From SARS coronavirus to novel animal and human coronaviruses

Kelvin K. W. To[1,2], Ivan F. N. Hung[1,3], Jasper F. W. Chan[1,2], Kwok-Yung Yuen[1,2]

[1]State Key Laboratory of Emerging Infectious Diseases, [2]Department of Microbiology, and [3]Department of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

ABSTRACT

In 2003, severe acute respiratory syndrome coronavirus (SARS-CoV) caused one of the most devastating epidemics known to the developed world. There were two important lessons from this epidemic. Firstly, coronaviruses, in addition to influenza viruses, can cause severe and rapidly spreading human infections. Secondly, bats can serve as the origin and natural animal reservoir of deadly human viruses. Since then, researchers around the world, especially those in Asia where SARS-CoV was first identified, have turned their focus to find novel coronaviruses infecting humans, bats, and other animals. Two human coronaviruses, HCoV-HKU1 and HCoV-NL63, were identified shortly after the SARS-CoV epidemic as common causes of human respiratory tract infections. In 2012, a novel human coronavirus, now called Middle East respiratory syndrome coronavirus (MERS-CoV), has emerged in the Middle East to cause fatal human infections in three continents. MERS-CoV human infection is similar to SARS-CoV in having a high fatality rate and the ability to spread from person to person which resulted in secondary cases among close contacts including healthcare workers without travel history to the Middle East. Both viruses also have close relationships with bat coronaviruses. New cases of MERS-CoV infection in humans continue to occur with the origins of the virus still unknown in many cases. A multifaceted approach is necessary to control this evolving MERS-CoV outbreak. Source identification requires detailed epidemiological studies of the infected patients and enhanced surveillance of MERS-CoV or similar coronaviruses in humans and animals. Early diagnosis of infected patients and appropriate infection control measures will limit the spread in hospitals, while social distancing strategies may be necessary to control the outbreak in communities if it remained uncontrolled as in the SARS epidemic.

KEY WORDS

Severe acute respiratory syndrome coronavirus (SARS-CoV); novel coronaviruses; Middle East respiratory syndrome coronavirus (MERS-CoV)

J Thorac Dis 2013;5(S2):S103-S108. doi: 10.3978/j.issn.2072-1439.2013.06.02

Introduction

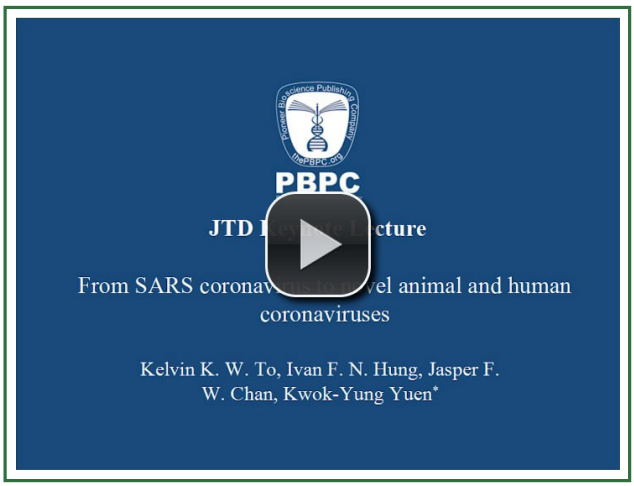
Ten years ago in 2003, severe acute respiratory syndrome coronavirus (SARS-CoV) shocked the world by its high virulence and efficient transmissibility among humans (1-3), causing the first large-scale epidemic of the 21st century. More than 8,000 patients were infected worldwide, resulting in 774 deaths. In addition to the substantial burden to the healthcare system, SARS also negatively affected the economy with reduced domestic demands and international travel (4). Attributable global economic loss due to SARS-CoV has been estimated to be 40 billion dollars (5). Two novel human coronaviruses (HCoV), HCoV-HKU1 and HCoV-NL63, were identified shortly after the discovery of SARS (6,7) as agents of self-limiting upper respiratory tract infections (8,9) although fatal cases were occasionally reported among the elderly and immunocompromised patients (10-13). On the other hand, the novel Middle East respiratory syndrome coronavirus (MERS-CoV), previously also known as human betacoronavirus 2c EMC/2012 and human coronavirus EMC (HCoV-EMC), which has caused fatal infections in humans as early as April 2012 in the Middle East and has recently spread to Europe and North Africa, is a timely reminder for the global health community of the importance of coronavirus as a deadly human respiratory tract pathogen (14-16). As of 30 May 2013, there have been 50 laboratory-confirmed MERS-CoV human infections, including 27 deaths (17).

Coronaviruses belong to the enveloped RNA virus family Coronaviridae capable of causing disease in humans and animals. They consist of single-stranded positive-sense genomes, and

Corresponding to: Kwok-Yung Yuen. Carol Yu Centre for Infection, Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong Special Administrative Region, China. Email: kyyuen@hkucc.hku.hk.

Submitted May 15, 2013. Accepted for publication Jun 04, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439



Video 1. From SARS coronavirus to novel animal and human coronaviruses.

are currently classified into four genera based on the differences in their protein sequences (15). HCoV-229E and HCoV-NL63 belong to *Alphacoronavirus*. HCoV-OC43 and HCoV-HKU1 belong to lineage A *Betacoronavirus*, while SARS-CoV and MERS-CoV belong to lineages B and C *Betacoronavirus*, respectively. Currently, *Gammacoronavirus* and *Deltacoronavirus* have not been reported to cause human disease. Both SARS-CoV and MERS-CoV are phylogenetically closely related to coronaviruses in bats (18-20). In this article, we review the clinical aspects of the novel human coronaviruses identified in the past ten years, and discuss the relationship between these human coronaviruses with their ancestral animal coronaviruses (Video 1).

Clinical aspects of human coronavirus infection

Before the emergence of SARS-CoV, the only coronaviruses that were known to cause human respiratory tract infections were HCoV-229E and HCoV-OC43, which accounted for 15-30% of the common cold, with severe disease being rare (21). In November 2002, an unusual atypical pneumonia due to SARS-CoV started to emerge in Foshan, Guangdong Province, Mainland China (2). In February 2003, the infection spread to Hong Kong and then to Vietnam, North America and Europe. The virus was first isolated from the open lung biopsy of the 53-year-old male relative of the index case in Hong Kong, who was a 65-year-old doctor who traveled to Hong Kong from Guangzhou (3). The first three criteria of the modified Koch's postulate, namely the isolation of the virus from diseased hosts, cultivation in host cells and proof of filterability were fulfilled from initial clinical and *in vitro* studies (3,22-24), while the last three criteria including the production of comparable disease in a related species, reisolation of the virus and detection of specific immune response to the virus were fulfilled in studies conducted in cynomolgus macaques shortly after the discovery of the virus (25). SARS-CoV was characterized by rapidly progressive pneumonia (3). The primary mode of transmission of SARS-CoV appeared to be by respiratory droplets (26) although fecal-oral transmission might also be (3). Apart from the super-spreaders, each case was estimated to infect two to four secondary cases (27). The median incubation period was estimated to be four to seven days (28) and the peak viral load was reached on the 10th day of illness (3). All age groups could be affected by SARS-CoV. Healthcare workers and immunocompromised patients were particularly at risk (29). Presentation with fever was universal, and myalgia and malaise were common early symptoms. Cough, dyspnea, tachypnea, pleurisy, and diarrhea tended to appear as late symptoms (3). Lymphopenia, deranged liver function tests, and elevated creatine kinase were common laboratory abnormalities (3). Thoracic computed tomography (CT) scans frequently showed ground-glass opacifications despite initial normal chest radiographs. Approximately two-thirds of the patients deteriorated in the second week of illness, characterized by persistent fever, increasing dyspnea, and oxygen desaturation. This was correlated by progression to multifocal air-space consolidations on thoracic CT scans with occasional pneumomediastinum (3). Approximately 20-30% of patients subsequently required intensive care and mechanical ventilation. Pathological analysis of lung biopsy at autopsy demonstrated diffuse alveolar damage, desquamation of pneumocytes, and inflammatory infiltrates with hyaline membrane formation (30).

In January 2004, the novel HCoV-HKU1 was first identified in a 71-year-old man with community-acquired pneumonia in Hong Kong (6) and was subsequently found globally. Both children and elderly with underlying illnesses were affected (8,31). In addition to community-acquired pneumonia, HCoV-HKU1 is associated with acute bronchiolitis and asthmatic exacerbation (31). The incidence of febrile seizure is higher in HCoV-HKU1 infection than infections caused by other human coronaviruses (31). HCoV-HKU1 was also found in a patient with meningitis (32). Most cases occurred during winter and spring coinciding with the influenza season (31-34).

HCoV-NL63 was first reported from the Netherlands (7). The first patient was a 7-month-old child hospitalized for fever, coryza and conjunctivitis, with chest radiographic evidence of bronchiolitis. HCoV-NL63 is associated with croup (20,35), and has also been reported in a patient with diabetes mellitus who developed pericarditis and rhabdomyolysis (11). On the other hand, the association between HCoV-NL63 and Kawasaki disease remains controversial (36). The peak incidence occurs during early summer and autumn in tropical and subtropical areas like Hong Kong (31,37), and during winter in European countries including the Netherlands and the United Kingdom (7,32). Co-infections with other respiratory viruses especially

respiratory syncytial virus may sometimes occur (32).

MERS-CoV was first identified in 2012, with Koch's postulate being fulfilled using a macaque model soon afterwards (38). All reported patients were adults, with a median age of 56 (39). The clinical feature resembled closely to that of the SARS outbreak in 2003 (13), characterized by rapidly progressive acute pneumonia. In contrast with SARS, many patients with MERS-CoV also developed acute renal failure (14). One patient presented with fever, diarrhea and abdominal pain without respiratory symptoms (40). Severe complications included acute respiratory distress syndrome, consumptive coagulopathy, and pericarditis. Although most of the laboratory-confirmed cases originated from the Middle East (the Kingdom of Saudi Arabia, Qatar, Jordan, and the United Arab Emirates), imported cases with occasional secondary spread to close contacts have been reported in the United Kingdom, Germany, France, Italy and Tunisia. Person-to-person transmission is suspected in at least six intra-familial or healthcare-related clusters (41,42). The high fatality of MERS-CoV of over 50% in humans is consistent with *in vitro* experiments showing rapid viral replication and broad human tissue tropism in cell lines (43,44).

Definitive laboratory confirmation of coronavirus infection by viral culture is limited by the relative difficulty of growing most of these viruses in cell culture and the lack of appropriate biosafety facilities in routine clinical laboratories for SARS-CoV and MERS-CoV. For HCoV-HKU1, viral culture has been reported using human ciliated airways epithelial cell cultures, but this is not widely available (45). Other diagnostic methods include direct antigen detection, serology, and RT-PCR. For example, direct antigen detection in respiratory tract specimens using monoclonal antibody against the nucleocapsid protein has been reported for SARS-CoV and HCoV-HKU1 (33,46,47). Serological testing using neutralization assays can compare the acute and convalescent serum samples, with infection confirmed if there is a four-fold increase in the antibody titers. However, testing requires repeated sampling, and cross-reactive antibodies have been reported. For example, although SARS-CoV and MERS-CoV are phylogenetically distinct, cross-reactive neutralizing antibodies against MERS-CoV are found in 60.7% of SARS patients (48). This may be related to the similarity of the heptad repeat-2 region of the spike protein, which is a significant B cell epitope. Further study of the host immunological response to infection by these viruses might facilitate the understanding of this phenomenon.

Currently, there is no specific antiviral for coronavirus infection approved for clinical use. Many compounds have *in vitro* activity, but none has undergone randomized placebo controlled trials (2). No antiviral or immunomodulator, including convalescent plasma, was found to be efficacious, and possible harmful effects have been reported for ribavirin and corticosteroid (49). For MERS-CoV, *in vitro* antiviral activity has been demonstrated for cyclosporin A, interferon-α, interferon-α 2b and ribavirin (50,51). Intensive care with mechanical ventilation and extracorporeal membrane oxygenation support remains to be the main modalities of treatment (52).

Zoonotic origin of human coronaviruses

Epidemiological studies have found that the initial patients with SARS had contact with game animals. Seroprevalence studies showed that animal traders had a higher prevalence of SARS-CoV IgG than the general population (53). The first animals found to carry SARS-CoV-like viruses were the Himalayan palm civets and a racoon dog in live animal markets (54). Subsequent searches for the natural animal host in a surveillance study among non-caged animals from wild areas in Hong Kong revealed that a closely related bat coronavirus, SARS-related *Rhinolophus* bat coronavirus HKU3 (SARSr-Rh-BatCoV HKU3), existed in Chinese horseshoe bats (*Rhinolophus* sp.) (20). Phylogenetic analysis suggested that HCoV-NL63 may have originated from bat coronaviruses that have diverged 563-822 years ago (55), while HCoV-HKU1 also likely originated from a bat coronavirus (56). Initial phylogenetic analysis of the replicase gene of MERS-CoV showed that the virus was most closely related to bat CoV-HKU4 and CoV-HKU5 (14,15,57). More recently phylogenetic analysis using partial RdRp sequences showed that the MERS-CoV was more closely related to betacoronaviruses in bats from Europe and Africa (58,59). At the time of writing, related coronaviruses have yet to be isolated from animals in the Middle East. Continued search for the natural definitive and intermediate animal hosts may help to halt the ongoing epidemic.

The hunt for novel coronaviruses in bats accelerated after bats were identified as the natural host of SARS-CoV. Bats are the only flying mammals capable of travelling long distances which facilitates transmission of viruses (60,61). In addition to the SARSr-Rh-BatCoV HKU3, Bat coronaviruses identified in Hong Kong include the *Rhinolophus* bat CoV-HKU2 (62), *Tylonycteris* bat coronavirus CoV-HKU4 (18), *Pipistrellus* bat CoV-HKU5 (18), *Myotis* bat CoV-HKU6 (18), *Miniopterus* bat CoV-HKU7 (18) and *Miniopterus* bat CoV-HKU8 (18), *Hipposideros* and *Rousettus* bat CoV-HKU10 (63). Other bat coronaviruses have also been found in different parts of the world (64,65). In addition to bats, birds are also an important origin and reservoir of emerging viruses causing human infections such as avian-origin influenza viruses (61). Numerous coronaviruses were also found in a wide range of birds (66). Bird coronaviruses identified in Hong Kong include bulbul CoV-HKU11, thrush CoV-HKU12, munia CoV-HKU13, white-eye CoV-HKU16, sparrow CoV-HKU17, magpie robin CoV-HKU18, night heron CoV-HKU19, wigeon CoV-HKU20, and common moorhen CoV-HKU21. Most of the bat coronaviruses belong to

Alphacoronavirus and *Betacoronavirus*, while bird coronaviruses belong to *Gammacoronavirus* and *Deltacoronavirus* (67). Besides bats and birds, coronaviruses were also found in many other domestic and wild mammals, such as dogs, cats, pigs, whales and alpacas (66,68-70). Camels are suspected to be a reservoir of MERS-CoV since the virus has originated from the Middle East and some patients had contacted with camels prior to symptom onset. Indeed, enteric coronaviruses have been identified in a camel previously (71).

Conclusions

In the past 16 years, coronaviruses including SARS-CoV and MERS-CoV, together with the avian-origin influenza A viruses H5N1 and H7N9 (72,73), have led to human epidemics with high case-fatality rates ranging from 10-60%. The zoonotic origin has been found for SARS-CoV, influenza A (H5N1) and A (H7N9), while phylogenetic analysis suggests that MERS-CoV has likely originated from bat coronaviruses. Continued surveillance in mammals and birds will allow better understanding of the ecology of coronaviruses and may aid in the prevention of animal-to-human transmissions and outbreaks in the future. Since person-to-person transmission has been reported in multiple clusters of MERS-CoV infection, stringent infection control measures should be implemented in hospitals for suspected or confirmed human infections. Patients with respiratory symptoms and history of travel to affected areas or contact with MERS-CoV patients within ten to twelve days of symptom onset should be isolated and tested early to avoid nosocomial spread of disease. Ventilatory and ECMO appeared to be effective in some severe cases. Development of an effective vaccine and randomized, placebo-controlled clinical trials on potential specific antiviral agents are urgently needed.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1977-85.
2. Cheng VC, Lau SK, Woo PC, et al. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 2007;20:660-94.
3. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003;361:1319-25.
4. Siu A, Wong Y. Economic Impact of SARS: The Case of Hong Kong. Asian Economic Papers 2004;3:62-83.
5. Knobler S. Institute of Medicine (U.S.). Forum on Microbial Threats., Institute of Medicine (U.S.). Board on Global Health. Learning from SARS preparing for the next disease outbreak: workshop summary. Washington, DC: National Academies Press, 2004.
6. Woo PC, Lau SK, Chu CM, et al. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J Virol 2005;79:884-95.
7. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med 2004;10:368-73.
8. Woo PC, Lau SK, Tsoi HW, et al. Clinical and molecular epidemiological features of coronavirus HKU1-associated community-acquired pneumonia. J Infect Dis 2005;192:1898-907.
9. Bastien N, Anderson K, Hart L, et al. Human coronavirus NL63 infection in Canada. J Infect Dis 2005;191:503-6.
10. Oosterhof L, Christensen CB, Sengeløv H. Fatal lower respiratory tract disease with human corona virus NL63 in an adult haematopoietic cell transplant recipient. Bone Marrow Transplant 2010;45:1115-6.
11. Cabeça TK, Bellei N. Human coronavirus NL-63 infection in a Brazilian patient suspected of H1N1 2009 influenza infection: description of a fatal case. J Clin Virol 2012;53:82-4.
12. Szczawinska-Poplonyk A, Jonczyk-Potoczna K, Breborowicz A, et al. Fatal respiratory distress syndrome due to coronavirus infection in a child with severe combined immunodeficiency. Influenza Other Respi Viruses 2012. [Epub ahead of print].
13. Uhlenhaut C, Cohen JI, Pavletic S, et al. Use of a novel virus detection assay to identify coronavirus HKU1 in the lungs of a hematopoietic stem cell transplant recipient with fatal pneumonia. Transpl Infect Dis 2012;14:79-85.
14. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814-20.
15. Chan JF, Li KS, To KK, et al. Is the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) the beginning of another SARS-like pandemic? J Infect 2012;65:477-89.
16. Chan JF, Lau SK, Woo PC. The emerging novel Middle East Respiratory Syndrome Coronavirus: the "knowns" and "unknowns". J Formos Med Assoc 2013. [Epub ahead of print].
17. Centers for Disease Control and Prevention. MERS Cases and Deaths 2013. Available online: http://www.cdc.gov/coronavirus/index.html. accessed on 10 June 2013.
18. Woo PC, Lau SK, Li KS, et al. Molecular diversity of coronaviruses in bats. Virology 2006;351:180-7.
19. Woo PC, Wang M, Lau SK, et al. Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. J Virol 2007;81:1574-85.
20. Lau SK, Woo PC, Li KS, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci U S A 2005;102:14040-5.
21. Holmes KV. SARS coronavirus: a new challenge for prevention and therapy. J Clin Invest 2003;111:1605-9.
22. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med 2003;348:1995-2005.
23. Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med

2003;348:1967-76.
24. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953-66.
25. Fouchier RA, Kuiken T, Schutten M, et al. Aetiology: Koch's postulates fulfilled for SARS virus. Nature 2003;423:240.
26. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348:1986-94.
27. Peiris JS, Yuen KY, Osterhaus AD, et al. The severe acute respiratory syndrome. N Engl J Med 2003;349:2431-41.
28. Scales DC, Green K, Chan AK, et al. Illness in intensive care staff after brief exposure to severe acute respiratory syndrome. Emerg Infect Dis 2003;9:1205-10.
29. Donnelly CA, Ghani AC, Leung GM, et al. Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. Lancet 2003;361:1761-6.
30. Nicholls JM, Poon LL, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. Lancet 2003;361:1773-8.
31. Lau SK, Woo PC, Yip CC, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. J Clin Microbiol 2006;44:2063-71.
32. Gaunt ER, Hardie A, Claas EC, et al. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. J Clin Microbiol 2010;48:2940-7.
33. Gerna G, Percivalle E, Sarasini A, et al. Human respiratory coronavirus HKU1 versus other coronavirus infections in Italian hospitalised patients. J Clin Virol 2007;38:244-50.
34. Lee WJ, Chung YS, Yoon HS, et al. Prevalence and molecular epidemiology of human coronavirus HKU1 in patients with acute respiratory illness. J Med Virol 2013;85:309-14.
35. van der Hoek L, Sure K, Ihorst G, et al. Croup is associated with the novel coronavirus NL63. PLoS Med 2005;2:e240.
36. Dominguez SR, Anderson MS, Glodé MP, et al. Blinded case-control study of the relationship between human coronavirus NL63 and Kawasaki syndrome. J Infect Dis 2006;194:1697-701.
37. Wu PS, Chang LY, Berkhout B, et al. Clinical manifestations of human coronavirus NL63 infection in children in Taiwan. Eur J Pediatr 2008;167:75-80.
38. Munster VJ, de Wit E, Feldmann H. Pneumonia from human coronavirus in a macaque model. N Engl J Med 2013;368:1560-2.
39. World Health Organization. Global overview of an emerging novel coronavirus (MERS-CoV). Available online: http://www.who.int/csr/disease/coronavirus_infections/WHA_CoV_update_KeijiFukuda_23May13.pdf. accessed on 30 May 2013.
40. World Health Organization. Novel coronavirus summary and literature update - as of 17 May 2013. Available online: http://www.who.int/csr/disease/coronavirus_infections/update_20130517/en/index.html. Accessed on 30 May 2013.
41. Centers for Disease Control and Prevention. Novel Coronavirus. Update, case definitions, and guidance. Available online: http://www.cdc.gov/coronavirus/ncv/case-def.html. accessed on 29 May 2013.
42. Memish ZA, Zumla AI, Al-Hakeem RF, et al. Family Cluster of Middle East Respiratory Syndrome Coronavirus Infections. N Engl J Med 2013;368:2487-94.
43. Chan JF, Chan KH, Choi GK, et al. Differential Cell Line Susceptibility to the Emerging Novel Human Betacoronavirus 2c EMC/2012: Implications for Disease Pathogenesis and Clinical Manifestation. J Infect Dis 2013;207:1743-52.
44. Kindler E, Jónsdóttir HR, Muth D, et al. Efficient replication of the novel human betacoronavirus EMC on primary human epithelium highlights its zoonotic potential. MBio 2013;4:e00611-12.
45. Pyrc K, Sims AC, Dijkman R, et al. Culturing the unculturable: human coronavirus HKU1 infects, replicates, and produces progeny virions in human ciliated airway epithelial cell cultures. J Virol 2010;84:11255-63.
46. Liu IJ, Chen PJ, Yeh SH, et al. Immunofluorescence assay for detection of the nucleocapsid antigen of the severe acute respiratory syndrome (SARS)-associated coronavirus in cells derived from throat wash samples of patients with SARS. J Clin Microbiol 2005;43:2444-8.
47. Lau SK, Che XY, Woo PC, et al. SARS coronavirus detection methods. Emerg Infect Dis 2005;11:1108-11.
48. Chan KH, Chan JF, Tse H, et al. Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests. J Infect 2013;67:130-40.
49. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2006;3:e343.
50. de Wilde AH, Raj VS, Oudshoorn D, et al. MERS-coronavirus replication induces severe in vitro cytopathology and is strongly inhibited by cyclosporin A or interferon-α treatment. J Gen Virol 2013;94:1749-60.
51. Falzarano D, de Wit E, Martellaro C, et al. Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin. Sci Rep 2013;3:1686.
52. Bermingham A, Chand MA, Brown CS, et al. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. Euro Surveill 2012;17:20290.
53. Centers for Disease Control and Prevention (CDC). Prevalence of IgG antibody to SARS-associated coronavirus in animal traders--Guangdong Province, China, 2003. MMWR Morb Mortal Wkly Rep 2003;52:986-7.
54. Guan Y, Zheng BJ, He YQ, et al. Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. Science 2003;302:276-8.
55. Huynh J, Li S, Yount B, et al. Evidence supporting a zoonotic origin of human coronavirus strain NL63. J Virol 2012;86:12816-25.
56. Woo PC, Lau SK, Huang Y, et al. Coronavirus diversity, phylogeny and interspecies jumping. Exp Biol Med (Maywood) 2009;234:1117-27.
57. van Boheemen S, de Graaf M, Lauber C, et al. Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans. MBio 2012;3. pii: e00473-12.
58. Cotten M, Lam TT, Watson SJ, et al. Full-genome deep sequencing and phylogenetic analysis of novel human betacoronavirus. Emerg Infect Dis 2013;19:736-42B.
59. Annan A, Baldwin HJ, Corman VM, et al. Human Betacoronavirus 2c

EMC/2012-related Viruses in Bats, Ghana and Europe. Emerg Infect Dis 2013;19:456-9.
60. Zhang G, Cowled C, Shi Z, et al. Comparative analysis of bat genomes provides insight into the evolution of flight and immunity. Science 2013;339:456-60.
61. Chan JF, To KK, Tse H, et al. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. Trends Microbiol 2013. [Epub ahead of print].
62. Lau SK, Woo PC, Li KS, et al. Complete genome sequence of bat coronavirus HKU2 from Chinese horseshoe bats revealed a much smaller spike gene with a different evolutionary lineage from the rest of the genome. Virology 2007;367:428-39.
63. Lau SK, Li KS, Tsang AK, et al. Recent transmission of a novel alphacoronavirus, bat coronavirus HKU10, from Leschenault's rousettes to pomona leaf-nosed bats: first evidence of interspecies transmission of coronavirus between bats of different suborders. J Virol 2012;86:11906-18.
64. Tong S, Conrardy C, Ruone S, et al. Detection of novel SARS-like and other coronaviruses in bats from Kenya. Emerg Infect Dis 2009;15:482-5.
65. Yang L, Wu Z, Ren X, et al. Novel SARS-like Betacoronaviruses in Bats, China, 2011. Emerg Infect Dis 2013;19:989-91.
66. Woo PC, Lau SK, Lam CS, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. J Virol 2012;86:3995-4008.
67. Woo PC, Huang Y, Lau SK, et al. Coronavirus genomics and bioinformatics analysis. Viruses 2010;2:1804-20.
68. Mihindukulasuriya KA, Wu G, St Leger J, et al. Identification of a novel coronavirus from a beluga whale by using a panviral microarray. J Virol 2008;82:5084-8.
69. Crossley BM, Mock RE, Callison SA, et al. Identification and characterization of a novel alpaca respiratory coronavirus most closely related to the human coronavirus 229E. Viruses 2012;4:3689-700.
70. Perlman S, Netland J. Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 2009;7:439-50.
71. Wünschmann A, Frank R, Pomeroy K, et al. Enteric coronavirus infection in a juvenile dromedary (Camelus dromedarius). J Vet Diagn Invest 2002;14:441-4.
72. Chen Y, Liang W, Yang S, et al. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. Lancet 2013;381:1916-25.
73. To KK, Ng KH, Que TL, et al. Avian influenza A H5N1 virus: a continuous threat to humans. Emerg Microbes Infect 2012;1:e25.

Cite this article as: To KK, Hung IF, Chan JF, Yuen KY. From SARS coronavirus to novel animal and human coronaviruses. J Thorac Dis 2013;5(S2):S103-S108. doi: 10.3978/j.issn.2072-1439.2013.06.02