




POSITION STATEMENT

Emerging respiratory infections threatening public health in the Asia-Pacific region: A position paper of the Asian Pacific Society of Respirology*

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ABSTRACT

In past decades, we have seen several epidemics of respiratory infections from newly emerging viruses, most of which originated in animals. These emerging infections, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the pandemic influenza A(H1N1) and avian influenza (AI) viruses, have seriously threatened global health and the economy. In particular, MERS-CoV and AI A(H7N9) are still causing infections in several areas, and some clustering of cases of A(H5N1) and A(H7N9) may imply future possible pandemics. Additionally, given the inappropriate use of antibiotics and international travel, the spread of carbapenem-resistant Gram-negative bacteria is also a significant concern. These infections with epidemic or pandemic potential present a persistent threat to public health and a huge burden on healthcare services in the Asia-Pacific region. Therefore, to enable efficient infection prevention and control, more effective international surveillance and collaboration systems, in the context of the 'One Health' approach, are necessary.

Key words: avian influenza, pandemic, respiratory infection, virus.

INTRODUCTION

Emerging infectious diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory

syndrome (MERS), pandemic influenza A(H1N1) 2009 (influenza A(H1N1)pdm09) and avian influenza (AI) pose a threat to global health. Bird and swine influenza viruses continuously obtain new gene segments through reassortment with human strains. Moreover, infections by multidrug-resistant Gram-negative bacteria are also increasing worldwide. Hence, action is needed to curtail the dissemination of these organisms. For this position paper, members of the Asian Pacific Society of Respirology (APSR) Respiratory Infections Assembly selected respiratory pathogens that are most likely to pose significant threats to humans, particularly in the Asia-Pacific region. The members reviewed epidemiological features of the pathogens and put together a consensus opinion. The recommendations presented here are, in essence, expert opinion based on case reports or serious outbreaks that may not represent a high level of evidence.

PANDEMIC AND SEASONAL INFLUENZA

Unlike seasonal influenza, pandemic influenza virus is a new virus that has not circulated in humans before, and to which humans have little or no immunity. Hence, the virus can cause significant illness or death and, when it acquires the ability of human-to-human transmission, could easily spread globally.

Four pandemics (Spanish flu in 1918, Asian flu in 1957, Hong Kong flu in 1968 and pandemic influenza A(H1N1) in 2009) have occurred since the early 20th century. Although the most recent pandemic due to A(H1N1)pdm09 was not as severe as the Spanish flu, the rate of patients requiring intensive care unit (ICU) admission was much higher than that due to seasonal influenza.¹ However, the disease severity and impact on public health of an influenza strain can be determined by various factors, including the characteristics of circulating viruses (e.g. transmissibility), the time in the season, vaccine strains being used and the vaccination rate of the population. The World Health Organization (WHO) reported that the predominant influenza

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viruses in Asia, Europe, America and Africa were A(H1N1)pdm09 and influenza B during the 2015–2016 season.² In East Asia, the predominant circulating virus was A(H1N1)pdm09 in the first half of the season, followed by influenza B virus in the second half of the season.²

Although vaccination is the most effective way to prevent influenza infections, the current vaccination rates vary and are suboptimal in many countries (21–78% in the elderly).³ Furthermore, considering the variable and moderate effectiveness of current vaccines, rapid development of efficacious vaccines with long-lasting and cross-protective immunity or broad-spectrum neutralizing antibody will be needed.⁴

Summary and Recommendations

- Antiviral treatment (e.g. 75 mg oseltamivir twice daily (bd) for 5 days in adults) should be started as soon as possible after illness onset, ideally within 48 h of symptom onset, for hospitalized patients or those with severe disease or at higher risk of influenza complications
- For post-exposure prevention, antiviral agents (e.g. 75 mg oseltamivir once daily for >7 days in adults) are recommended
- Annual seasonal influenza vaccines (trivalent or quadrivalent vaccines) are recommended for the high-risk group, which includes pregnant women, children aged 6–59 months, the elderly, individuals with specific chronic medical conditions and healthcare workers
- Considering the suboptimal vaccination rates, strategies for improving the vaccination rates, including free vaccination programme provided by government or non-profit organization, should be encouraged
- New approaches for the development of universal influenza vaccines or broad-spectrum neutralizing antibody should be investigated

AVIAN INFLUENZA

A(H7N9) virus

A human case of A(H7N9) infection was first reported in March 2013 in China. There have been five epidemics of A(H7N9) since the virus was first discovered; China is currently experiencing the fifth.^{5–7} As of 25 July 2018, a total of 1625 human infections have been reported since 2013 and the mortality rate is 38.3% (Table 1).^{5,7,10} To date, although no human or animal infections by A(H7N9) have been detected at a poultry farm, the majority of infected patients had a link to infected live poultry or contaminated environments such as live poultry markets.²⁵

Li *et al.* reported that 81.6% of patients had a history of exposure to live animals, including chickens and ducks (hospitalization rate: 98.6%, pneumonia or respiratory failure rate: 91.2%).¹¹ In particular, they found four family clusters and suggested the possibility of

human-to-human transmission. However, while most human cases were caused by the low pathogenic AI A(H7N9), new cases of highly pathogenic A(H7N9) virus infection have also been confirmed since 2017.^{10,24}

A(H5N1) virus

Influenza A(H5N1) viruses are endemic among poultry in parts of Asia, Africa and the Middle East. Human cases of A(H5N1) were first detected in Hong Kong in 1997.²⁶ After a 6-year absence, human cases with confirmed influenza A(H5N1) virus infection re-emerged in 2003 in Southeast Asia. Since then, the highly pathogenic influenza haemagglutinin (H5) has evolved into many phylogenetically distinct clades and subclades,²⁷ and the infection has spread from East Asia to West Asia and Africa, with a high incidence in Egypt since November 2014.²⁶ Vietnam has seen a total of 123 cases and 61 deaths since 2004, when the strain was first found there, through to 2012.²⁸

Overall, 903 cases of A(H5N1) virus were reported between 1997 and 2015, and most cases occurred between December and April.⁸ The rate of hospitalization was 90.3% and the case fatality rate was 53.5%. Eighty percent of cases were aged under 30 years⁸ and upper respiratory tract symptoms were less prominent in human H5N1 cases, as compared to seasonal influenza.²⁷ Compared to influenza A(H1N1)pdm09 virus, few clustering cases were reported and evidence for human-to-human transmission is still insufficient for A(H5N1) viruses.^{29,30}

Other AI viruses

The first reported human case of A(H6N1) infection was a young woman with influenza-like illness in Taiwan in 2013.³¹ The virus had a characteristic G228S substitution in the haemagglutinin protein, which might increase its affinity for the human α 2-6 linked sialic acid receptor and, therefore, increase the potential for human-to-human transmission.³¹

The A(H5N6) virus is a new reassortant strain that contains gene segments from A(H5N1) and A(H5N2). The first human A(H5N6) infection was reported in a 5-year-old girl who had visited a live poultry market in China in 2014.¹³ Influenza A(H5N6) outbreaks in birds and poultry have been reported in Vietnam and mainland China since 2014. To date, 16 human infections and six deaths due to A(H5N6) have occurred in mainland China.¹⁴

Regarding A(H10N8) infection, three human cases have been confirmed in Jiangxi Province in China since December 2013.^{19,20} All three cases had severe bilateral pneumonia and two died. Surveillance at the suspected live poultry markets showed an increased prevalence of A(H10N8) viruses. Notably, this virus contains genes from A(H9N2) and was frequently co-infected with A(H9N2). This implies that novel reassortants could emerge.

Since 1990, influenza A(H9N2) has circulated among domestic poultry in Asian countries and has now globally expanded.³² So far, human infections have mainly been reported in Hong Kong and

Table 1 Comparisons of clinical and epidemiological features among AI infections in humans

	A(H5N1) ^{8,9}	A(H7N9) ^{6,10-12}	A(H5N6) ¹³⁻¹⁵	A(H9N2) ¹⁶⁻¹⁸	A(H10N8) ^{19,20}	A(H3N2)v ²¹⁻²³
Pathogenicity	HPAI	LPAl/HPAI	HPAI	LPAl	LPAl	N/A
First human case	Hong Kong in 1997	China in 2013	China in 2014	Hong Kong in 1999	China in 2013	United States in 2011
Regions with human cases	China, Laos, Cambodia, Thailand, Vietnam, Indonesia, Pakistan, Azerbaijan, Bangladesh, Turkey, Nigeria and Egypt	China, Taiwan, Malaysia and Hong Kong	China	Hong Kong, China, Bangladesh, serological evidence in Asia, Africa and Middle East	China	United States
Total number of human cases (years)	903 cases (1997–2015)	1625 cases (2013–2018) ²	17 cases (2014–2016)	28 cases (1999–2016)	3 cases (2013–2014)	405 cases (2011–2017)
Median ages (years)	19 (5–32)	61 (46–73)	35 (26–45) in recent 9 cases reported by WHO	Mostly children	73, 56, 75	7 (range, 3 months–74 years)
Onset of illness to hospitalization (days)	4 (2–6)	4 (3–6)	3 (1–7) in recent 9 cases	N/A	3, 7, 2	<18 years in 92% 4 (1–16) in illness duration
Clinical characteristics	Less URT symptoms Admission rate: 90.3% Advanced life supports: 63% 53.3%	ARDS: 57.8% MV: 61.5% 38.3%	Usually severe infections	Mild or asymptomatic illness	Bilateral severe pneumonia in all cases	Mild illness
Mortality rate	67.2% between December and April	Five epidemics Currently the largest epidemic	58.8%	0%	66.6%	1/405
Epidemiological features	Recent epidemic in Egypt (2014)	Exposure to live poultry (81.6%)	Sporadic infections	Sporadic infections	Sporadic infections	Sporadic infections
Risk factors	Exposure to sick and dead poultry, and live poultry market	Exposure to live poultry (81.6%)	Exposure to dead poultry and live poultry	Exposure to live poultry and poultry farm	Exposure to live poultry market	A large epidemic in 2012 (n = 306) Exposure to pigs

[†]Thirty-two cases with HPAI A(H7N9) were recently reported.²⁴

A(H3N2)v, A(H3N2) variant; AI, avian influenza; ARDS, acute respiratory distress syndrome; HPAl, highly pathogenic AI; LPAl, low pathogenic AI; MV, mechanical ventilation; N/A, not applicable; URT, upper respiratory tract; WHO, World Health Organization.

mainland China.^{33,34} Although A(H9N2) infection results in mild disease or asymptomatic illness, the emergence of this virus is worrisome because it could potentially transfer its genes to another strain. Recent analyses of A(H7N9) and A(H10N8) viruses suggest that they have acquired gene segments from influenza A(H9N2) virus.^{35,36}

AI is a notifiable disease listed by the OIE (World Organization for Animal Health). The early detection of outbreaks, followed by a prompt response, is the first step. Monitoring and controlling AI virus at its poultry source is also crucial.

Summary and recommendations

- Individuals who are engaged in activities in close contact with infected poultry or wild animals should wear appropriate personal protective equipment (PPE) and be monitored for 7 days after their last contact
- Although the optimal dose and duration of antiviral agents are uncertain, we recommend oseltamivir (75 mg bd for 5 days in adults) for the treatment of patients with influenza A(H5N1) infection; however, higher doses are also considerations in severe cases
- Adults who have been in close contact with confirmed or highly suspicious cases should commence a course of prophylactic oseltamivir (75 mg/day) for 7–10 days
- Poultry workers in affected countries by AI should also receive seasonal influenza vaccines
- To reduce AI, source control measures, such as the regular closure of live poultry markets or prevention of the overnight storage of live poultry in markets, are recommended
- In case of outbreaks, destruction of infected poultry as well as poultry that have been in contact with infected birds is recommended
- Poultry vaccination at farm level also needs to be considered for infection control

HUMAN CORONAVIRUS

SARS-coronavirus (CoV) caused an outbreak that began in China in 2002 and eventually led to 8422 infections and 916 deaths in 37 countries.³⁷ No SARS cases have been reported since 2004.³⁷ However, in September 2012, a novel CoV infection (i.e. MERS-CoV) was reported in Saudi Arabia and a large number of people died from severe respiratory illness and acute kidney injury (i.e. 40–60%).³⁸ In 2015, a large outbreak began in South Korea with a single case and eventually reached 186 cases through household and nosocomial transmission.³⁹ As of September 2017, the WHO has reported 2103 cases of MERS-CoV and 733 deaths.^{40,41}

Importantly, the SARS-CoV and MERS-CoV human outbreaks were epidemiologically similar in terms of healthcare-associated infections (Table 2).^{45,49} In

China, 966 (18%) out of 5323 SARS cases were healthcare providers, and in the early days of the outbreak almost 90% of SARS patients were frontline healthcare providers.⁵⁰ In the Korean MERS-CoV outbreak, five 'super-spreaders' spread MERS-CoV to a large number of people in hospitals.⁴⁵ About 20% of patients with SARS progressed to hypoxia and required mechanical ventilation, with a case fatality rate of 9.6%.^{51,52} However, during the Korean MERS outbreak, pneumonia was detected in 80.8% (mechanical ventilation: 24.5%, extracorporeal membrane oxygenation: 7.1%).⁴¹

MERS virus is stable in aerosol form, thus exacerbating the nosocomial spread of the virus during aerosol-generating procedures. Hence, employment of strict infection control measures is needed to prevent nosocomial outbreaks.^{46,53}

Summary and recommendations

- The SARS-CoV and MERS-CoV human outbreaks are characterized by healthcare-associated infections
- All individuals who develop respiratory illness within 14 days after travelling to countries in the Arabian peninsula or who have had close contact with MERS cases should report to a healthcare provider for an evaluation and be on home isolation to prevent transmission
- Healthcare personnel should adhere to the recommended infection prevention and control (IPC) measures, including standard, contact and airborne precautions
- Healthcare personnel should be aware of the increased risk of nosocomial spread during aerosol-generating procedures in MERS cases, thus they are recommended to use PPE during those procedures

MULTIDRUG-RESISTANT GRAM-NEGATIVE ORGANISMS

Carbapenem-resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPA) are of significant concern worldwide.^{54,55}

In particular, CRE have also been found in the environment and community in India, Pakistan and Vietnam.⁵⁶ Among many carbapenemases, *Klebsiella pneumoniae* carbapenemases (KPC) are the most common transmissible class A genes in *Enterobacteriaceae*, characterized by the clonal expansion of CC258 strains.^{54,57} However, after the discovery of the New Delhi metallo-β-lactamase-1 (NDM-1) gene in 2008, there has been global concern for the rapid spread of NDM genes among countries and bacterial species; currently, NDM-type genes predominate in India and Pakistan.^{55,58} Notably, however, transmissible polymyxin-resistance gene (*mcr-1*) was also discovered, and cases infected by *Enterobacteriaceae* harbouring both carbapenemase and *mcr-1* genes have been reported.^{56,59}

Table 2 Comparisons of clinical and epidemiological features between SARS-CoV and MERS-CoV infections in human

	SARS-CoV ^{37,42–44}	MERS-CoV ^{39–41,45–48}
Genus	Beta-CoV lineage B	Beta-CoV lineage C
First human case	China in 2002	Saudi Arabia in 2012
Regions with human cases	China, Hong Kong, Singapore, Vietnam, United States and Canada	Saudi Arabia, United Kingdom, South Korea Arab Emirates, Qatar, Oman and Iran
Total number of human cases (years)	8422 cases (November 2002–July 2003) But, the last case was reported in May 2004	2182 (September 2012–February 2018) ⁴⁶ One recent case in Oman in November 2017
Median ages (years)	Less than or equal to 45 years	56 (14–94)
Incubation period (days)	4.6 (3.8–5.8)	5.2 (1.9–14.7)
Clinical characteristics	Invasive mechanical ventilation in 17%	Invasive mechanical ventilation in 37% (70% in another case series) Frequent acute kidney injury (~43%) Frequent vasopressor use Pneumonia in 80.8% (Korea) ³⁹
Mortality rate	9.6% (774/8098 cases) ³⁷ 11.0% (916/8422 cases) ⁴⁴	39.0% in Saudi Arabia 20.4% in Korea ³⁹
Epidemiological features	Female predominance Nosocomial transmission Healthcare worker: 22% in China or >40% in Canada Mostly young people	Most cases from Arabian Peninsula Underlying co-morbidities (96%) Human-to-human transmission (~50%) in Saudi Arabia Nosocomial transmission Healthcare worker: 21% in Korea A large outbreak in Korea (2015)
Risk factors	Employment in an occupation associated with an increased SARS-CoV exposure Close contact of a person under investigation for SARS Travelling to areas experiencing an outbreak	Direct contact to dromedaries Travel to Middle East and North Africa

CoV, coronavirus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

To prevent the dissemination of these organisms, infection control measures should be implemented in healthcare facilities.⁶⁰ In addition, considering the indiscriminate use of antibiotics worldwide, strengthening the surveillance of antibiotic resistance and strict controls on antibiotic use (e.g. stewardship programme) should be emphasized.^{61–64}

Summary and recommendations

- Healthcare personnel should be alert to the spread of carbapenem-resistant Gram-negative bacteria, particularly in Asian countries
- Infection control measures, such as hand hygiene, surveillance, isolation or cohorting of patients, contact precautions and environmental cleaning, should be employed in healthcare facilities
- Strengthening the surveillance of antibiotic resistance and strict controls on antibiotic use are needed to tackle the increasing antibiotic resistance

HOW TO PREVENT THE TRANSMISSION OF INFECTIOUS DISEASES IN HEALTHCARE SETTINGS

In an era of emerging infectious diseases, multimodal IPC strategies are of great importance in healthcare settings in terms of the safety of patients and healthcare workers.⁶⁵ In 2014, the WHO released revised guidelines for IPC of epidemic- and pandemic-prone acute respiratory diseases in healthcare settings. We recommend that healthcare workers follow the guidelines to prevent transmission of infectious diseases.⁶⁵

Summary and recommendations

- In healthcare settings, IPC measures including droplet precaution (e.g. wearing a surgical mask), contact precaution (e.g. hand washing or wearing gloves and gown) and airborne precaution (e.g. isolation room with negative pressure) should be implemented

- We recommend the use of clinical triage for the early identification of patients with acute respiratory infections (ARI)
- Isolation or cohorting of patients is recommended to prevent the transmission of ARI pathogens
- We recommend the use of appropriate PPE when providing care to patients with ARI (e.g. masks, gloves, long-sleeved gowns, and eye protections with goggles or facial shields)
- We recommend the use of PPE and adequately ventilated single rooms when performing aerosol-generating procedures
- Vaccination of healthcare workers caring for patients at high risk of ARI is recommended

AIR TRAVEL

Most modern aircraft have air recirculation systems, using high-efficiency particulate air (HEPA) filters for air quality, and research has shown that the risk of infectious disease transmission is low during flight.^{66,67} However, the spread of SARS and A(H7N9) viruses indicated an important role for air travel in spreading respiratory pathogens among countries.^{5,6,68}

If a passenger develops symptoms suggesting respiratory infection during flight, the passenger should be isolated, if possible, and wear a surgical face mask. The flight attendant should notify public health authorities at the destination airport via air traffic control, in accordance with the International Civil Aviation Procedures for Air Navigation Services-Air Traffic Management (ICAO PANS-ATM).⁶⁹⁻⁷¹ For novel influenza virus with pandemic potential or AI virus, we can refer to the recommendations by the Centers for Disease Control and Prevention (CDC)⁷⁰ or the guidelines by the European CDC.⁶⁹

Summary and recommendations

- People who are acutely ill or have a fever should delay their travel until they have recovered
- If a passenger develops symptoms suggesting respiratory infection during flight, the passenger should be isolated, if possible, and wear a surgical face mask. The flight attendant should notify public health authorities at the destination airport.
- Passengers seated within a distance of two seats in all directions around the index case and close contacts (e.g. crew, travel companions and persons providing care) should be subject to contact investigation based on the situational risk assessment

'ONE HEALTH' APPROACH

Adopting the 'One Health' approach may lead to further improvement of global pandemic preparedness⁷²⁻⁷⁴ and

enable a paradigm shift from detection and response to the prevention of emerging infections, resulting in better protection of animals and humans.⁷⁵⁻⁷⁷

Summary and recommendations

- For the 'One Health' approach, communication and collaboration between countries are of paramount importance
- The first step should be building trust between countries and between communities
- Academic or commercial barriers, which can hamper information sharing, should be removed

Abbreviations: AI, avian influenza; ARI, acute respiratory infection; CDC, Centers for Disease Control and Prevention; CoV, coronavirus; CRE, Carbapenem-resistant *Enterobacteriaceae*; HPAI, highly pathogenic AI; Influenza A(H1N1)pdm09, 2009 pandemic influenza A(H1N1); IPC, infection prevention and control; LPAI, low pathogenic AI; MERS, Middle East respiratory syndrome; NDM, New Delhi metallo- β -lactamase; PPE, personal protective equipment; SARS, severe acute respiratory syndrome; WHO, World Health Organization.

REFERENCES

- 1 Kotsimbos T, Waterer G, Jenkins C, Kelly PM, Cheng A, Hancox RJ, Holmes M, Wood-Baker R, Bowler S, Irving L *et al.*; Thoracic Society of Australia and New Zealand H1N1 Influenza 09 Task Force. Influenza A/H1N1_09: Australia and New Zealand's winter of discontent. *Am. J. Respir. Crit. Care Med.* 2010; **181**: 300-6.
- 2 WHO. Weekly epidemiological record. [Accessed 5 Nov 2017.] Available from URL: http://apps.who.int/iris/bitstream/10665/252537/1/WER9151_52.pdf?ua=1
- 3 Yoo BK. How to improve influenza vaccination rates in the U.S. *J. Prev. Med. Public Health* 2011; **44**: 141-8.
- 4 Elbahesh H, Saletti G, Gerlach T, Rimmelzwaan GF. Broadly protective influenza vaccines: design and production platforms. *Curr. Opin. Virol.* 2018; **26**: 1-9.
- 5 Hui DSC, Lee N, Chan PKS. A clinical approach to the threat of emerging influenza viruses in the Asia-Pacific region. *Respirology* 2017; **22**: 1300-12.
- 6 CDC. Asian lineage avian influenza A(H7N9) virus. [Accessed 5 Nov 2017.] Available from URL: <https://www.cdc.gov/flu/avianflu/h7n9-virus.htm>
- 7 WHO. Emergencies preparedness, response. Human infection with avian influenza A(H7N9) virus - China. [Accessed 5 Nov 2017.] Available from URL: <http://www.who.int/csr/don/26-october-2017-ah7n9-china/en/>
- 8 Lai S, Qin Y, Cowling BJ, Ren X, Wardrop NA, Gilbert M, Tsang TK, Wu P, Feng L, Jiang H *et al.* Global epidemiology of avian influenza A H5N1 virus infection in humans, 1997-2015: a systematic review of individual case data. *Lancet Infect. Dis.* 2016; **16**: e108-18.
- 9 Hui DS. Review of clinical symptoms and spectrum in humans with influenza A/H5N1 infection. *Respirology* 2008; **13**(Suppl. 1): S10-3.
- 10 Animal Production and Health. H7N9 situation update. [Accessed 20 Aug 2018.] Available from URL: http://www.fao.org/ag/againfo/programmes/en/empres/h7n9/situation_update.html
- 11 Li Q, Zhou L, Zhou M, Chen Z, Li F, Wu H, Xiang N, Chen E, Tang F, Wang D *et al.* Epidemiology of human infections with

- avian influenza A(H7N9) virus in China. *N. Engl. J. Med.* 2014; **370**: 520–32.
- 12 Tanner WD, Toth DJ, Gundlapalli AV. The pandemic potential of avian influenza A(H7N9) virus: a review. *Epidemiol. Infect.* 2015; **143**: 3359–74.
 - 13 Zhang R, Chen T, Ou X, Liu R, Yang Y, Ye W, Chen J, Yao D, Sun B, Zhang X *et al.* Clinical, epidemiological and virological characteristics of the first detected human case of avian influenza A(H5N6) virus. *Infect. Genet. Evol.* 2016; **40**: 236–42.
 - 14 WHO. Avian influenza weekly update number 584. [Accessed 15 Nov 2017.] Available from URL: http://www.wpro.who.int/emerging_diseases/ai_weekly_584_wpro_20170512.pdf
 - 15 Yang ZF, Mok CK, Peiris JS, Zhong NS. Human infection with a novel avian influenza A(H5N6) virus. *N. Engl. J. Med.* 2015; **373**: 487–9.
 - 16 WHO. Influenza at the human-animal interface. [Accessed 17 Nov 2017.] Available from URL: http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_25_02_2016.pdf
 - 17 Cheng VC, Chan JF, Wen X, Wu WL, Que TL, Chen H, Chan KH, Yuen KY. Infection of immunocompromised patients by avian H9N2 influenza A virus. *J. Infect.* 2011; **62**: 394–9.
 - 18 Bui CM, Chughtai AA, Adam DC, MacIntyre CR. An overview of the epidemiology and emergence of influenza A infection in humans over time. *Arch. Public Health* 2017; **75**: 15–21.
 - 19 Liu M, Li X, Yuan H, Zhou J, Wu J, Bo H, Xia W, Xiong Y, Yang L, Gao R *et al.* Genetic diversity of avian influenza A (H10N8) virus in live poultry markets and its association with human infections in China. *Sci. Rep.* 2015; **5**: 7632.
 - 20 Xu Y, Cao H, Liu H, Sun H, Martin B, Zhao Y, Wang Q, Deng G, Xue J, Zong Y *et al.* Identification of the source of A (H10N8) virus causing human infection. *Infect. Genet. Evol.* 2015; **30**: 159–63.
 - 21 CDC. Morbidity and Mortality Weekly Report. [Accessed 20 November 2017.] Available from URL: <https://www.cdc.gov/mmwr/volumes/65/wr/mm6542a1.htm>
 - 22 CDC. Influenza (flu). Case count: detected U.S. human infections with H3N2v by state since August 2011. [Accessed 20 Nov 2017.] Available from URL: <https://www.cdc.gov/flu/swineflu/h3n2v-case-count.htm>
 - 23 Jhung MA, Epperson S, Biggerstaff M, Allen D, Balish A, Barnes N, Beaudoin A, Berman L, Bidol S, Blanton L *et al.* Outbreak of variant influenza A(H3N2) virus in the United States. *Clin. Infect. Dis.* 2013; **57**: 1703–12.
 - 24 Zhou L, Tan Y, Kang M, Liu F, Ren R, Wang Y, Chen T, Yang Y, Li C, Wu J *et al.* Preliminary epidemiology of human infections with highly pathogenic avian influenza A(H7N9) virus, China, 2017. *Emerg. Infect. Dis.* 2017; **23**: 1355–9.
 - 25 World Organization for Animal Health. OIE expert mission finds live bird markets play a key role in poultry and human infections with influenza A(H7N9). [Accessed 5 Nov 2017.] Available from URL: <http://www.oie.int/en/for-the-media/press-releases/detail/article/oie-expert-mission-finds-live-bird-markets-play-a-key-role-in-poultry-and-human-infections-with-infl/>
 - 26 Yuen KY, Chan PK, Peiris M, Tsang DN, Que TL, Shortridge KF, Cheung PT, To WK, Ho ET, Sung R *et al.* Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; **351**: 467–71.
 - 27 Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, Hayden FG, Nguyen DH, de Jong MD, Naghdaliyev A, Peiris JS, Shindo N, Soerose S *et al.*; 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.
 - 28 WHO. Emergencies preparedness, response. Avian influenza – situation in Viet Nam – update. [Accessed 5 Dec 2017.] Available from URL: http://www.who.int/csr/don/2012_03_12/en/
 - 29 Wang H, Feng Z, Shu Y, Yu H, Zhou L, Zu R, Huai Y, Dong J, Bao C, Wen L *et al.* Probable limited person-to-person transmission of highly pathogenic avian influenza A (H5N1) virus in China. *Lancet* 2008; **371**: 1427–34.
 - 30 Wang TT, Parides MK, Palese P. Seroprevalence for H5N1 influenza infections in humans: meta-analysis. *Science* 2012; **335**: 1463.
 - 31 Wei SH, Yang JR, Wu HS, Chang MC, Lin JS, Lin CY, Liu YL, Lo YC, Yang CH, Chuang JH *et al.* Human infection with avian influenza A H6N1 virus: an epidemiological analysis. *Lancet Respir. Med.* 2013; **1**: 771–8.
 - 32 WHO. Zoonotic influenza viruses: antigenic and genetic characteristics and development of candidate vaccine viruses for pandemic preparedness. [Accessed 13 Nov 2017.] Available from URL: <http://apps.who.int/iris/bitstream/10665/259277/1/WER9242-633-647.pdf?ua=1>
 - 33 Khan SU, Anderson BD, Heil GL, Liang S, Gray GC. A systematic review and meta-analysis of the seroprevalence of influenza A(H9N2) infection among humans. *J. Infect. Dis.* 2015; **212**: 562–9.
 - 34 Gu M, Xu L, Wang X, Liu X. Current situation of H9N2 subtype avian influenza in China. *Vet. Res.* 2017; **48**: 49–58.
 - 35 Liu D, Shi W, Shi Y, Wang D, Xiao H, Li W, Bi Y, Wu Y, Li X, Yan J *et al.* Origin and diversity of novel avian influenza A H7N9 viruses causing human infection: phylogenetic, structural, and coalescent analyses. *Lancet* 2013; **381**: 1926–32.
 - 36 Liu D, Shi W, Shi Y, Wang D, Xiao H, Li W, Bi Y, Wu Y, Li X, Yan J *et al.* Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study. *Lancet* 2014; **383**: 714–21.
 - 37 WHO. WHO guidelines for the global surveillance of severe acute respiratory syndrome (SARS). Updated recommendations, October 2004. [Accessed 20 Nov 2017.] Available from URL: http://www.who.int/csr/resources/publications/WHO_CDS_CSR_ARO_2004_1/en/
 - 38 Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet* 2015; **386**: 995–1007.
 - 39 Choi WS, Kang CI, Kim Y, Choi JP, Joh JS, Shin HS, Kim G, Peck KR, Chung DR, Kim HO *et al.* Clinical presentation and outcomes of Middle East respiratory syndrome in the Republic of Korea. *Infect. Chemother.* 2016; **48**: 118–26.
 - 40 WHO. Middle East respiratory syndrome coronavirus (MERS-CoV). [Accessed 26 Nov 2017.] Available from URL: <http://www.who.int/emergencies/mers-cov/en/>
 - 41 WHO. WHO MERS-CoV global summary and assessment of risk. [Accessed 20 Nov 2017.] Available from URL: <http://www.who.int/emergencies/mers-cov/risk-assessment-july-2017.pdf?ua=1>
 - 42 Yin Y, Wunderink RG. MERS, SARS and other coronaviruses as causes of pneumonia. *Respirology* 2018; **23**: 130–7.
 - 43 WHO. Emergencies preparedness, response. China's latest SARS outbreak has been contained, but biosafety concerns remain – Update 7. [Accessed 26 Nov 2017.] Available from URL: http://www.who.int/csr/don/2004_05_18a/en/
 - 44 Chan-Yeung M, Xu RH. SARS: epidemiology. *Respirology* 2003; **8** (Suppl.): S9–14.
 - 45 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.
 - 46 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.
 - 47 WHO. Emergencies preparedness, response. Middle East respiratory syndrome coronavirus (MERS-CoV) – Oman. [Accessed 26 Nov 2017.] Available from URL: <http://www.who.int/csr/don/10-november-2017-mers-oman/en/>
 - 48 Assiri A, Al-Tawfiq JA, Al-Rabeeh AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, Flemban H, Al-Nassir WN, Balkhy HH, Al-Hakeem RF *et al.* Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect. Dis.* 2013; **13**: 752–61.

- 49 Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, Ahuja A, Yung MY, Leung CB, To KF *et al.* A major outbreak of severe acute respiratory syndrome in Hong Kong. *N. Engl. J. Med.* 2003; **348**: 1986–94.
- 50 Chen WQ, Ling WH, Lu CY, Hao YT, Lin ZN, Ling L, Huang J, Li G, Yan GM. Which preventive measures might protect health care workers from SARS? *BMC Public Health* 2009; **9**: 81–8.
- 51 Christian MD, Poutanen SM, Loutfy MR, Muller MP, Low DE. Severe acute respiratory syndrome. *Clin. Infect. Dis.* 2004; **38**: 1420–7.
- 52 WHO. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. [Accessed 20 Nov 2017.] Available from URL: http://www.who.int/csr/sars/country/table2004_04_21/en/index.html
- 53 CDC. Middle East respiratory syndrome (MERS). People who may be at increased risk for MERS. [Accessed 10 Mar 2018.] Available from URL: <https://www.cdc.gov/coronavirus/mers/risk.html>
- 54 Logan LK, Weinstein RA. The epidemiology of carbapenem-resistant Enterobacteriaceae: the impact and evolution of a global menace. *J. Infect. Dis.* 2017; **15**: S28–36.
- 55 Hsu LY, Apisarntharak A, Khan E, Suwatarat N, Ghafur A, Tambyah PA. Carbapenem-resistant *Acinetobacter baumannii* and Enterobacteriaceae in South and Southeast Asia. *Clin. Microbiol. Rev.* 2017; **30**: 1–22.
- 56 Du H, Chen L, Tang YW, Kreiswirth BN. Emergence of the mcr-1 colistin resistance gene in carbapenem-resistant Enterobacteriaceae. *Lancet Infect. Dis.* 2016; **16**: 287–8.
- 57 Patel G, Bonomo RA. "Stormy waters ahead": global emergence of carbapenemases. *Front. Microbiol.* 2013; **4**: 48.
- 58 Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. *Biomed. Res. Int.* 2014; **2014**: 249856.
- 59 Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X *et al.* Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect. Dis.* 2016; **16**: 161–8.
- 60 WHO. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities. [Accessed 20 Aug 2018.] Available from URL: <http://www.who.int/infection-prevention/publications/guidelines-cre/en/>
- 61 European Centre for Disease Prevention and Control. European Antimicrobial Resistance Surveillance Network (EARS-Net). [Accessed 31 Dec 2018.] Available from URL: <https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks/ears-net>
- 62 WHO. Global antimicrobial resistance surveillance system (GLASS). [Accessed 31 Dec 2018.] Available from URL: <https://www.who.int/glass/en/>
- 63 Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther. Adv. Drug Saf.* 2014; **5**: 229–41.
- 64 WHO. Global action plan on antimicrobial resistance. [Accessed 31 Dec 2018.] Available from URL: <https://www.who.int/antimicrobial-resistance/global-action-plan/en/>
- 65 WHO. Emergencies preparedness, response. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care. [Accessed 10 Mar 2018.] Available from URL: http://www.who.int/csr/bioriskreduction/infection_control/publication/en/
- 66 Leder K, Newman D. Respiratory infections during air travel. *Intern. Med. J.* 2005; **35**: 50–5.
- 67 Mangili A, Vindenes T, Gendreau M. Infectious risks of air travel. *Microbiol. Spectr.* 2015; **3**: 1–10.
- 68 Leitmeyer K. European risk assessment guidance for infectious diseases transmitted on aircraft – the RAGIDA project. *Euro. Surveill.* 2011; **16**: pii: 19845.
- 69 ECDC. Risk assessment guidelines for infectious diseases transmitted on aircraft (RAGIDA): influenza. [Accessed 20 Aug 2018.] Available from URL: <https://ecdc.europa.eu/en/publications-data/risk-assessment-guidelines-infectious-diseases-transmitted-aircraft-ragida>
- 70 CDC. Quarantine and isolation. Protecting travelers' health from airport to community: investigating contagious diseases on flights. [Accessed 20 Aug 2018.] Available from URL: <https://www.cdc.gov/quarantine/contact-investigation.html>
- 71 WHO. WHO technical advice for case management of influenza A(H1N1) in air transport. [Accessed 20 Aug 2018.] Available from URL: [http://www.who.int/ihr/travel/A\(H1N1\)_air_transport_guidance.pdf](http://www.who.int/ihr/travel/A(H1N1)_air_transport_guidance.pdf)
- 72 WHO. FAO/OIE/WHO collaboration (tripartite). [Accessed 15 Nov 2017.] Available from URL: http://www.who.int/foodsafety/areas_work/zoonose/concept-note/en/
- 73 WHO. One Health. [Accessed 15 Nov 2017.] Available from URL: <http://www.who.int/features/qa/one-health/en/>
- 74 McCloskey B, Dar O, Zumla A, Heymann DL. Emerging infectious diseases and pandemic potential: status quo and reducing risk of global spread. *Lancet Infect. Dis.* 2014; **14**: 1001–10.
- 75 Heymann DL, Dar OA. Prevention is better than cure for emerging infectious diseases. *BMJ* 2014; **348**: g1499.
- 76 Vong S, O'Leary M, Feng Z. Early response to the emergence of influenza A(H7N9) virus in humans in China: the central role of prompt information sharing and public communication. *Bull. World Health Organ.* 2014; **92**: 303–8.
- 77 McNabb SJ, Shaikh AT, Nuzzo JB, Zumla AI, Heymann DL. Triumphs, trials, and tribulations of the global response to MERS coronavirus. *Lancet Respir. Med.* 2014; **2**: 436–7.