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Emerging viral respiratory tract infections—environmental risk factors and transmission

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Summary

The past decade has seen the emergence of several novel viruses that cause respiratory tract infections in human beings, including Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia, an H7N9 influenza A virus in eastern China, a swine-like influenza H3N2 variant virus in the USA, and a human adenovirus 14p1 also in the USA. MERS-CoV and H7N9 viruses are still a major worldwide public health concern. The pathogenesis and mode of transmission of MERS-CoV and H7N9 influenza A virus are poorly understood, making it more difficult to implement intervention and preventive measures. A united and coordinated global response is needed to tackle emerging viruses that can cause fatal respiratory tract infections and to fill major gaps in the understanding of the epidemiology and transmission dynamics of these viruses.

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Introduction

Since the recognition of severe acute respiratory syndrome (SARS) in 2003, several new viruses have emerged in different parts of the world. Middle East respiratory syndrome coronavirus (MERS-CoV) was first identified in Saudi Arabia and Jordan in 2012, with several cases documented in European travellers who had visited the Middle East. More than 840 human cases of MERS-CoV infection have been confirmed as of July, 2014. Most patients had respiratory disease with a range of clinical manifestations from mild, asymptomatic cases to severe multisystem illness; mortality was about 38%. Human adenovirus 14 (HAdV14) was first recognised in 1955 and it re-emerged in 2006 in the USA in a slightly different form (HAdV-14p1). Outbreaks have been restricted to the USA and China, with cases totalling in the hundreds, and mortality has been low. Influenza A H7N9 virus emerged in eastern China in early 2013 with very few cases occurring outside of China. As of June, 2014, more than 448 confirmed human cases have been documented with an estimated 39% mortality rate. Avian influenza A H10N8, the first strain of which was isolated from birds several decades ago, emerged in 2013 to infect at least three people in China, leading to one death. Similarly, in 2011 a novel swine-like influenza H3N2 variant virus emerged in two states in the USA, causing disease in 12 people. By the end of 2013, the virus had spread to ten states and caused at least 340 people to be ill (with one death). In this paper, we review the epidemiology of these emerging viruses, including their geographical distribution, modes of transmission, and where appropriate their zoonotic characteristics.

MERS

Geographical distribution

MERS-CoV infection is a new human disease that was first reported in Saudi Arabia in June, 2012 (figure).[1] Retrospective investigation of a hospital outbreak of 13 cases of respiratory infections in Zarqa, Jordan in April, 2012, identified two confirmed and 11 probable cases of which ten were among health-care workers.[2] As of the end of July, 2014, 841 confirmed cases, including 327 deaths (38·4%), have been reported by local

Key messages

- Over the past decade, several new viruses causing respiratory tract disease in human beings have emerged in different parts of the world.
- Human adenovirus (HAdV) 14p1 has been identified in people only, but Middle East respiratory syndrome coronavirus (MERS-CoV), influenza A H7N9, influenza A H10N8, and influenza A H3N2 variant are zoonotic diseases.
- HAdV14 first recognised in 1955 re-emerged in 2006 in the USA and China.
- As of June, 2014, more than 448 confirmed human cases of avian Influenza A H7N9 virus infection have been documented since its first discovery in early 2013.
- Influenza A H7N9 virus can survive for months in the environment, and the absence of clinical signs in poultry, ducks, and wild birds makes it particularly difficult to control.
- An avian influenza H10N8 virus has recently emerged in 2013 to infect at least three people in China.
- In 2011 a novel swine-like influenza A H3N2 variant virus emerged in two states in the USA, and by the end of 2013 it had spread to ten states and caused illness in at least 340 people. The absence of clinical signs among influenza A H3N2 variant infected pigs is a major concern in that people are essentially serving as sentinels of infection.
- First identified in Saudi Arabia in 2012, the number of human cases of MERS-CoV infection have steadily increased to more than 840. Nosocomial transmission to patients and health-care workers has been documented.
- While geographically restricted to the Middle East, MERS-CoV is of major public health concern since millions of pilgrims from 184 countries visit Saudi Arabia for pilgrimage throughout the year.
- There is a mounting evidence suggesting that camels are the likely reservoir of MERS-CoV human infections although the precise mode of transmission to humans remains unknown.
- A united and coordinated global response is needed to tackle new infectious diseases threats posed by novel viruses that can cause fatal respiratory tract infections over the past decade and to fill major gaps that remain in the understanding of their epidemiology and transmission dynamics.

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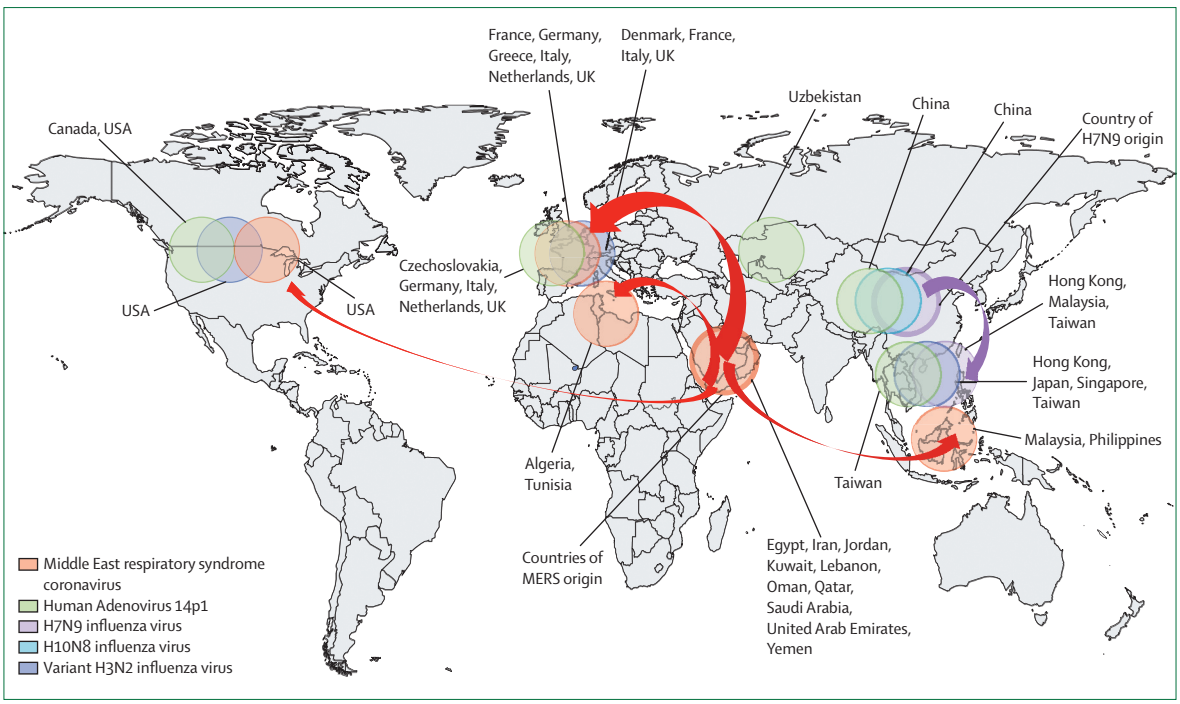

Figure: **Geographical distribution of human cases of emerging respiratory viruses**

authorities worldwide.[3] Almost all confirmed cases were reported from the Middle East, notably Saudi Arabia, but also neighboring countries including Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, United Arab Emirates (UAE), and Yemen. According to the European Centre for Disease Prevention and Control (ECDC), cases have been reported in Algeria, France, Germany, Greece, Italy, Malaysia, the Netherlands, Philippines, Tunisia, the UK, and the USA. Overall, all cases originated from or had a history of travel to the Middle East, with few secondary cases.[3]

Most cases of MERS-CoV infection have been in Saudi Arabia where the Hajj, a large religious mass gathering, takes place each year. The Hajj draws 2–3 million pilgrims from within Saudi Arabia and around the world. Worldwide attention has focused on the potential spread of MERS-CoV after the Hajj pilgrimage because pilgrims have a high risk of respiratory tract infections because of crowded conditions.[4] In 2013, the Saudi Ministry of Health recommended that elderly people (older than 65 years), people with chronic diseases (eg, heart disease, kidney disease, respiratory disease, and diabetes), the immunocompromised (congenital and acquired), people with malignant disease or terminal illnesses, pregnant women, and children (age less than 12 years) postpone their participation in the Hajj and Umrah for their own safety.[5] Investigations done among French pilgrims participating in the 2013 Hajj showed that 48% had at least one disorder for which the Saudi Ministry of Health recommends participation in the Hajj be postponed.[6,7] None of 179 individuals at risk decided to cancel participation, even after receiving this advice during consultation.[6,7] All countries (particularly those with returning pilgrims) were advised by the International Health Regulations Emergency Committee to strengthen their surveillance capacities and ensure robust reporting of any identified cases.[8] Cohort surveys of returning French pilgrims with systematic screening of MERS-CoV nasal carriage by PCR were done in 2012 and 2013, and the results were negative despite high rates of respiratory symptoms.[9,10] However, pilgrims rapidly acquired other respiratory viruses during their stay in Saudi Arabia (especially rhinovirus and influenza viruses, which emphasises the potential of these infections to spread in the pilgrims' home countries on their return.[10,11] Screening of pilgrims from 22 countries before (3210 pilgrims) and after (2025) Hajj in 2013 did not reveal any positive cases by RT-PCR.[12]

Between human transmission of MERS-CoV

Most MERS-CoV cases reported have probably acquired infection through human-to-human transmission. Among 144 confirmed and 17 probable cases analysed by the MERS-CoV Research Group in November, 2013, 95 (59%) were classified as secondary cases with epidemiological links to other confirmed cases. Among these, most acquired the infection in health-care settings (63·2%), followed by those infected in household settings (13·7%).[13] In the same report, clusters of cases secondary to human-to-human transmission occurred with a cluster size ranging from two to 25 patients. The largest cluster was in Al-Hasa

(Saudi Arabia) with 25 cases among patients undergoing hemodialysis, visiting family members, and health-care workers.[14] However, a description of the geographical distribution and phylogenetic relation of MERS-CoV infections across time suggests that the Al-Hasa hospital outbreak might have been caused by more than one virus introduction.[15] Other clusters in the health-care setting have been described in France, Jordan, Qatar, Saudi Arabia, and UAE.[13] Several clusters have been described in the context of the household setting in Saudi Arabia and Tunisia, or in both the contexts of health-care and household settings in the UK.[13,16,17] Transmission in all reported clusters is restricted, and evidence from contact-tracing suggests that transmission did not extend beyond close contacts into the community. Assessment of the between-human transmissibility of MERS-CoV by two teams with available non-hospital epidemiological data confirmed the restricted pattern of transmission. The estimated R_0 was 0·60–0·69 in one study and 0·8–1·3 in another (table 1).[18,19] In the absence of appropriate hospital infection control, R_0 might be greater than 1 in hospitals admitting patients with MERS-CoV.

	Total human cases	Total human deaths	Clusters	Environmental properties	R_0
MERS-CoV*	841	327	Family and health-care settings	Stable at low temperature and low humidity	0·60–0·69 *vs* 0·8–1·3
Human adenovirus 14p1	Many	13	Military and school settings	Unknown	Unknown
H7N9 avian influenza virus	448	157	Family settings	Survives for months in the environment	0·11–0·45
H10N8 avian influenza virus	3	1	None	Water persistence	Unknown
H3N2 variant influenza virus	340	1	Geriatric ward settings	..	Unknown

MERS-CoV=Middle East respiratory syndrome coronavirus. *Data to end of July, 2014.

***Table 1*: Emerging respiratory viruses as of June, 2014**

	Potential sources	Transmission patterns
Middle East respiratory syndrome coronavirus	Human patients, camels, bats, and environment (camel farms)	Human-to-human (59%), sporadic
Human adenovirus 14p1	Human patients and asymptomatic shedders	Sporadic, human-to-human (close and frequent contact)
H7N9 avian influenza virus	Live birds, poultry, environment (bird markets, poultry farms, wet markets — soil and surface waters), and human patients	Direct contact with live poultry, human-to-human (possible but restricted and non-sustainable)
H10N8 avian influenza virus	Live birds and poultry, environment (soil and surface water)	Exposure to poultry
H3N2 variant influenza virus	Pigs, pig environments (agriculture fairs), and human patients	Direct or indirect contact with pigs, human-to-human (possible but restricted and non-sustainable)

***Table 2*: Potential sources and transmission patterns of emerging respiratory viruses**

Evidence for a zoonotic source for MERS-CoV

MERS-CoV belongs to the lineage C βcoronaviruses, which are associated with bats.[20] Close relatives of MERS-CoV have been identified in European, Asian, Central American, and South African bats.[21–27] A new β-coronavirus related to MERS-CoV has also been characterised in European hedgehogs.[28] The genome diversity of human MERS-CoV isolates suggests that human infections result from several independent zoonotic events from an unknown reservoir in the Middle East.[15,29] Among 161 patients with MERS-CoV analysed by the MERS-CoV Research Group in November, 2013, 51 (32%) were classified as probably sporadic (table 2) or index cases (no exposure to other known cases). Contact of patients with camels was documented in only five of 51 cases; however, reliable information was available from only 28 cases.[13] MERS-CoV spike-protein-binding antibodies and virus neutralising antibodies are reported in high proportions of camels from the Canary Islands, Egypt, Jordan, Oman, Qatar, Saudi Arabia, UAE, but not from other livestock including sheep, goats, cattle, and chickens.[30–37] A higher seroprevalence was reported in adults than in juvenile camels.[33,36] Furthermore, MERS-CoV was detected by quantitative (q) RT-PCR from nasal samples in 11 of 14 camels from a farm in Qatar linked to two confirmed human cases, five of 76 camels from Oman, 36 of 104 juvenile camels from Saudi Arabia, 15 of 98 adult camels from Saudi Arabia, and four of 110 camels from Egypt, two of which were imported from Sudan and Ethiopia.[31,33,38,39] Genomic sequences of MERS-CoV isolates from two patients and from their infected camels were almost identical, suggesting camel-to-human transmission.[40,41]

A novel coronavirus (DcCoV UAE-HKU23) was detected by qRT-PCR in 21% of faecal samples from dromedary calves in UAE. 97–100% of camels were positive for MERS-CoV antibody testing by various methods, whereas 52% only had antibodies against DcCoV UAE-HKU23, which shows that little correlation exists between seropositivity to the two viruses.[35] Additionally, a gene fragment was recovered from a faecal sample from a bat in Saudi Arabia, near the home of a confirmed human case; bat and human isolates were 100% homologous.[42] Studies addressing the seroprevalence of MERS-CoV among human beings are highly demanding from a technical perspective, because titres are generally low, and there is crossreactivity between coronaviruses.[43]

Studies done on 624 serum specimens from people in Saudi Arabia, including slaughterhouse workers, by discriminative methods failed to show evidence for the presence of antibodies.[43,44] Dromedary camels harbour the virus and shed MERS-CoV in respiratory secretions. The frequency of positive serology in camels versus human beings strongly suggests that camels are the reservoir for human exposure. Unpasteurised camel

milk is a possible route of transmission, but so far few studies have assessed the prevalence of MERS-CoV in camel milk. A study in April, 2014 showed that camel milk was positive for MERS-CoV by qRT-PCR.[45] Finally, the reservoirs might have complex ecology, and bats might play a part.

Evidence for environmental source for MERS-CoV

Only one study has investigated the stability of MERS-CoV under different environmental conditions.[46] MERS-CoV was stable at low temperatures and low humidity and could be recovered after 48 h at 20°C and 40% relative humidity. Aerosolisation of MERS-CoV did not affect its stability. These data show the potential for MERS-CoV to be transmitted via contact or fomite transmission as a result of prolonged environmental presence.

Putative mode of transmission of MERS-CoV

The exact mode of transmission of MERS-CoV is unknown. However, several MERS-CoV clusters have implicated human-to-human transmission among health-care worker, hospital inpatient, and family cluster case series.[47] Such transmission could be through respiratory droplets or direct or indirect contact.[48] With a model developed by measurement of the hardness of coronavirus inner and outer protein shells, MERS-CoV was predicted to be readily transmitted through an oral–faecal route and also possibly via respiratory secretions.[49]

Human adenovirus 14

Geographical distribution

HAdDV-14 was first discovered in 1955 during an outbreak of acute respiratory infections among military trainees in the Netherlands.[50] Soon after, other outbreaks were reported in Czechoslovakia, England, and Uzbekistan (figure).[51–54] The circulation and case reports of HAdV-14 infections ceased during the early 1960s until the beginning of the 1970s when the virus was again detected in the Netherlands.[53] In the early part of this century, suspected cases of HAdV-14 were identified in Taiwan.[55] During 2006, a variant of HAdV-14 (later dubbed HAdV-14p1) caused epidemics among US military trainees in five states: California, Georgia, Illinois, Montana, and Texas.[53,56,57] From 2003 until now, sporadic HAdV-14p1 cases and clusters of cases were also described among civilians throughout the USA (Alaska, California, Kansas, New York, Oklahoma, Oregon, Pennsylvania, South Carolina, Texas, Washington, and Wisconsin)[53,58–61] In 2009–10, nine sporadic cases were reported in Ireland.[61] In October 2010, HAdV-14p1 was detected by culture in a 17-month-old child with tonsillitis living in Guangzhou, southern China.[62] In December 2010, HAdV-14p1 was isolated from a 6-month-old child presenting with pneumonia in Beijing, China.[63] In April 2011, an outbreak occurred affecting 43 children (8–15 years old) attending school in the Tongwei County of the Gansu province (northwestern China), of whom 11 were identified with infection of HAdV-14p1.[64] During summer 2011, three sporadic epidemiologically unrelated HAdV-14p1 cases were identified in the Canadian province of New Brunswick.[65]

Between-human transmission of HAdV-14p1

HAdVs are chiefly transmitted via direct contact, aerosol, or contact with fomites. HAdV-14 strains are predominantly associated with upper and lower respiratory infections, and hence respiratory secretions are infectious. Adenoviruses are ubiquitous in military training facilities.[66] People at risk of HAdV-14p1 infection include military trainees, young children, and the immunocompromised (table 1). During HAdV outbreaks, the high prevalence of asymptomatic infected individuals renders the surveillance and targeted countermeasures very difficult to enforce (table 2). So far, the basic reproductive rate (R_0) has not been estimated for HAdV-14p1.

Evidence for a zoonotic source for HAdV-14p1

Cross-species transmission of a simian adenovirus from monkeys to man has been documented with scarce human-to-human infection.[67,68] HAdV-14 strains are human adenovirus B (mastadenoviruses of the family Adenoviridae); all other adenovirus B are human viruses (HAdV-3, 7, 11, 16, 21, 34, 35, 50) except for the simian adenovirus 21.[69] Most of the simian adenoviruses isolated from non-human primates are phylogenetically related to human adenoviruses and belong to the species B, C, and E.[70] However, there are no observational data to suggest that human HAdV-14p1 infections might be epidemiologically linked to contact with non-human primates. There is no evidence that HAdV-14p1 is zoonotic.

Evidence for environmental sources of HAdV-14p1

No specific data for HAdV-14p1 suggest either an environmental reservoir or an environmental source of infection. However, other human adenoviruses are stable in the environment, and HAdV-B14p1 probably has similar characteristics. The infectivity of mastadenoviruses is suppressed after 10 min at 56°C or above; they are infectious when frozen, stable when exposed to mild acids, and insensitive to lipid solvents.[69]

Putative mode of transmission of HAdV-14

No study is specifically dedicated to the transmissions of HAdV-14p1; however, this virus is probably transmitted through mechanisms similar to those recorded for other human adenoviruses that cause respiratory tract infections. Adenoviruses frequently cause epidemics among military trainees, children (especially newborns), institutionalised people in hospitals and nursing homes, and immunocompromised people.[71–74] Because of their innate nature, adenoviruses are hardy and resistant to

environmental changes; they can be transmitted directly from person to person, and indirectly from environment to person.[69] For HAdV-14p1, the substantial proportion of epidemic episodes that occurred in a community (eg, schools and military camps) suggests that close proximity is a key factor for outbreaks.[53]

Avian influenza H7N9 virus

Geographical distribution

The outbreak of a human novel influenza A H7N9 virus infection that occurred in early 2013 in eastern China (figure) raised serious concerns among public health professionals about the possibility of an imminent influenza pandemic.[75,76] As of June, 2014, more than 440 laboratory-confirmed cases and more than 150 deaths from influenza A H7N9 have occurred.[77] Novel influenza A H7N9 spread rapidly, involving numerous provinces in China, Hong Kong, Malaysia, and Taiwan.[76,78] Influenza A H7N9 virus infections are associated with fever, chills, shivering, cough, chest pain, dyspnoea, nausea and vomiting,[79] lymphocytopenia, leucopenia,[80] hyperpyrexia, respiratory failure, acute respiratory distress syndrome, multiorgan failure,[81] fulminant pneumonia, septic shock, rhabdomyolysis, and encephalopathy.[82]

Between-human transmission

The poorly understood pathogenesis and unknown mode of transmission of H7N9,[83] coupled with the absence of mass deaths in poultry and wild birds before disease outbreaks makes public health intervention measures difficult to implement.[84] The risk of human-to-human transmission of influenza A H7N9 is controversial since cases of family clustering could be a result of between-human transmission or a result of common exposure to infected poultry or other environmental risk factors.[85] Some researchers argue that routes of human infections are only through exposure to poultry, wild birds, or via avian environmental exposures.[75] They claim that between-human transmission is unlikely since many close contacts of confirmed H7N9 cases did not have evidence for influenza A H7N9 infection.[80] Supporters of the bird-exposure hypothesis also argue that the reduction in human H7N9 cases after the April 2013 closure of live poultry and bird markets supports their view.[86] Furthermore, they argue that recorded family clustering can be explained as a result of common exposure to birds or their environments and not as a result of human-to-human transmission.[79] Some researchers also used mathematical models to suggest that the reproduction number for human-to-human transmission of the novel influenza A H7N9 is well below unity[87] Other researchers argue that there is a strong possibility of restricted and non-sustainable H7N9 human-to-human transmission.[81] They argue that a confirmed case, without exposure to live birds or live poultry markets, developed the disease and died of multiorgan failure after taking care of a confirmed sick close relative who also died of the disease, with the genome sequencing of the viruses isolated from the two patients being almost identical.[81] A case-control study also excluded a participant from the study on the grounds of being infected with a possible human-to-human transmission.[88] Another study showed that some close relatives of confirmed cases developed respiratory symptoms but did not give positive results for influenza A H7N9 virus, thereby stating that, although low, the risk of human-to-human transmission is still a possibility.[89]

Evidence for a zoonotic source

Exposure to infected poultry seems to be the major cause of human infection with influenza A H7N9 (table 2)[75,76,87] because of the strong similarity between influenza A H7N9 isolates detected among human beings and poultry.[80] Almost all cases had either a direct contact with live poultry[89] or were exposed to environmental sources such as live bird markets, poultry farms, and wet markets where live birds are slaughtered and processed.[75,76,79] Most outbreaks occurred in provinces along the eastern Asian–Australian flyway, along which migratory birds travel, flying over areas with densely populated poultry farms, live bird markets, rice farms, and free grazing ducks.[84,90,91] Influenza A H7N9 viruses have been isolated from chickens and pigeons in markets in some of the affected provinces,[79,80] and from poultry cages and faeces in some live poultry and bird markets in the provinces.[88]

Evidence for an environmental source

Environmental factors have important roles in the onset and maintenance of H7N9 outbreaks.[90] Many of the confirmed cases had occupational exposures such as being a poultry worker, slaughtering birds in wet poultry markets, or visiting or purchasing live birds or poultry from live bird markets.[76,85,89] Environmental samples in live poultry markets yielded positive results for the novel influenza H7N9 virus,[76] which was also isolated from contaminated soils and surface water[90] and from the immediate environment of a confirmed case.[76] H7N9 can survive for months in the environment thereby leading to risk of infections to poultry or human beings long after initial detection (table 1).[76,90] Since the closure of live bird markets, which create environments allowing prolonged and repeated exposure of live birds and people (thereby increasing the risk of disease outbreaks), there has been a substantial decrease in the number of human cases of H7N9 in the affected regions.[92]

Putative modes of transmission

The transmissibility and pathogenesis of the novel influenza A H7N9 are still poorly understood,[76] but direct contact to host agents and exposure to environmental risk factors seem to be the generally approved means of transmission to human beings.[90] Bird-to-human route,

poultry-to-human route, and exposure to environmental risk factors are probably the major causes of human infection with the novel influenza A H7N9,[75,76,79] though some researchers believe that human-to-human transmission is thus far non-sustainable.

Avian influenza H10N8

Geographical distribution

In December, 2013, WHO reported the first human case of avian influenza A H10N8 virus in China (figure),[93,94] but the virus was first isolated from birds in Italy in 1965.[95] Though usually without clinical signs in birds,[96] H10N8 has been isolated in both North America and Asia.[95] All three human cases (including one death) were detected in Nanchang City, Jiangxi Province, China.[93,94] Signs and symptoms are consistent with other influenza-like illnesses and include chills,[93,94] cough, chest pain, shivering, pneumonia, respiratory failure, acute respiratory distress syndrome, and multiorgan failure.[79,82,94] Despite the few human cases,[92] these H10N8 infections are a cause for concern because this is the first H10N8 influenza virus to affect human beings.[95]

Between-human transmission

The small number of human cases of illness caused by influenza A H10N8 infection[94] and absence of adequate information with respect to the reported human cases[95] have made it difficult to fully understand the transmission potential of influenza A H10N8 virus. So far, there is no evidence of between-human transmission of influenza A H10N8 virus because close contacts of the cases have not yet developed influenza A H10N8 infection.[93]

Evidence for a zoonotic source

Evidence points to zoonotic sources as the major cause of infection with influenza A H10N8 virus. All three human cases had live bird market exposures (table 2).[94,96] Avian sources seem to be the major reservoir for H10N8 since the viruses are believed to be circulating without clinical signs among poultry and have been isolated from migratory species.[95]

Evidence for environmental source

Environmental factors seem to have key roles in maintaining the transmission of influenza A H10N8 virus with persistence in water being particularly important to transmission both among birds and to human beings.[96] Influenza A H10N8 has been isolated from water samples from Dongting Lake in Hunan province China in 2007,[96] and a live poultry market in southern China in 2012, thereby showing the importance of environmental factors in its transmission (table 1).

Putative modes of transmission

Since human-to-human transmission of influenza A H10N8 has not been documented,[94] the avian-to-human route of transmission seems to be the main route of human infection.[93] Despite being considered as having low or non-pathogenicity in avian species,[96] the small number of patients might make it difficult to know the actual virulence of influenza A H10N8 virus in people.[93] Studies suggest that nucleotide changes or substitution can increase the transmissibility of the virus in human beings,[95] since wild strains that were non-pathogenic in mice later caused weight loss and death in mice after two lung passages;[96] and genetic analysis of all influenza A H10N8 isolates obtained from the NCBI Influenza Virus Resource Database showed the presence of genetic markers that favour mammalian adaptation or increased virulence in mammals.[95]

Influenza A H3N2 virus

Geographical distribution

Pig H3N2 virus is believed to have circulated among human beings since 1968,[97] with more than 30 human cases reported from 2005 to June 2011 in the USA and Canada (figure).[98–100] The emergence of a variant swine-like influenza A H3N2 virus in July, 2011,[101] however, alarmed public health officials. The variant virus likely evolved from the 2009 pandemic influenza A H1N1,[102] many cases had direct or indirect exposure to pigs in agricultural fairs,[98,99,103,104] and this virus seemingly has more pandemic potential than other swine-like viruses.[105] As of June 5, 2014, 340 laboratory-confirmed cases of human influenza A H3N2 and one death have been documented in 13 US states.[101,103,105–108] Additional cases of human influenza A H3N2 have been reported in various countries including Denmark,[109] the UK,[110] Italy,[111] Hong Kong,[112] France,[100] Japan,[113] Taiwan, and Singapore.[114] Disease symptoms are consistent with other influenza-like symptoms, which include fever (temperature >38°C), sore throat, cough, rhinorrhoea, vomiting or diarrhoea, fatigue, myalgia or joint pain,[103,115] headache, lethargy, rhinorrhoea, emesis, dyspnoea, and eye irritation.[99,100]

Between human transmission

Seroepidemiological studies suggest that roughly 90% of US children less than 10 years of age were susceptible to influenza A H3N2 infection.[115–117] Although many studies suggest the occurrence of no or restricted and unsustainable human-to-human transmission of influenza A H3N2,[98,113,118] some researchers believe there is every possibility of human-to-human transmission.[99–104,119] Evidence includes an outbreak of influenza A H3N2 in three geriatric wards in France (table 1),[100] a US daycare centre,[99] and other US case series involving infected people without exposure to pigs.[101,103]

Evidence for a zoonotic source

Pig species are mixing bowls through which avian influenza viruses might mix with other influenza viruses and cross over to human beings (table 2).[120] Many studies suggest that zoonotic sources had important roles in the outbreak of influenza A H3N2 since most confirmed

Search strategy and selection criteria

References for this Series paper were identified through searches of PubMed for articles published in the English and French languages from January, 1994, to June, 2014, through use of the terms "respiratory tract infections", "Middle East Respiratory Syndrome", "MERS-CoV", "influenza", "human adenovirus 14", "H7N9", "H10N8", "H3N2 variant", "Environmental", and "Risk factor". We reviewed articles resulting from these searches and relevant references cited in those articles.

human cases had direct or indirect exposure to pigs during agricultural fairs.[99,100,104,105] Pig samples taken from agricultural fairs have tested positive for H3N2,[97,121,122] and one study documented antigenic similarity between H3N2 taken from pigs in agricultural fairs and those associated with commercial pig farms,[107] thereby showing the importance of pigs in the transmission and maintenance of H3N2 among human beings.

Evidence for an environmental source

The high rate of outbreaks of human influenza A H3N2 among people that attended or exhibited at the agricultural fairs,[98,99,103,104] suggests that there is a substantial association between disease outbreaks and physical location of individuals. Agricultural fairs are recognised as a potential place for pigs and human beings to share pathogens,[98] thereby creating enabling environments for the re-assortment of pig and human viruses with the potential of generating novel viruses.[118]

Putative modes of transmission

The pig-to-human route is probably the main transmission route for influenza A H3N2, whereas human-to-human transmission is likely a secondary mechanism.[98,99,103,104] As a respiratory virus, common means of H3N2 transmission include direct contact, respiratory droplets, and aerosol particles from infected pigs or people. The acquisition of the matrix gene from the 2009 pandemic virus is believed to have caused influenza A H3N2 to be more virulent than the seasonal H3N2 strains.[101]

Conclusion

While HAdV-14p1 has been identified in humans only, MERS-CoV, influenza A H7N9, influenza A H10N8, and influenza A H3N2 are zoonotic diseases. There is a mounting evidence suggesting that camels are the likely reservoir of human exposure to MERS-CoV. Influenza A H7N9 and influenza A H10N8 reservoirs consist of poultry, ducks, and wild birds. The influenza A H3N2 reservoir consists of pigs. One possible way to prevent these zoonotic infections is avoiding direct contact with these animals or their dairy products in the respective areas of endemicity. It is advisable avoiding staying in environments where such animals are concentrated, including farms and markets. The absence of massive deaths and even of clinical signs among the reservoir animals leaves little or no time for public health preparations and intervention measures to curtail the impacts by culling. Given the possible interhuman transmission of these viruses (notably MERS-Cov and HAdV-14p1), the individual preventive measures aiming at reducing the risk of respiratory infections (use of face-mask, hand hygiene, cough etiquette, social distancing) should be reinforced.

Because of the poor current knowledge of the specific pathogenesis and mode of transmission of HAdV-14p1, recommendations for control and preventive measures have to be extrapolated by reference to other human adenoviruses causing respiratory infections.[123] Fortunately, most HAdV-14p1 infections do not cause severe illness.[124] Thus, direct methods to detect and identify HAdV-14p1, which have been recently described, will help to improve rapidly surveillance and diagnosis.[125] The high mutation or reassortment rate of influenza viruses could lead to the emergence of more virulent and transmissible strains.[76,126] The identification of several novel viruses that can cause fatal respiratory tract infections over the past decade, and major gaps that remain in the understanding of their epidemiology and transmission dynamics, calls for a more united and coordinated global response for tackling new infectious diseases threats.

Contributors

ZAM, AIZ, and JAA-T developed the outlines and assigned lead authors. PG coordinated this Series paper, further developed the manuscript outline, contributed specific text, and oversaw the manuscript development. The other authors all contributed relevant text and tables according to their expertise, and helped in drafting the final manuscript.

Declaration of interests

AZ is the principal investigator of the European Union FP7 grant, RiD-RTI. All other authors declare no competing interests.

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