Official Journal of the Asian Pacific Society of Respirology
Respirology

COMMENTARY

Severe acute respiratory syndrome and other emerging severe respiratory viral infections

Key words: respiratory infections, severe acute respiratory syndrome, viral infections.

In the World Health Organization (WHO) updated list of blue-print priority diseases, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are included together with disease X, which represents the concept that a pathogen currently unknown to cause human disease may lead to a serious international epidemic.[1]

SARS-coronavirus (SARS-CoV) first emerged in November 2002 in Foshan, China, where many healthcare workers (HCW) became infected. On 21 February 2003, a 64-year-old male nephrologist from Guangdong Province took the infection to Hong Kong (HK) where the infection spread to 29 countries/regions within a few weeks by 16 hotel guests and visitors who were infected by the physician. The SARS-CoV international outbreak finally ended in July 2003, with 8096 probable cases and 774 deaths.[2] A novel CoV, now classified as a lineage B beta-CoV, was confirmed in March 2003 as the causative agent responsible for SARS-CoV infection.[3] A similar variant of SARS-CoV was detected in palm civets in a wild-game animal market located in Shenzhen, indicating that the interface of initial zoonotic transmission to humans were these markets. In 2005, CoV with a high degree of sequence similarity with human or civet cat isolates were detected in Chinese horseshoe bats,[4] suggesting that bats were the natural source of SARS-CoV.

SARS-CoV spreads predominantly via respiratory droplets and contact with fomite[2] but opportunistic airborne transmission is possible. Computer fluid dynamics modelling suggested possible virus dispersion by wind flow, causing long-range airborne transmission (>200 m) to nearby buildings, infecting over 300 residents in a private residential complex in HK.[5] The mean incubation period of SARS-CoV infection was 4.6 days (95% CI: 3.8–5.8 days), whereas 95% of illness onset was within 10 days. Peaking of nasopharyngeal viral loads in an 'inverted v' shape on day 10 of illness[6] was found to correspond temporally to peaking of the extent of consolidation radiographically,[7] and a maximal risk of nosocomial transmission, particularly to HCW. A systematic review has identified four aerosol-generating procedures that would increase the risk of nosocomial SARS transmission to HCW, including tracheal intubation, manual ventilation before intubation, tracheotomy and non-invasive ventilation.[8] Due to the lack of prospective randomized, placebo-controlled clinical trial (randomized controlled trial, RCT) data, none of the therapies (ribavirin, protease inhibitors, convalescent plasma and interferon) applied in 2003 for the treatment of SARS-CoV infection have well proven benefit. Data from an RCT suggest that systemic corticosteroids given early in the course of SARS-CoV infection might prolong viraemia.[9]

Although no secondary spread occurred despite the re-emergence of SARS involving laboratory personnel in Singapore and Taiwan, and four community-acquired cases in Guangdong, an outbreak is possible if there is breach of laboratory biosecurity measures, bioterrorism and emergence or mutation of other SARS-like cluster of circulating CoV in bat populations.

MERS-CoV was first detected in September 2012 when a novel β-CoV was isolated from a male patient who had died of severe pneumonia in Saudi Arabia in June 2012. Globally, from September 2012 to the end of 2018, WHO has been informed of 2266 laboratory-confirmed cases of MERS-CoV infection in 27 countries, with at least 804 deaths.[10] Bats are possibly the natural reservoir of MERS-CoV. Dromedary camels are a major source of zoonotic human infection as the virus has been isolated widely from dromedary camels in the Arabian Peninsula and across Africa. However, direct camel exposure occurs only in a minority of MERS human cases.[11,12]

The incubation period of MERS-CoV infection is over 5 days, but may be as long as 2 weeks (median: 5.2 days (95% CI: 1.9–14.7)). MERS-CoV viral loads peaked during the second week of illness, while patients can transmit MERS-CoV from day 1 to day 11 of their illness (median: 7 days; interquartile range (IQR): 5–8 days).[13] Direct dromedary exposure in the fortnight before illness onset was strongly associated with primary MERS-CoV infection, along with having diabetes mellitus or heart disease, and current cigarette smoking, while sleeping in an index patient's room and touching respiratory secretions from an index patient are risk factors for household transmission. Nosocomial transmission was common during 2013–2016 due to poor compliance of HCW with appropriate personal protection equipment (PPE) when assessing patients with febrile respiratory illness, application of aerosol-generating procedures, lack of proper isolation room facilities and exposure of HCW patients and visitors to overcrowded and contaminated healthcare facilities.[14]

The more feasible clinical trial options for MERS-CoV infection include protease inhibitor (lopinavir/ritonavir), interferon (IFN)-β1b, passive immunotherapy with convalescent plasma or human monoclonal or polyclonal antibody.[12] In a study of 309 patients in 14 intensive care units (ICU) in Saudi Arabia, systemic corticosteroid therapy was associated with delay in MERS-CoV RNA clearance (adjusted hazard ratio (HR): 0.35; 95% CI: 0.17–0.72; $P = 0.005$).[15]

doi: 10.1111/resp.13501

Human cases of the highly pathogenic *avian influenza A(H5N1)* were first detected in HK in 1997. As of 13 December 2018, there have been 454 deaths out of 860 human cases in 16 countries since 2003. Some of the A(H5N1) human cases have been linked to consumption of raw, contaminated poultry blood. However, defeathering, slaughtering, handling carcasses of infected poultry and preparing poultry for consumption especially in household settings appear to be important risk factors.[16]

There have been six seasonal epidemics of human infections due to *avian influenza A(H7N9)* virus in China since it was first discovered in March 2013, with 1567 laboratory-confirmed human cases and at least 615 deaths.[17] Human cases of A(H7N9) infection have been exported to HK (n = 21), Taiwan (n = 4), Macau (n = 2), Canada (n = 2) and Malaysia (n = 1) in visitors who developed illness after returning from the mainland of China to their home cities but zoonotic transmission has so far been confined to mainland China. Following the introduction of a bivalent H7/H5 vaccination of poultry in mainland China in October 2017, only three human cases were detected from October 2017 to September 2018, with a corresponding reduction of A(H7N9) viruses detected in poultry and environmental samples of A(H7N9) in China.[18] Early treatment of patients with avian influenza A (H5N1 or H7N9) within 5 days from illness onset with a neuraminidase inhibitor can reduce mortality,[16,19] while systemic corticosteroids would increase mortality and prolong viral shedding.[16,20]

Sporadic human cases with severe pneumonia due to *avian A(H5N6), A(H10N8) and A(H7N4) viruses* have also emerged in recent years. A(H5N1) viruses have recently reassorted to generate *A(H5N6)* viruses with zoonotic potential and *A(H5N8)* viruses which have been carried by wild migratory birds to Europe and North America without evidence of zoonotic disease but leading to outbreaks in poultry. Although avian A(H5N8) virus has so far not caused zoonotic disease, its geographic dissemination and continued evolution poses concern for human health.[21]

SARS-CoV, MERS-CoV and these emerging avian influenza viruses are pandemic-prone and pose an enormous public health threat. More research is needed to guide public health measures for controlling the interface of zoonotic transmission of these viruses to humans. Early detection and isolation of patients with these emerging severe acute respiratory infections are most important to prevent spread of disease. There is an urgent need for developing more effective antiviral agents and exploring immunomodulating therapies for managing these severe respiratory infections.[21,22]

David S. Hui, MD, FRACP[1,2] and Malik Peiris, MBBS, DPhil, FRCPath[3]
[1]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong;* [2]*Stanley Ho Center for Emerging Infectious Diseases, The Chinese University of Hong Kong, Hong Kong;* [3]*School of Public Health, University of Hong Kong, Hong Kong*

REFERENCES

1 WHO. List of blue print priority diseases. [Accessed 7 Jan 2019.] Available from URL: https://www.who.int/blueprint/priority-diseases/en/
2 Peiris JS, Guan Y, Yuen KY. Severe acute respiratory syndrome. *Nat. Med.* 2004; **10** (12 Suppl.): S88–97.
3 Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, Nicholls J, Yee WK, Yan WW, Cheung MT *et al.*; SARS Study Group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; **361:** 1319–25.
4 Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, Wong SS, Leung SY, Chan KH, Yuen KY. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. *Proc. Natl. Acad. Sci. U. S. A.* 2005; **102**: 14040–5.
5 Yu IT, Qiu H, Tse LA, Wong TW. Severe acute respiratory syndrome beyond Amoy Gardens: completing the incomplete legacy. *Clin. Infect. Dis.* 2014; **58**: 683–6.
6 Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS *et al.*; HKU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; **361:** 1767–72.
7 Hui DS, Wong KT, Antonio GE, Lee N, Wu A, Wong V, Lau W, Wu JC, Tam LS, Yu LM *et al.* Severe acute respiratory syndrome: correlation between clinical outcome and radiologic features. *Radiology* 2004; **233**: 579–85.
8 Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012; **7**: e35797.
9 Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, Wong VW, Chan PK, Wong KT, Wong E *et al.* Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J. Clin. Virol.* 2004; **31**: 304–9.
10 WHO. Epidemic and pandemic prone diseases. MERS situation update Oct 2018. [Accessed 7 Jan 2019.] Available from URL: http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-october-2018.html
11 Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, Selim MA, Al Mutairi M, Al Nakhli D, Al Aidaroos AY *et al.* Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int. J. Infect. Dis.* 2014; **29**: 301–6.
12 Hui DS. Epidemic and emerging coronaviruses (severe acute respiratory syndrome and Middle East respiratory syndrome). *Clin. Chest Med.* 2017; **38**: 71–86.
13 Kang CK, Song KH, Choe PG, Park WB, Bang JH, Kim ES, Park SW, Kim HB, Kim NJ, Cho SI *et al.* Clinical and epidemiologic characteristics of spreaders of Middle East respiratory syndrome coronavirus during the 2015 outbreak in Korea. *J. Korean Med. Sci.* 2017; **32**: 744–9.
14 Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect. Dis.* 2018; **18**: e217–27.
15 Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, Jose J, Pinto R, Al-Omari A, Kharaba A *et al.*; Saudi Critical Care Trial Group. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am. J. Respir. Crit. Care Med.* 2018; **197:** 757–67.
16 Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. *N. Engl. J. Med.* 2008; **358**: 261–73.
17 WHO. Human infection with avian influenza A(H7N9) virus – China: update. Disease outbreak news. 2018. [Accessed 7 Jan 2019.] Available from URL: https://www.who.int/csr/don/05-september-2018-ah7n9-china/en/

18 Wu J, Ke C, Lau EHY, Song Y, Cheng KL, Zou L, Kang M, Song T, Peiris M, Yen HL. Influenza H5/H7 virus vaccination in poultry and reduction of zoonotic infections, Guangdong Province, China, 2017-18. *Emerg. Infect. Dis.* 2019; **25**: 116–8.
19 Zheng S, Tang L, Gao H, Wang Y, Yu F, Cui D, Xie G, Yang X, Zhang W, Ye X *et al*. Benefit of early initiation of neuraminidase inhibitor treatment to hospitalized patients with avian influenza A(H7N9) virus. *Clin. Infect. Dis.* 2018; **66**: 1054–60.
20 Cao B, Gao H, Zhou B, Deng X, Hu C, Deng C, Lu H, Li Y, Gan J, Liu J *et al*. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. *Crit. Care Med.* 2016; **44**: e318–28.
21 Hui DS, Lee N, Chan PK. A clinical approach to the threat of emerging influenza viruses in the Asia-Pacific region. *Respirology* 2017; **22**: 1300–12.
22 Hui DS, Lee N, Chan PK, Beigel JH. The role of adjuvant immunomodulatory agents for treatment of severe influenza. *Antiviral Res.* 2018; **150**: 202–16.