading nosocomial outbreaks of SARS-CoV1 infection: performance of resuscitation, minimum distance between beds < 1m,

staff working while experience symptoms, SARS-CoV1 patients requiring oxygen therapy or non-invasive ventilation (NIV) whereas availability of washing or changing facilities for staff was protective (Table 1)[45]. A systematic review has shown that 4 aerosol-generating procedures would increase the risk of nosocomial SARS-CoV1 transmission to HCWs including tracheal intubation, NIV, tracheotomy, and manual ventilation before intubation (**Table 2**)[46]. Thus it is important for HCWs to adopt airborne precaution measures before carrying out aerosol-generating procedures.

MERS

Epidemiology

MERS-CoV was first identified in September 2012 when a novel βCoV was isolated from a male patient who had died of severe pneumonia and multi-organ failure in Saudi Arabia in June 2012 [52]. MERS-CoV infection has spread to 27 countries since its discovery in 2012. Globally, from September 2012 to September 2019 2016, WHO has been informed of 2468 laboratory-confirmed cases of infection with MERS-CoV, with at least 851 deaths [53].

Although the natural reservoir of MERS-CoV is still unclear, dromedary camels are an important natural host for the diversification and maintenance of MERS-CoV and appear to be the major source of zoonotic human infection [54]. The virus has been isolated from dromedary camels in the Arabian Peninsula and across North, East, West and Central Africa, but is not found in dromedary camels in other countries such as Kazakhstan [55] or in Bactrian camels in Mongolia [56]. However, only a minority of reported MERS human cases have reported direct camel exposure [57].

Transmission

While MERS-CoV was first described in September 2012 [52], a retrospective study of a cluster of hospital cases dated back to April 2012 in Jordan by RTPCR and serology confirmed MERS-CoV as the etiology of the outbreak which involved at least 10 HCWs [58]. The epidemiology of MERS-CoV is characterised by sporadic zoonotic transmission events, sometimes followed by nosocomial outbreaks within healthcare settings due to failure in infection control and prevention measures. Saudi Arabia has the largest MERS-CoV case load, followed by South Korea as the country with the highest case load outside the Arabic Peninsula [53].

The risk factors for primary MERS-CoV infection were examined in a case–control study of thirty primary MERS-CoV cases reported from March to November 2014 in Saudi Arabia, with two to four controls matched by age, sex and neighbourhood for each case patient [59]. The investigators demonstrated by multivariate analyses that direct dromedary exposure in the two weeks before illness onset was strongly associated with MERS-CoV illness (adjusted OR 7.45, 95% CI 1.57–35.28), along with having diabetes mellitus (adjusted OR 6.99, 95% CI 1.89–25.86) or heart disease (adjusted OR 6.87, 95% CI 1.81–25.99) and current tobacco smoking (adjusted OR 6.84, 95% CI 1.68–27.94) [59]. The risk for secondary transmission from patients to household contacts was estimated at about 4% [60]. Risk factors for household transmission included sleeping in an index patient's room and touching respiratory secretions from an index patient whereas casual contact and simple proximity were not associated with transmission [61] (Table 3).

In a cross-sectional sero-surveillance study of 10,009 healthy individuals in Saudi Arabia, 0.15% had evidence of positive MERS-CoV serology, suggesting that the number of mild or asymptomatic infections far exceeds those that are recognized [62]. Sero-positivity

was more common in males than in females, in central than in coastal provinces, and in camel shepherds (2.3%) and slaughterhouse workers (3.6%) than in others [62].

Nosocomial transmission is a hallmark of MERS-CoV infection. Super-spreading events of MERS-CoV infection were reported in Jordan [58], Al Hasa [63], Jeddah [64], Abu Dhabi [65] while the major outbreak in South Korea in 2015 was due to several super-spreading events in the hospital settings [66]. Failure in infection control and prevention measures in healthcare facilities (HCFs) resulted in large numbers of secondary cases of MERS-CoV infection involving HCWs, existing patients, and visitors in Saudi Arabia [63,64] and several other countries over the past few years [58,65,66]. Common predisposing factors include exposure to contaminated and overcrowded HCFs, poor compliance with appropriate personal protection equipment (PPE) when assessing patients with febrile respiratory illness, application of potentially AGPs (resuscitation, CPAP, nebulized medications), and lack of proper isolation room facilities [58,63-67]. The customs of patients seeking care at different HCFs ("doctor shopping") and having friends and family members to stay with patients as caregivers at already overcrowded HCFs were unique factors in South Korea [68].

Cases specifically reported as "asymptomatic" or "mild disease" in Saudi Arabia occurred only among secondary cases [63,64] while most (90%) of index or sporadic cases had severe disease [63].

Summary/Conclusions:

Bats appear to be the common natural source of SARS-CoV1 while more research is needed to examine their role in SARS-CoV2 and MERS-CoV. The sale and consumption

of the intermediary source of SARS-CoV1 (civet cats) have been banned in China since 2003 and the transmission chain was cut.

In the Middle East, the intermediary reservoir (camels) is still widely available and there is sporadic spill-over infection from camels to humans through close contact while nosocomial transmission has become less frequent due to improvement in hospital infection control and prevention measures in recent years.

SARS-CoV-2 shows distinct transmission dynamics - being uniquely infectious in the pre-symptomatic and asymptomatic stages with high viral load peaking in the first week of illness and so the pattern of spread is different from SARS-CoV1 and MERS-CoV because of these differing patterns of host-virus interactions. Peaking of viral loads of SARS-CoV2 on day 2-4 of symptom onset leads to high transmission potential in the community[22]. Asymptomatic and pre-symptomatic transmission occurs commonly in COVID-19[18,19].

Nosocomial outbreaks are hallmarks of SARS-CoV1 [27-30] and MERS-CoV infections [58,63-66] while these are less common in COVID-19. Civet cats [32,33]and dromedary camels [59]are the intermediary animal sources for SARS-CoV1 and MERS-CoV infection respectively while that of SARS-CoV2 remains unclear (Table 4).

The emergence of genetic variants, such as D614G, N501Y variants 1 and 2 [26], has led to an increase in transmissibility without increase in individual's severity and raised concern about the possibility of re-infection and impaired vaccine response. While COVID-19 vaccination programmes have commenced in many countries, continual surveillance for viral mutations is essential to monitor changing epidemiology due to viral variants and other factors.

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- * of special interest
- *** of outstanding interest*

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Figure legend

Figure 1. A maximum likelihood tree of the full genomes of the 7 known human coronaviruses, including SARS-CoV1, SARS-CoV2 (including South African 501Y.V2, Brazilian B.1.1.28(K417N/E484K/N501Y) and UK VOC-202012/01 variants), MERS-CoV and seasonal coronaviruses 229E, OC43, NL63, HKU1. Sequences were aligned using MAFFT (https://www.ebi.ac.uk/Tools/msa/mafft/) and manually edited using BioEdit v7.2.5. Phylogenetic tree construction was performed using FastTree v2.1.11 and displayed using FigTree v1.4.4. Shimodaira-Hasegawa-like local values (as implemented in FastTree) are shown as branch supports.

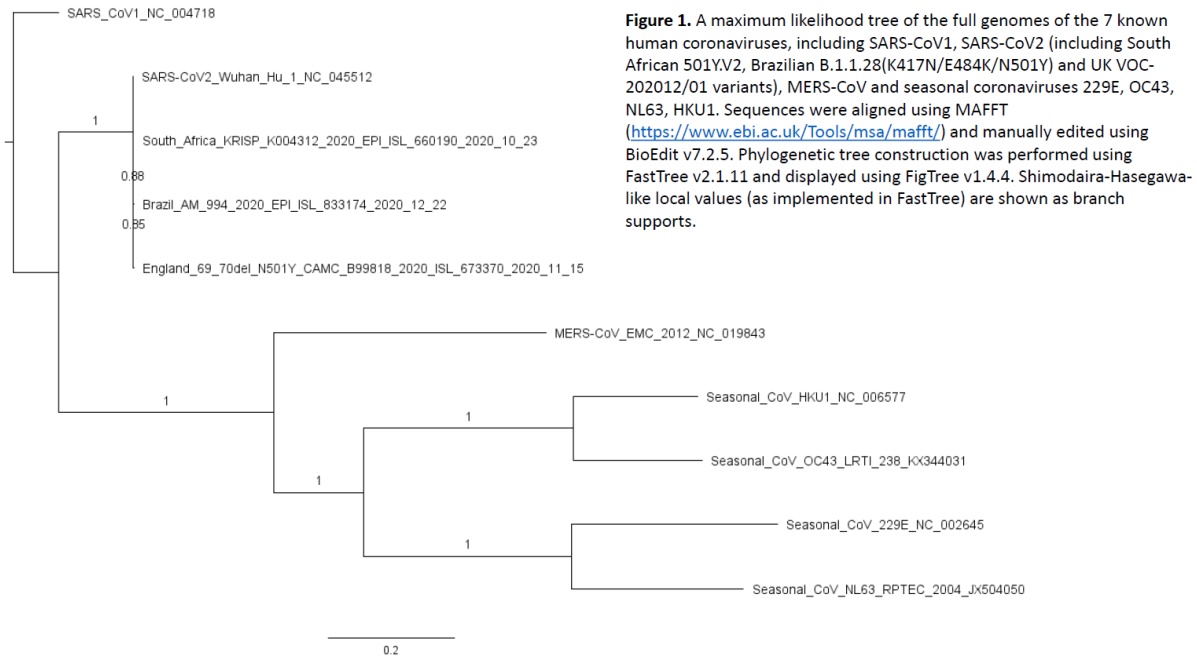

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Table 1

Independent factors associated with increased risk of *super-spreading events of SARS-CoV infection in the healthcare setting [50]:

- **Performance of resuscitation (OR 3.81, 95%CI 1.04-13.87, p=0.04)**
- **Staff working while experiencing symptoms (OR 10.55, 95%CI 2.28-48.87, p=0.003)**
- **SARS patients requiring oxygen therapy at least 6L/min (OR 4.30, 95%CI 1.00-18.43, p=0.05)**
- **SARS patients requiring non-invasive positive pressure ventilation (OR 11.82, 95%CI 1.97-70.80, p=0.007)**
- **Minimum distance between beds <1m (OR 6.94, 95%CI 1.68-28.75, p=0.008)**
- **Washing or changing facilities for staff (OR 0.12, 95%CI 0.02-0.97, p=0.05)**

***A super-spreading event was defined as one patient that could infect at least 3 others.**

Table 2

Respiratory procedures reported to present an increased risk of transmission of SARS-CoV to healthcare workers [n; pooled OR(95%CI)] [51]:

- Tracheal intubation [n=4 cohort; 6.6 (2.3, 18.9), and n=4 case-control; 6.6 (4.1, 10.6)],
- Non-invasive ventilation [n=2 cohort; OR 3.1(1.4, 6.8)],
- Tracheotomy [n=1 case-control; 4.2 (1.5, 11.5)] and
- Manual ventilation before intubation [n=1 cohort; OR 2.8 (1.3, 6.4)].

Table 3. Risk factors for Primary and Household transmission

Independent factors associated with primary MERS-CoV illness (Saudi Arabia) [59]:

a) Direct dromedary exposure in the 2 weeks before illness onset (adjusted OR 7.45, 95% CI 1.57–35.28),

b) Diabetes mellitus (adjusted OR 6.99, 95% CI 1.89–25.86)

c) Heart disease (adjusted OR 6.87, 95% CI 1.81–25.99) or currently smoking tobacco (adjusted OR 6.84, 95% CI 1.68–27.94).

d) Direct physical contact with dromedaries in the previous 6 months (adjusted OR 14.59, 95% CI 2.38–89.55).

Risk factors for household transmission [61]:

a) Sleeping in an index patient's room [RR 4.1 (1.5–11.2)]

b) Removing patient's waste (urine, stool and sputum) [RR 3.2 (1.2–8.4)]

c) Touching respiratory secretions from an index patient [RR 4.0 (1.6–9.8)]

Table 4

Comparative Epidemiological, Demographic and Clinical features of SARS-CoV2, MERS-CoV and SARS-CoV1

	SARS-CoV2[13,14]	MERS-CoV[63,64]	SARS-CoV1[27-29,31]
Natural reservoir	Unclear (possibly bats)	Unclear (possibly bats)	Chinese horse shoe bats
Intermediate host	Unclear	Dromedary camels	Civet cats
Date of first case report (place)	Dec 2019 (Wuhan, China)	April 2012 (Jordan) June 2012 (First KSA case)	Nov 2002 (Foshan, China)
Incubation period	Median 4 days (IQR 2-7) Range 2-14 days	Mean: 5.2 days(95%CI:1.9-14.7). Range: 2-13 days	Mean: 4.6 days (95%CI:3.8-5.8) Range: 2-14 days
Reproduction number	2.5	<1	2.4
Age group			
Adults Children	Adults (98%) Children (2%)	Adults (98%) Children (2%)	Adults (93%) Children (5-%7%)
Mortality			
Case fatality rate (CFR)-overall	2.2%	34.5%	9.6%

CFR in patients with co-morbidities	73.3%	60%	46%
Time from onset to death	Mean 15.4 days	Median 11.5 days	Mean 23.7 days
Presenting symptoms			
Fever	43.8% on admission; 88.7% on hospitalization	98%	99-100%
Chills / rigors	11.4%	87%	15-73%
Cough -dry -productive	 67.8% 33.7%	83% 56% 44%	62-100% 29-75% 4-29%
Haemoptysis	0.9%	17%	0-1%
Headache	13.6%	11%	20-56%
Myalgia	14.9%	32%	45-61%
Malaise	38.1%	38%	31-45%
Shortness of breath	18.7%	72%	40-42%
Nausea	5%	21%	20-35%
Vomiting	5%	21%	20-35%
Diarrhoea	3.8%	26%	20-25%
Sore throat	13.9%	14%	13-25%
Rhinorrhoea	4.8%	6%	2-24%
Anosmia	NK	NK	40-80%