A Global Perspective on H9N2 Avian Influenza Virus

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Abstract: H9N2 avian influenza viruses have become globally widespread in poultry over the last two decades and represent a genuine threat both to the global poultry industry but also humans through their high rates of zoonotic infection and pandemic potential. H9N2 viruses are generally hyperendemic in effected countries and have been found in poultry in many new regions in recent years. In this review we examine the current global spread of H9N2 avian influenza viruses as well as their host range, tropism, transmission routes and the risk posed by these viruses to human health.

Keywords: H9N2; avian influenza viruses; zoonotic; pandemic potential; poultry
1. Introduction

Influenza A viruses are enveloped members of the *Orthomyxoviridae* family and contain a segmented, negative sense genome encoding 10 core proteins and a variable number of accessory proteins. Influenza A viruses are commonly characterised by their combinations of surface proteins, haemagglutinin (HA) and neuraminidase (NA), giving rise to subtype names such as H1N1, H5N6, or H9N2.

The natural host of influenza viruses are wild waterfowl and sea birds which contain almost every known subtype of influenza (with the exceptions of H17N10 and H18N11 which have only been found in bats) [1]. Viruses sporadically and periodically spill over from wild bird hosts to infect domestic poultry. Generally, these viruses circulate briefly before dying out (either through natural causes or by human interventions such as biosecurity and vaccination), for example the repeated incursions of H7Nx viruses into Europe and North America during the 1990s and 2000s [2-4], occasionally however a lineage of avian influenza will become well adapted to poultry and continue circulating endemically, for example the panzootic goose/Guangdong lineage H5Nx viruses, the recent Chinese H7N9 viruses, and multiple Eurasian H9N2 lineages [5-7].

Avian influenza viruses (AIVs) can be broadly categorised into two groups based on a combination of their pathogenicity in chickens and molecular markers in the HA protein. Highly pathogenic avian influenza viruses (HPAIV) display high pathogenicity in chickens (when tested using an intra-venous pathogenicity index; IVPI) and contain polybasic cleavage sites in HA, resulting in the protein being cleaved by endogenous cellular furin-like proteases, allowing the virus to replicate systemically in birds. Only subtypes H5 and H7 ever show this phenotype in the field with examples of HPAIV including goose/Guangdong-lineage H5Nx viruses, sporadic H7Nx outbreaks, and recent H7N9 viruses. Low pathogenicity avian influenza viruses (LPAIVs) are characterised by low pathogenicity in chickens (as measured by IVPI) and mono- di- or occasionally tri-basic cleavage sites in haemagglutinin, these only allow cleavage of HA by extracellular trypsin-like proteases restricting the virus largely to the respiratory and gastrointestinal tracts.

H9N2 viruses, the topic of this review, are an LPAIV subtype found worldwide in wild birds and are endemic in poultry in many areas of Eurasia and Africa. Compared to H5 and H7 viruses they are somewhat neglected, however recent evidence, summarised in this review, suggests they could potentially have a major role in the emergence of the next influenza pandemic, either directly as an H9N2 subtype virus or through the donation of internal genes to a pandemic virus.

2. History and phylogeography of H9N2 virus in poultry

H9N2 viruses were first isolated from turkeys in the US state of Wisconsin in 1966 [8]. In the following decades the virus was occasionally isolated during sporadic outbreaks in poultry in the Northern USA, and from wild birds and domestic ducks throughout Eurasia [9]. In the early 1990s the virus was first isolated from chickens in China and in the following decades viruses related to this Chinese progenitor have become endemic in farmed poultry across much of Asia, the Middle East, North and West Africa [10] (see Error! Reference source not found.).

H9N2 viruses are nearly uniformly low pathogenicity in the laboratory when tested by IVPI [5,11], however in the field they often exhibit moderate-to-high morbidity and mortality. This is usually associated with confounding factors such as co-infection with bacterial or viral pathogens,
and other factors such as poor nutrition and housing [12-14]. However certain strains can show high
morbidity and mortality in controlled in vivo experiments [5,15].

H9N2 viruses are often found co-circulating in poultry with other AIV subtypes, such as H5 and
H7 HPAIVs. There is good evidence to suggest that prior or concurrent H9N2 infection can mask the
high mortality rate of these viruses allowing ‘silent’ spread of HPAIVs, thwarting surveillance and
subsequent intervention efforts [16,17].

2.1. Phylogeography of H9N2 viruses
Phylogenetically, the HA gene of H9N2 viruses can be broadly split into two major branches, a
Eurasian branch and an American branch. American H9N2 viruses are mostly found in wild birds
though have been known to sporadically infect farmed turkeys and have not been found to stably
circulate in poultry [8]. Eurasian H9N2 viruses, conversely, have established at least 3 stable poultry
lineages, named after their prototypic viruses, A/quail/Hong Kong/G1/1997, A/chicken/Beijing/1/94,
and A/chicken/Hong Kong/Y439/1997, known consequently as the G1, BJ94 (also sometimes known
as the Y280 or G9 lineage) and Y439 (also sometimes known as the Korean lineage) lineages [5]. The
G1 lineage can further be split into two phylogenetic and geographical sub-lineages referred to as the
‘Western’ and ‘Eastern’ sub-lineages.

Global surveillance of LPAIV, such as H9N2, has a problem when compared to HPAIV viruses
in that LPAIV H9N2 is not a notifiable disease and causes relatively few overt human infections. In
many resource-limited regions surveillance is performed sporadically, or not at all. Furthermore,
when the virus is found there is no obligation to report the finding, due to the H9N2 subtype not
being a notifiable disease, therefore presence of virus is only generally reported through publications
or WHO reports (in the case of confirmed human cases). It is likely that H9N2 viruses are present or
even endemic in more countries, particularly in low- and middle-income countries in Africa and Asia,
than is reported below.

2.1.1. East and Southeast Asia
H9N2 viruses are considered endemic in China, Vietnam, and South Korea (see Table 1) [5,18,19].
In recent years, virus has been isolated for the first time in Cambodia, Myanmar, Indonesia, Malaysia
and the Russian Far East; serological evidence suggests the virus may also be present in poultry in
Laos and Thailand [20-26]. BJ94 lineage viruses are found throughout China, Vietnam, Cambodia,
Myanmar and Indonesia. G1 ‘Eastern’ viruses are also found in South China and Vietnam, mostly
infecting minor poultry such as quail. Y439 lineage viruses have been found in wild birds (and
sporadically in poultry) throughout Eurasia but a distinct subset circulates endemically in poultry in
South Korea. Vaccination of poultry has been used in recent years to try to control endemic diseases
in large areas of China and South Korea [27,28].

2.1.2. South Asia
H9N2 viruses are considered endemic in Bangladesh and Pakistan and are likely endemic in
regions of India, Afghanistan and Nepal [29-32]. G1 ‘Western’ viruses constitute the majority of
viruses found in poultry in South Asia, with a few Y439 viruses occasionally spilling over into poultry
from wild birds (but apparently not maintaining sustained transmission). The predominant G1
‘Western’ sub-lineage of viruses in this region (as well as in Iran) appears to have arisen from a
reassortment event between co-circulating HPAIV H7N3 and LPAIV H9N2 viruses, which replaced other local clades [11,33].

2.1.3. The Middle East

H9N2 is frequently isolated from, and therefore probably endemic in poultry in many Middle Eastern countries including Egypt, Iran, Israel, Saudi Arabia, and the United Arab Emirates [29,34-36]. Virus has also been isolated on occasion from Iraq, Jordan, Lebanon and Oman [37-40]. In Israel mass vaccination of poultry, which began in 2003, has had some success in limiting the endemicity of the virus. This vaccine regime has necessitated an update of the vaccine seed strain at least once due to antigenic drift [41]. Extensive surveillance in Israel between 2006 and 2012 has indicated that rather than there being a single in situ evolving strain, viruses appear to be periodically eradicated, then reintroduced into the country.

As with the case in South Asia, the majority of H9N2 viruses found in the Middle East are of the G1 ‘Western’ sub-lineage, with occasional isolation of Y439 lineage viruses, likely originating from direct spillover events from wild birds.

2.1.4. Africa

H9N2 viruses have been isolated from several African countries, the virus appears endemic in poultry in Egypt and has been repeatedly isolated from chickens in Libya and Tunisia [34,42,43]. Additionally, since 2016 the virus has recently been isolated for the first time in countries across West Africa including Morocco, Burkina Faso, Ghana and Algeria as well as in East Africa in Uganda [44-48]. Morocco has subsequently undertaken a mass poultry vaccination programme [44]. All viruses isolated from poultry in Africa have been of the G1 ‘Western’ sub-lineage, related to those circulating in the Middle East in Israel, Jordan, Lebanon and the United Arab Emirates.

H9N2 viruses have been isolated from farmed ostriches in South Africa on several occasions, however due to their homology to wild bird virus isolates (of the Y439 lineage), and subsequent sampling that found no further evidence of circulation of the viruses, it appears these viruses most likely represent dead-end spillover events from wild migratory birds [49].

Finally, there is a single study showing high seropositivity against H9N2 in Nigerian agricultural workers, however no virus has been isolated from this country and H9N2 serological studies are notorious for giving false positives due to cross-reactivity with human influenza viruses [50]. Although surveillance for HPAIVs is ongoing in Nigeria it is unclear whether protocols are used that would pick up presence (or absence) of H9N2 viruses, therefore it remains unclear whether the virus is/was present in this region.

The presence of H9N2 virus in poultry across non-contiguous regions of Africa suggests that additional countries may harbour infection. However, there is no confirmation due to virus not being actively surveyed for, or if found, not being reported due to LPAIs such as H9N2 not being diseases that are notifiable to the OIE.

2.1.5. Europe

There is currently no evidence of endemic H9N2 in poultry in Europe, despite rigorous sampling (especially within the European Union). There is, however, good evidence for the virus in wild birds in Europe, mostly of the Y439 lineage, which occasionally spills over into farmed poultry (generally
turkeys), for example in the UK, the Netherlands, Poland, Hungary, Germany, Italy, and Ireland [51-54]. There is a single report of a G1 lineage H9N2 virus in Germany; however, due to no subsequent reports of this virus, it appears likely this was an anomalous spillover event from wild birds.

Finally, there is a single study showing sero-prevalence of H9N2 antibodies in Romanian agriculture workers [55], similarly to the Nigerian study, H9N2 virus has not been isolated from poultry in this country, therefore it remains to be seen if the virus is truly present here.

2.1.6. The Americas

H9N2 viruses have been isolated from poultry in the USA periodically throughout the second half of the 20th Century, in fact the prototypic H9N2 isolate (A/turkey/Wisconsin/1/1966) was isolated in this period [8]. All isolated viruses have been of the American lineage and appear to be spillover events from wild birds, possibly sea birds which carry genetically closely related viruses in this region. Since the turn of the Century, there has been no evidence of the virus in poultry in the Americas, despite routine surveillance and extensive evidence of other non-H9N2 viruses in poultry (particularly in North America).
| Country          | Years of poultry isolates | Lineages | Status | Recorded human cases/serology |
|------------------|---------------------------|----------|--------|------------------------------|
| Afghanistan      | 2008-09, 2016-17          | G1-W     | Potentially endemic             | No               |
| Algeria          | 2017                      | G1-W     | Potentially endemic             | No               |
| Bangladesh       | 2006-18                   | G1-W, Y439| Endemic                  | Virus isolated  |
| Belgium          | 1983                      | Y439     | H9N2-free                   | No               |
| Burkina Faso     | 2017                      | G1-W     | Potentially endemic           | No               |
| Cambodia         | 2013, 2015                | BJ94, G1-E, Y439 | Potentially endemic     | Serology only |
| China            | 1994-2018                 | BJ94, G1-E, Y439 | Endemic                   | Virus isolated and serology |
| Egypt            | 2011-18                   | G1-W     | Endemic                     | Virus isolated and serology |
| France           | 2003                      | Y439     | H9N2-free                   | No               |
| Germany          | 1994-96, 1998, 2015       | Wild bird, G1-W | H9N2-free          | No               |
| Ghana            | 2017-18                   | G1-W     | Potentially endemic          | No               |
| Hong Kong SAR    | 1999-2000, 2003, 2005-12, 2014-15 | BJ94, G1-E, Y439 | Potentially endemic     | Virus isolated and serology |
| Hungary          | 2001                      | Y439     | H9N2-free                   | No               |
| India            | 2003-04, 2006, 2008-13, 2015 | G1-W     | Potentially endemic          | Serology only    |
| Indonesia        | 2002, 2016-19             | BJ94, Y439| Likely endemic               | No               |
| Iran             | 1998-2017                 | G1-W     | Endemic                     | Serumology only  |
| Iraq             | 2005, 2008, 2014-2016     | G1-W     | Potentially endemic          | No               |
| Israel           | 2000-2014, 2016-2017      | G1-W     | Potentially endemic¹         | No               |
| Italy            | 1983-85, 1989, 1994, 1996 | Y439     | H9N2-free                   | No               |
| Japan (Imported goods only) | 1997, 2001-02, 2015-16 | BJ94     | H9N2-free                   | No               |
| Jordan           | 2003-05, 2007, 2010       | G1-W     | Likely endemic               | No               |
| Kuwait           | 2004, 2010                | G1-W     | Potentially endemic          | No               |
| Laos²            | 2009                      | n/a      | Potentially endemic          | No               |
| Lebanon          | 2004, 2010, 2017-18       | G1-W     | Potentially endemic          | No               |
| Libya            | 2013                      | G1-W     | Potentially endemic          | No               |
| Country          | Year(s) | Subtype | Endemicity            | Notes                                      |
|------------------|---------|---------|-----------------------|--------------------------------------------|
| Malaysia         | 2018    | n/a     | Potentially endemic   | No                                         |
| Morocco          | 2016    | G1-W    | Potentially endemic   | No                                         |
| Myanmar          | 2014-15 | BJ94    | Potentially endemic   | No                                         |
| Nepal            | 2009-11 | G1-W    | Potentially endemic   | No                                         |
| Netherlands      | 2010-11 | Y439    | H9N2-free             | No                                         |
| Nigeria          | n/a     | n/a     | Potentially endemic   | Serology only                              |
| Oman             | 2005-2006, 2019 | G1-W | Potentially endemic | Virus isolated                             |
| Pakistan         | 1998-99, 2003-17, 2019 | G1-W | Endemic | Virus isolated and serology |
| Poland           | 2013-2014 | Y439 | H9N2-free | No                                         |
| Portugal         | 2004    | Y439    | H9N2-free             | No                                         |
| Qatar            | 2008    | G1      | Potentially endemic   | No                                         |
| Romania          | n/a     | n/a     | Unknown               | Serology only                              |
| Russia (Eastern) | 2018    | G1-W, BJ94 | Unknown | No                                         |
| Saudi Arabia     | 1998-2000, 2002, 2005-08, 2010-11, 2013, 2015-16, 2018 | G1-W | Potentially endemic | No                                         |
| South Africa     | 1995, 2008-09 | Y439 | H9N2-free | No                                         |
| South Korea      | 1996, 1999-2012 | Y439 | Potentially endemic | No                                         |
| Thailand         | n/a     | n/a     | Potentially endemic   | Serology only                              |
| Tunisia          | 2010-12, 2014 | G1-W | Potentially endemic | No                                         |
| USA              | 1966, 1978, 1981, 1983, 1985, 1988-89, 1993, 1995, 1997, 1999 | USA | H9N2-free | No                                         |
| UAE              | 1999-2003, 2005-08, 2011, 2015 | G1-W | Potentially endemic | No                                         |
| Uganda           | 2017    | G1-W    | Potentially endemic   | No                                         |
| UK               | 1970, 2010, 2013 | Y439 | H9N2-free | No                                         |
| Vietnam          | 2009, 2012-17 | BJ94, G1-W, Y439 | Likely endemic | Serology only                              |

1 Potential endemicity of Israel is based on apparent recurring epidemics, it is unclear how much is in situ circulation and how much is incursions from surrounding countries. 2 Evidence for H9N2 virus isolated from poultry/humans in these countries (though it is unclear whether any active surveillance has been performed that would detect H9N2). 3 Years where only viruses most likely transmitted directly from wild birds to poultry are shown in italics. All data provided in this table based on
references used in this paper supplemented with sequences from GISAID, NCBI influenza virus resource and FluDB databases as of June 2019 [56-58].

2.2. Hyper-Prevalence of H9N2 viruses in poultry

Whenever H9N2 virus prevalence has been investigated in lower- and middle-income countries, either by poultry sero-surveys or by passive sampling (i.e. random sampling of apparently healthy birds), the virus has been found to be present at extremely high rates, particularly in live bird markets (LBMs). LBMs act as hubs for poultry traders and their birds and are a major component of the disease transmission pathway, shown to maintain AIV dissemination among poultry as well as facilitate zoonotic infection [59,60]. In recent surveys in Vietnam, prevalence of the virus exceeded 3.5% in chickens in LBMs [61,62]; in various Chinese provinces prevalence was found to be upwards of 10% [63-66]. Several separate studies have shown that the prevalence in Bangladesh and Pakistan of H9 viruses in chickens at LBMs and farms was almost 10% [30,67-69]. Another recent study has shown prevalence of upwards of 10% at LBMs in Egypt [70]. Overall, these studies imply a degree of hyperendemicity not seen for other influenza virus subtypes, potentially due to the low pathogenicity phenotype of the virus allowing repeated re-infections of the same birds (in the case of longer-lived layers and breeders) and silent spread between farms and smallholdings.

2.3. H9N2 virus transmission and host tropism in poultry

Four routes of transmission are widely accepted for influenza viruses; droplet, aerosol, faecal-oral, and direct contact [71]. Droplet transmission describes exhaled particles >10 µm which are deposited into the upper respiratory tract, whereas aerosol droplets are typically less than 5 µm and can reach the lower respiratory tract [71]. Contact transmission relies on the transfer of particles to mucous membranes directly, or via a fomite intermediate. For a successful transmission event to occur, enough virus must persist long enough in the external environment to reach the target tissue. Transmission is therefore determined via several viral, host, and environmental aspects, including; (i) the major site of viral replication and viral titres shed. (ii) The distance and frequency between contacts. (iii) Environmental conditions and virus stability. In wild aquatic birds such as ducks and gulls AIVs generally exhibit gastrointestinal tropism and are thought to be spread primarily through the oral-faecal route. In poultry adapted AIVs there exists some heterogeneity in tropism and transmission routes; HPAIV, such as H5N1, have a systemic distribution and are probably transmitted by a combination of the oral-faecal route and airborne transmission, whereas, LPAIVs in chickens tend to show more respiratory tropism, though some strains also show gastrointestinal tropism [15,71-76]. One of the key molecular markers that facilitates adaptation of an AIV from wild aquatic birds to poultry is the deletion of amino acids from the stalk domain of NA, which have been shown to mediate the switch to respiratory tropism in chickens [77,78]. There is good evidence to suggest that many LPAIV strains transmit by the airborne route, the oral-faecal route and the waterborne route [15,75,79]. However, the favoured mechanism of transmission between individuals varies by host species and viral strain.

Many studies have implicated direct contact as an important transmission route for H9N2 viruses in chickens, although indirect routes such as aerosol and faecal-oral have been shown to be important for some strains and many viruses show primarily a respiratory tropism. Although some H9N2 strains have been shown to have an extended tropism in the kidneys or oviducts [80-85].
in the field and experimentally poultry adapted H9N2 viruses are mostly detected from buccal rather than cloacal swabs [15,67,86]. Additionally inoculation of some H9N2 viruses into the respiratory tract is 40 times more effective than gastrointestinal inoculation at initiating infection [84]. However, many of these routes appear to be environmentally contextual, for example, at LBMs communal water sources have been implicated as the major route of transmission of endemic H5N1 and H9N2 viruses [67]. Together these studies indicate that for H9N2 and other enzootic poultry adapted H9N2 viruses, respiratory and contact transmission are likely the primary routes of transmission and that respiratory transmission may partly arise initially as an adaptation to poultry.

3. H9N2 reassortment and evolution

H9N2 viruses, although a threat in their own right, have been recognised recently as having donated gene segments to highly zoonotic viruses, therefore it is suggested that to prevent the emergence of new zoonotic viruses better control of H9N2 viruses is required [87].

3.1. H9N2 viruses as gene donors

The 1997 HPAIV H5N1 outbreak in Hong Kong (the so-called clade zero viruses) has retrospectively been shown to have received its internal gene cassette (all genes except HA and NA) from co-circulating G1 lineage H9N2 viruses [10]. Genotype 57 (G57, also known as genotype S) viruses in China have recently become the predominant genotype circulating in poultry due to their enhanced fitness in poultry [73]. From 2013 onwards, reassortment between these G57 H9N2 viruses and other circulating subtypes resulted in the generation of multiple zoonotic AIVs with a high propensity to cause disease and death in humans as well as poultry such as; H7N9 [7], H10N8 [88] and, most recently, H5N6 [89] all of which contain the 6 genes of the G57 internal gene cassette.

3.2. H9N2 viruses as a gene recipients

As well as donating its entire internal gene cassette there have been multiple instances of H9N2 viruses donating or receiving individual or multiple combinations of genes to or from other AIVs. For example, the predominant H9N2 lineage circulating Pakistan and Bangladesh is known to have received several genes from HPAIV H7N3 and H5N1 viruses [11,33,90]. Additionally, several Chinese H9N2 genotypes contain polymerase genes from H5N1 HPAIV [91]. Conversely several circulating HPAIV H5Nx viruses contain single or multiple genes from H9N2 [89,92,93], including the predominant genotype of H5 HPAIVs circulating in West Africa which contain a PB2 gene most likely donated from an H9N2 virus [94].

3.3. H9N2 Intrasubtypic reassortment

Overall, considering the large overlap and frequent coinfections between different influenza subtypes in chickens, intersubtypic reassortments remain rare, when such reassortants are found, or experimentally generated, they rarely outcompete the currently circulating parental viruses to become the predominant genotypes (with the rare exceptions of the examples in the previous paragraphs) [11,94,95]. However phylogenetic analysis suggests intrasubtypic reassortment (between different H9N2 viruses) occurs at a very high rate and has been shown to greatly contribute to the increasing fitness seen in these viruses in recent years [11,61,73]. This is likely due to the more similar
host ranges, tropisms, and geographic spreads found between H9N2 viruses, as well as the fundamental greater compatibility between gene segments that are more closely related to each other.

4. H9N2 virus in Humans

4.1. History of human infections with H9N2

H9N2 viruses are fairly regularly isolated from humans, the first reported human cases came from two children in Hong Kong in 1999 who exhibited flu-like symptoms, retrospectively several H9N2 infections on the Chinese mainland were also found to have occurred in 1998 [96,97]. Subsequent human infections have been reported from Egypt, Bangladesh, Pakistan and Oman [98-101]. Human H9N2 infections are generally mild; there has only been a single reported death due to the virus, likely due to an underlying health problems [102]. Human H9N2 cases are more often isolated during periods where other more pathogenic zoonotic influenza viruses are being surveyed for; many H9N2 cases have been found recently in China, most likely due to the ongoing screening for zoonotic H7N9 [75], and in Egypt and Bangladesh due to ongoing screening for zoonotic H5N1 infections [34,98]. As of June 2019, there have been a total of 57 laboratory-confirmed human H9N2 infections with half of those being recorded since 2016 (see Table 2). The majority of those infected were young children (36 of 54 cases were aged 7 years or below) and in many of the infections contact with poultry was confirmed as the likely source of the infection (28 with confirmed poultry exposure compared to 9 without any known poultry exposure). There remains no confirmed human-to-human transmission of H9N2 viruses. Virus sequencing indicates the majority of human H9N2 isolates contain HA genes from the G1 or BJ94 lineages with virus isolates highly related to local poultry isolates [5,64,96].
| Year  | Location                        | Patient        | Clinical signs | Viral Lineage | Poultry Exposure? | Reference |
|-------|---------------------------------|----------------|----------------|---------------|-------------------|-----------|
| 1998  | Guangdong province, China       | 14-year-old, male | ARI\textsuperscript{a} | BJ94          | Yes               | [97]      |
| 1998  | Guangdong province, China       | 75-year-old, male | ARI            | BJ94          | Yes               | [97]      |
| 1998  | Guangdong province, China       | 4-year-old, male | ARI            | BJ94          | Unknown           | [97]      |
| 1998  | Guangdong province, China       | 1-year-old, female | ARI          | BJ94          | Unknown           | [97]      |
| 1998  | Guangdong province, China       | 36-year-old, female | ARI         | BJ94          | Yes               | [97]      |
| 1998  | Guangdong province, China       | 22-month-old, female | Fever, cough | BJ94          | No                | [103]     |
| 1999  | Hong Kong                       | 13-month-old, female | Fever     | G1 'Eastern' | Yes               | [96]      |
| 1999  | Hong Kong                       | 4-year-old, female | Fever, malaise | G1 'Eastern' | Unknown           | [96]      |
| 2003  | Hong Kong                       | 5-year-old, male | Fever, cough  | BJ94          | No                | [104]     |
| 2007  | Hong Kong                       | 9-month-old, female | ARI        | ND\textsuperscript{c} | Yes               | [105]     |
| 2008  | Guangdong province, China       | 2-month-old, female | ILI\textsuperscript{b} | ND            | Unknown           | [105]     |
| 2009  | Hong Kong                       | 33-month-old, female | Fever, cough | G1 'Eastern' | Unknown           | [106]     |
| 2011  | Dhaka, Bangladesh               | 47-year-old, female | Fever, cough | G1 'Eastern' | No                | [107]     |
| 2011  | Guangdong province, China       | 4-year-old, female | Fever, cough  | G1 'Eastern' | Yes               | [98]      |
| 2013  | Hunan province, China           | 7-year-old, male | Cough         | BJ94          | No                | [108]     |
| 2014  | Sichuan Province, China         | 2.5-year-old, male | Mild illness | BJ94          | Unknown           | [100,109] |
| 2014  | Guangdong province, China       | Unknown          | Mild illness  | BJ94          | Unknown           | [100]     |
| 2014  | Guangdong province, China       | 3-year-old, male | Unknown       | ND            | Yes               | [100]     |
| 2014  | Guangdong province, China       | 7-year-old, female | ILI          | ND            | Yes               | [100]     |
| 2014  | Guangdong province, China       | 9-month-old, female | ILI        | ND            | Yes               | [100]     |
| 2015  | Bangladesh                      | 3-year-old, female | Mild illness | ND            | Yes               | [110]     |
| 2015  | Anhui province, China           | 4-year-old, female | Mild illness | BJ94          | Yes               | [111]     |
| 2015  | Hunan province, China           | 2-year-old, male  | Mild illness  | BJ94          | Unknown           | [65,111]  |
| Year | Location                      | Age | Gender | Symptom          | Viral Type |� | Unknown | Notes |
|------|-------------------------------|-----|--------|------------------|------------|---|---------|-------|
| 2016 | Dhaka, Bangladesh             | 15-year-old, female | Mild illness | ND               | No         | [65,111] |
|      | Guangdong province, China     | 1-year-old, female  | Mild illness | ND               | Unknown    | [111]  |
|      | Punjab district, Pakistan     | 46-year-old, male   | Fever         | ND               | Yes  | [112]  |
|      | Sichuan Province, China       | 84-year-old, female | Unknown       | ND               | Yes  | [102]  |
|      | Cairo, Egypt                  | 36-year-old         | Non-symptomatic | GI ‘Western’   | Yes  | [99]   |
|      | Guangdong province, China     | 57-year-old         | ARI, Died<sup>d</sup> | ND               | Unknown    | [113]  |
|      | Guangdong province, China     | 18-month-old, male  | ILI            | ND               | Yes  | [114]  |
|      | Guangdong province, China     | 4-year-old, female  | ARI            | BJ94             | Yes  | [115,116] |
|      | Guangdong province, China     | 29-year-old, female | ARI            | ND               | Unknown    | [102]  |
|      | Guangdong province, China     | 10-month-old, male  | ILI            | ND               | Unknown    | [102]  |
|      | Guangdong province, China     | 4-year-old, female  | Mild illness   | ND               | Unknown    | [102]  |
|      | Guangdong province, China     | 5-year-old, female  | Unknown        | ND               | Unknown    | [102]  |
|      | Guangdong province, China     | 3-year-old, male    | Unknown        | ND               | Unknown    | [102]  |
|      | Guangdong province, China     | 7-month-old, female | Mild illness   | ND               | Yes  | [117]  |
|      | Beijing, China                | 3-year-old, male    | Mild illness   | BJ94             | Yes  | [118]  |
|      | Gansu province, China         | 11-month-old, male  | Mild illness   | ND               | Yes  | [119]  |
|      | Beijing, China                | 32-year-old, male   | Mild illness   | BJ94             | No  | [118,120] |
| 2017 | Guangdong province, China     | 2-month-old, female | ILI            | ND               | Yes  | [121]  |
|      | Child                         | 9-month-old, female | Mild illness   | ND               | No  | [122]  |
|      | 20-month-old, male            | n/a                | BJ94           | Unknown          |       |
|      | Hunan province, China         | Child              | ILI            | BJ94             | Unknown    | [65,123] |
|      | China                         | 9-year-old, female  | Mild illness   | ND               | Yes  | [124]  |
|      | Anhui province, China         | 3-year-old, female  | Mild illness   | BJ94             | Unknown    | [125]  |
|      | Guangdong province, China     | 51-year-old, female | Mild illness   | ND               | Yes  | [125]  |
| 2018 | Beijing, China                | 24-year-old, female | Mild illness   | ND               | Yes  | [125]  |
|      | Guangdong province, China     | (pregnant)          | Mild illness   | ND               | Yes  | [126]  |
| Province/Region          | Age                      | Sex   | Illness     | Lineage | Antigenic Cross Reactivity | Reference |
|--------------------------|--------------------------|-------|-------------|---------|---------------------------|-----------|
| Guangdong, China         | 10-month-old, female     |       | Mild illness| ND      | Yes                       | [127]     |
| Guangxi, China           | 3-year-old, male         |       |             | BJ94    | No                        | [127]     |
| Guangdong, China         | 32-year-old, female      |       | Mild illness| ND      | Unknown                   | [128]     |
| Hunan, China             | 2-year-old, male         |       | Mild illness| BJ94    | No                        | [129]     |
| Yunnan, China            | 8-year-old, female       |       | Mild illness| ND      | No                        | [129]     |
| Hunan, China             | 9-year-old, male         |       | Severe pneumonia | ND | Yes                       | [130]     |
| Jiangsu, China           | 13-month-old, female     |       | ILI         | G1 'Western' | Yes                       | [101]     |
| Oman                     |                          |       |             |         |                           |           |

aARI – acute respiratory infection. bILI – influenza-like illness. cND – strain lineage not reported.
dUnderlying health conditions were cited as contributing factor.

4.2. Seropositivity rates

The increase in H9N2 isolation rates due to greater screening of patients with influenza-like illness indicates that mild, or even symptomatic, human H9N2 cases may be relatively common. This possibility is supported by an extensive body of serological evidence showing particularly high seropositivity rates amongst poultry workers in many enzootic countries including India, Cambodia, China, Vietnam, Egypt, Hong Kong, Iran, Thailand, and Pakistan (reviewed in [50]). Serological assays looking at H9 exposure suffer several limitations such as H9-antigenic cross-reactivity with other HA subtypes, however in recent studies this limitation has been overcome through a number of approaches such as concurrent sero-typing against multiple human and avian HA subtypes, meta-analysis, and longitudinal studies of poultry workers [50,131]. Furthermore there is a single study which has managed to isolate a virus from an asymptomatic poultry worker in Pakistan [99]. Overall this suggests that although H9N2 infections may be fairly common, they are mostly mild or asymptomatic and do not transmit any further than the initial zoonotic infection implying poor adaption of H9N2 viruses to mammals.

4.3. Haemagglutinin and receptor binding

Receptor binding preference of HA protein is a well-established determinant of zoonotic and pandemic potential [132,133]. Multiple studies have therefore attempted to evaluate this property of H9N2 AIVs. Initial studies showed that some H9N2 virus lineages, particularly the G1 and BJ94 lineages, appeared to possess a preference towards human-like α2,6-linked SA over avian-like α2,3-linked SA. Subsequent studies utilised synthetic receptor analogues, including sulphated and fucosylated variants of the classically avian-like 3SLN receptor analogue, to show that H9N2 viruses, particularly those of the G1 ‘Eastern’ sub-lineage and BJ94 lineage viruses, displayed high binding towards analogues sulphated on the antepenultimate sugar though a few viruses of the G1 ‘Eastern’ sub-lineage also displayed moderate ‘human-like’ 6SLN binding [134,135]. A further study utilising purified recombinant H9 HA and glycan arrays found binding to α2,3-linked sialosides, as well as some binding to α2,6-, and α2,8- or α2,9- linked receptors. Furthermore, several studies have looked at the receptor binding of BJ94 lineage viruses using ELISA based methods, these have unanimously
showed that contemporary H9N2 viruses show a preference for the ‘human-like’ receptor analogue 6SLN over ‘avian-like’ 3SLN [136-138].

4.3.1. Molecular basis of receptor binding

Several studies have investigated the molecular basis of H9N2 receptor binding. In separate studies it has been found that the HA receptor binding site residues 155, 190, 193, 226 and 227 (H3 numbering) are all involved in the receptor binding avidity of H9N2 viruses [136,137,139-142]. As with many other influenza subtypes, the substitution Q226L, appears to significantly shift the receptor binding of H9 HA towards a human-like preference in certain viral backgrounds [140]. However there remains a need to better understand the molecular basis of receptor binding preference in H9N2 viruses to fully assess their zoonotic potential.

4.4. Ferret experiments

Ferrets are considered the gold standard for assessing influenza virus zoonotic and pandemic potential in humans and have therefore been utilised to assess the intrinsic and adaptive potential of H9N2 viruses to infect and transmit between humans [143]. G1 lineage viruses have been tested for their ferret infectivity, as well as airborne and contact transmission several times. In three separate studies three different G1 ‘Eastern’ sub-lineage viruses and a single G1 ‘Western’ sub-lineage virus were shown to transmit efficiently to direct contact ferrets, but not via airborne transmission to sentinel ferrets [144-146]. Several BJ94 lineage viruses belonging to genotype 57, conversely, have been shown to be able to transmit, with varying degrees of efficiency, by respiratory droplet to contact ferrets [137,138]. Several studies have gone further and deliberately adapted H9N2 viruses to ferrets or made reassortants between H9N2 viruses and human strains and then tested these viruses for their infectivity and transmissibility in ferrets. A series of experiments by the Perez group took both these approaches. They initially showed that making a reassortant between a contact transmissible G1 ‘Eastern’ H9N2 virus and a human H3N2 virus was not enough to provide the virus with airborne transmissibility [144], therefore 10 ferret passages were performed. After 10 passages respiratory droplet transmission between ferrets was achieved [147]. Furthermore, it was shown that an alternative reassortant containing the 6 internal genes from a 2009 pandemic H1N1 virus, and either the adapted, or unadapted H9N2 HA and NA were able to transmit between ferrets [148]. Overall these studies indicate that H9N2 viruses are indeed viruses with pandemic potential, however they would require some adaption and/or reassortment first to become a credible pandemic threat.

4.5. Other factors involved in zoonotic and pandemic potential in H9N2 viruses

Other than HA receptor binding several other factors have been well described as potentially giving H9N2 AIVs an intrinsic pandemic potential. HA pH stability is well described as being vital for adaptation of avian or swine influenza viruses to stable airborne transmission between ferrets or humans [132,133,149]. H9N2 viruses appear to have intrinsically more stable HAs compared to AIVs of the H5 and H7 subtype, in a similar range to early H1N1pdm09 viruses [135]. Furthermore, several adaptive mutations have been identified in field viruses that allow them to transmit by an airborne route between chickens, it is thought these would probably have the added effect of allowing more efficient transmission between humans as well [79,150].
5. H9N2 infection in other species

Although the focus on H9N2 control and surveillance is largely on poultry and zoonotic infections there is a growing body of evidence of the virus in other species.

5.1. Minor poultry species

Although chickens appear to be the primary host for most poultry adapted H9N2 lineages, the virus is also endemic in minor poultry in many regions and appears to have evolved and adapted separately to members of these species, for example; quail, guinea fowl, partridge, and pheasants [75,151]. The G1 ‘Eastern’ sub-lineage, in particular, appears to occupy a niche within these species [75,151]. Quail have been shown to possess a more ‘human-like’ receptor repertoire than chickens, containing a higher amount of α2,6-linked sialic acids [152,153], indicating that viruses adapted to these species may have a greater zoonotic potential than viruses circulating in chickens. This hypothesis is supported by the higher relative binding of viruses from this lineage to α2,6 linked receptor analogues, the higher replicative ability of these viruses in human primary tissues, and also by the higher than expected rate of zoonotic infections caused by these viruses, relative to their limited prevalence and geographical distribution [10,72,135,145,154]. Further, it has been shown that passage of a duck-origin H9N2 virus in quail leads to an expanded host range, with a virus that can more readily infect mice compared to the parental duck virus [155]. Poultry are also included in this host range expansion, which may explain the initial detection of an H9N2 virus in Japanese quail which preceded H9N2 establishment in poultry in endemic regions [83].

Due to the co-circulation G1 ‘Eastern’ sub-lineage and G57/H7N9 viruses we hypothesise that a potential reassortment event between a naturally α2,6-binding G1 ‘Eastern’ virus and the naturally mammalian pre-adapted internal gene cassette of a G57-lineage virus could result in a virus with higher pandemic and zoonotic potential than either parental virus, therefore continuous full genome surveillance of viruses, particularly in minor poultry, is vital in this region of Southern China.

5.2. Swine

Swine are often said to represent a potential ‘mixing vessel’ for human and avian viruses, a fact supported by semi-regular establishment of human and avian virus lineages in these hosts. There have been many recorded outbreaks of H9N2 virus in farmed pigs, mostly in Hong Kong and China [156-159]. As swine carry viruses closely related to human seasonal influenza viruses it has been hypothesised a swine influenza/H9N2 reassortant could emerge with high pandemic potential [156]. Un-adapted, H9N2 viruses do not transmit efficiently between pigs, and swine H9N2 isolates show little evidence of mammalian adaption suggesting repeated reintroduction from avian hosts rather than continuous within-species circulation [159,160]. Repeated serial passage through pigs can lead to partial adaptation allowing for modest replication and transmission [160]. Although H9N2 viruses don’t appear to actively circulate in pigs, there remains a possibility that these viruses could spill over into these hosts due to the proximity between poultry and pigs in many smallholding farms leading to the potential for reassortment with currently circulating swine influenza viruses.

5.3. Canids

Dogs play host to several lineages of canine influenza viruses (CIV), the most common being equine-origin H3N8 and avian-origin H3N2 [161,162]. H9N2 viruses of the BJ94 lineage have been
isolated in China several times from dogs with CIV-like illness [163], furthermore a pair of studies have shown high seropositivity against H9 HA in stray dogs at LBMs in China, potentially due to feeding upon infected birds [164,165]. In 2016 a single avian-origin H3N2 CIV isolate was found that contained a PA gene closely related to that of circulating avian H9N2 viruses suggesting the possibility of active reassortment between AIV and CIV viruses in canine hosts [166]. Furthermore, there is serological evidence for H9N2 infection of foxes and raccoon dogs in China, further indicating canids may be a potential host for these viruses [167].

5.4. Horses

Horses are hosts for several strains of equine influenza virus (EIV), most notably the currently circulating H3N8, and now extinct H7N7 strains. There is an isolated report of an H9N2 virus being isolated from a horse in Guanxi, China [168]. The virus was of the BJ94 lineage, the most common virus in poultry in the area, and most likely constituted a transmission event directly from poultry as no further, or follow up, cases were reported. However, as cases of equine influenza are rarely subtyped it is possible H9N2 viruses may be more common in these animals.

5.5. Mustelidae

As described earlier ferrets are a commonly used model for influenza virus infection and transmission due to their permissiveness to many different strains of influenza virus [143]. Mink, along with ferrets are members of the family Mustelidae, and are widely farmed for their fur. Like ferrets, farmed mink are susceptible to human and avian influenza viruses including H9N2; there are several reports of H9N2 being isolated from farmed mink in China [167,169-171]. All isolates were of the BJ94 lineage prevalent throughout China. Interestingly two of the mink H9N2 isolates contained the mammalian adaptation in PB2, E627K, which is commonly seen during experimental adaptation of AIVs to ferrets [132,171]. Furthermore, several serosurveys have been performed on mink to look for the prevalence of anti-H9N2 antibodies, all three studies have shown a high seropositivity in farmed minks in China of between 20% and 45% [167,171,172]. Sea otters are also members of the family Mustelidae, a single serosurvey has found antibodies against H9 HA, however this is perhaps unsurprising considering the presence of H9 viruses in seabirds and the relatively long lifespans of the otters [173].

5.6. Lagomorpha

Pikas are small rodent-like mammals of the order lagomorpha (which also includes rabbits.) There is evidence from serosurveys and from direct virus isolation that H9N2 viruses naturally infect pikas in China [174,175]. HA phylogeny of the pika isolates show these viruses are of the American lineage, known to occasionally infect wild birds in Asia [175]. As pikas are known to be able to be experimentally infected with avian influenza viruses, and due to the lack of any signature of mammalian adaptation (i.e. PB2 E627K), it appears more likely these infections are due to direct contact with infected birds or virus contaminated water sources rather than continuously circulating, mammalian adapted viruses (as may be the case with the H9N2 infected minks described previously) [175,176].
5.7. Chiroptera

Recently there has been a single report of an H9N2-like virus isolated from bats in Egypt [177]. Unlike other bat influenza subtypes H17 and H18, the H9N2-like bat virus was able to be isolated in eggs and binds sialic acid as its receptor [1]. It does still appear though that, although the virus is highly divergent from all known avian H9N2 viruses, it was likely a recent (compared to H17 or H18) cross-species jump from birds followed by stable circulation in bats as the virus has several markers of mammalian adaptation such as PB2-D701N.

6. Vaccination and control

Due to the economic damage caused by enzootic H9N2, many countries including China, Israel, South Korea, Morocco, Pakistan, Egypt and Iran have adopted vaccination at either a national or local level as a key approach for preventing H9N2 disease in poultry [28,36,44,178-181]. The most common vaccines in use are traditional inactivated vaccines, similar to those used in human seasonal vaccines. H9N2 viruses exhibit a wide antigenic variability, both between, and within lineages [10,73,142]. Unlike human vaccines, H9N2 vaccines are generally not as regularly assessed for their efficacy against antigenically drifted viruses and consequently are far less often updated. Therefore, in many regions H9N2 viruses continue to infect and cause disease in vaccinated poultry with tentative evidence suggesting that sub-optimal use of vaccination may be driving antigenic drift and/or clade replacement, and theoretically zoonotic potential and pathogenesis [27,28,41,73,86,181,182]. Because of this there is a real need for i) better understanding of the molecular determinants of H9 antigenicity, ii) better understanding of antigenic drift and the consequences upon viral fitness and zoonotic potential and iii) next generation vaccines that protect better against multiple strains and antigenically drifted variants.

Stamping out, which involves culling of potentially infected birds and birds presenting influenza-related morbidity has occasionally been used as a first line of defence against H9N2 in countries without a history of the virus. Such was the case during early outbreaks in Korea and the recent outbreaks in Russia and Ghana [26,48,178]. However, once the virus becomes endemic in a country stamping out becomes uneconomical and unfeasible, therefore vaccination is commonly used beyond this point. Stamping out is more often used during HPAIV outbreaks due to their status as notifiable diseases, regardless of a countries history with outbreaks/endemicity.

Other than vaccination and stamping out, several other interventions have been successfully used in the field to halt or reduce avian influenza virus spread in poultry and subsequent zoonotic infection. As discussed previously LBMs are a hotspot for influenza infection due to the convergence of a high density of different poultry species from across a wide geographic range. LBMs were identified early on as the main sources of AIV outbreaks in the late 1990s in China and Hong Kong and several interventions were utilised such as temporary closures, periodic rest days, and overnight market depopulation, as well as basic increases in biosecurity and hygiene practises. A detailed review of the effectiveness of these practises has previously been performed by Offeddu and colleagues, who concluded that these practises, particularly LBM closure, were effective at both halting the spread of AIV between birds, as well as having a knock-on effect at reducing zoonotic AIV cases [183]. A second detailed review by Fournié and colleagues indicated that individual as well as community-wide habits which expose humans to AIVs and risk of zoonotic infection are highly heterogeneous and may require control strategies tailored to individual communities [184].
7. Conclusions and perspectives

To conclude, in recent years outbreaks of H9N2 viruses have been found in an increasing number of countries, including for the first time, sub-Saharan Africa, far South-East Asia and Russia. Because of its expansive geographical range, it is speculated that H9N2 viruses may currently be causing greater economic damage to poultry production worldwide than highly pathogenic H5 or H7 subtypes which are generally much more localised. Additionally, as many human H9N2 cases have been detected in the last 3 years than in the two preceding decades. These two facts indicate a growing threat from H9N2 viruses to both animal and human health. Although the virus mostly causes mild disease and low mortality, as compared to highly pathogenic viruses, there is clear potential for the virus to continue to adapt and become more pathogenic in chickens and better adapted to humans. Additionally, there remains a clear threat, as highlighted by the repeated novel zoonotic AIV viruses that have emerged in recent years such as H7N9, H10N8 and H5N6, posed by reassortant H9N2-origin viruses.

This trend highlights a clear need for further surveillance efforts, particularly in countries where H9N2 has not been officially declared; surveillance should be continued in countries with endemic H9N2, in vaccinated poultry and poultry workers. Additionally, contemporary viruses circulating in poultry rearing systems need constant phenotypic characterisation to assess properties such as antigenic drift, viral pathogenicity and zoonotic potential.

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Conflict of Interest

The authors declare they have no conflict of interest.

References

1. Wu, Y.; Wu, Y.; Tefsen, B.; Shi, Y.; Gao, G.F. Bat-derived influenza-like viruses H17N10 and H18N11. *Trends in microbiology* **2014**, *22*, 183-191, doi:10.1016/j.tim.2014.01.010.
2. Berhane, Y.; Hisanaga, T.; Kehler, H.; Neufeld, J.; Manning, L.; Argue, C.; Handel, K.; Hooper-McGrevy, K.; Jonas, M.; Robinson, J., et al. Highly pathogenic avian influenza virus A (H7N3) in domestic poultry, Saskatchewan, Canada, 2007. *Emerging infectious diseases* **2009**, *15*, 1492-1495, doi:10.3201/eid1509.080231.
3. Capua, I.; Marangon, S. The avian influenza epidemic in Italy, 1999-2000: a review. *Avian pathology : journal of the W.V.P.A* **2000**, *29*, 289-294, doi:10.1080/0307945050118403.
4. Fouchier, R.A.; Schneeberger, P.M.; Rozendaal, F.W.; Broekman, J.M.; Kemink, S.A.; Munster, V.; Kuiken, T.; Rimmelzwaan, G.F.; Schutten, M.; Van Doornum, G.J., et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. *Proceedings of the National Academy of Sciences of the United States of America* **2004**, *101*, 1356-1361, doi:10.1073/pnas.0308352100.
527 5. Guo, Y.J.; Krauss, S.; Senne, D.A.; Mo, I.P.; Lo, K.S.; Xiong, X.P.; Norwood, M.; Shortridge, K.F.; Webster, R.G.; Guan, Y. Characterization of the pathogenicity of members of the newly established H9N2 influenza virus lineages in Asia. Virology 2000, 267, 279-288, doi:10.1006/viro.1999.0115.
531 6. Suarez, D.L.; Perdue, M.L.; Cox, N.; Rowe, T.; Bender, C.; Huang, J.; Swayne, D.E. Comparisons of highly virulent H5N1 influenza A viruses isolated from humans and chickens from Hong Kong. Journal of virology 1998, 72, 6678-6688.
534 7. Lam, T.T.; Wang, J.; Shen, Y.; Zhou, B.; Duan, L.; Cheung, C.L.; Ma, C.; Lycett, S.J.; Leung, C.Y.; Chen, X., et al. The genesis and source of the H7N9 influenza viruses causing human infections in China. Nature 2013, 502, 241-244, doi:10.1038/nature12515.
537 8. Homme, P.J.; Easterday, B.C. Avian influenza virus infections. I. Characteristics of influenza A-turkey-Wisconsin-1966 virus. Avian diseases 1970, 14, 66-74.
539 9. Shortridge, K.F. Pandemic influenza: a zoonosis? Semin Respir Infect 1992, 7, 11-25.
540 10. Guan, Y.; Shortridge, K.F.; Krauss, S.; Webster, R.G. Molecular characterization of H9N2 influenza viruses: were they the donors of the "internal" genes of H5N1 viruses in Hong Kong? Proceedings of the National Academy of Sciences of the United States of America 1999, 96, 9363-9367.
544 11. Iqbal, M.; Yaqub, T.; Reddy, K.; McCauley, J.W. Novel genotypes of H9N2 influenza A viruses isolated from poultry in Pakistan containing NS genes similar to highly pathogenic H7N3 and H5N1 viruses. PLoS One 2009, 4, e5788, doi:10.1371/journal.pone.0005788.
547 12. Kishida, N.; Sakoda, Y.; Eto, M.; Sunaga, Y.; Kida, H. Co-infection of Staphylococcus aureus or Haemophilus paragallinarum exacerbates H9N2 influenza A virus infection in chickens. Arch Virol 2004, 149, 2095-2104, doi:10.1007/s00705-004-0372-1.
550 13. Pan, Q.; Liu, A.; Zhang, F.; Ling, Y.; Ou, C.; Hou, N.; He, C. Co-infection of broilers with Ornithobacterium rhinotracheale and H9N2 avian influenza virus. BMC veterinary research 2012, 8, 104, doi:10.1186/1746-6148-8-104.
553 14. Seifi, S.; Asasi, K.; Mohammadi, A. Natural co-infection caused by avian influenza H9 subtype and infectious bronchitis viruses in broiler chicken farms. Veterinarski archiv 2010, 80, 269-281.
556 15. James, J.; Howard, W.; Iqbal, M.; Nair, V.; Barclay, W.S.; Shelton, H. Influenza A Virus PB1-F2 Protein Prolongs Viral Shedding in Chickens Lengthening the Transmission Window. The journal of general virology 2016, 97, 2516-2527, doi:10.1099/jgv.0.000584.
559 16. Khalenkov, A.; Perk, S.; Panshin, A.; Golender, N.; Webster, R.G. Modulation of the severity of highly pathogenic H5N1 influenza in chickens previously inoculated with Israeli H9N2 influenza viruses. Virology 2009, 383, 32-38, doi:10.1016/j.virol.2008.09.026.
562 17. Naguib, M.M.; Grund, C.; Arafa, A.S.; Abdelwhab, E.M.; Beer, M.; Harder, T.C. Heterologous post-infection immunity against Egyptian avian influenza virus (AIV) H9N2 modulates the course of subsequent infection by highly pathogenic AIV H5N1, but vaccination immunity does not. The Journal of general virology 2017, 98, 1169-1173, doi:10.1099/jgv.0.000767.
566 18. Kim, K.L.; Choi, J.G.; Kang, H.M.; To, T.L.; Nguyen, T.D.; Song, B.M.; Hong, M.S.; Choi, K.S.; Kye, S.J.; Kim, J.Y., et al. Geographical distribution of low pathogenic avian influenza viruses of domestic poultry in Vietnam and their genetic relevance with Asian isolates. Poult Sci 2013, 92, 2012-2023, doi:10.3382/ps.2013-03105.
19. Kim, J.A.; Cho, S.H.; Kim, H.S.; Seo, S.H. H9N2 influenza viruses isolated from poultry in Korean live bird markets continuously evolve and cause the severe clinical signs in layers. Vet Microbiol 2006, 118, 169-176, doi:10.1016/j.vetmic.2006.07.007.

20. Horm, S.V.; Tarantola, A.; Rith, S.; Ly, S.; Gambaretti, J.; Duong, V.; Y, P.; Sorn, S.; Holl, D.; Allal, L., et al. Intense circulation of A/H5N1 and other avian influenza viruses in Cambodian live-bird markets with serological evidence of sub-clinical human infections. Emerging microbes & infections 2016, 5, e70, doi:10.1038/emi.2016.69.

21. Lin, T.N.; Nonthabenjawan, N.; Chaiyawong, S.; Bunpapong, N.; Boonyapisitsopa, S.; Janetanakit, T.; Mon, P.P.; Mon, H.H.; Oo, K.N.; Oo, S.M., et al. Influenza A(H9N2) Virus, Myanmar, 2014-2015. Emerging infectious diseases 2017, 23, 1041-1043, doi:10.3201/eid2306.161902.

22. Sonnberg, S.; Phommachanh, P.; Naipospos, T.S.; McKenzie, J.; Chanthavisouk, C.; Pathammavong, S.; Darnell, D.; Meeduangchanh, P.; Rubrum, A.M.; Souriya, M., et al. Multiple introductions of avian influenza viruses (H5N1), Laos, 2009-2010. Emerging infectious diseases 2012, 18, 1139-1143, doi:10.3201/eid1807.111642.

23. Krueger, W.S.; Khuntirat, B.; Yoon, I.K.; Blair, P.J.; Chittagarnpitch, M.; Putnam, S.D.; Supawat, K.; Gibbons, R.V.; Bhuddari, D.; Pattamadilok, S., et al. Prospective study of avian influenza virus infections among rural Thai villagers. PLoS One 2013, 8, e72196, doi:10.1371/journal.pone.0072196.

24. Jonas, M.; Sahesti, A.; Murwijati, T.; Lestariningsih, C.L.; Irine, I.; Ayesda, C.S.; Prihartini, W.; Mahardika, G.N. Identification of avian influenza virus subtype H9N2 in chicken farms in Indonesia. Preventive veterinary medicine 2018, 159, 99-105, doi:10.1016/j.prevetmed.2018.09.003.

25. Omar, A.R. Should we be concerned about the H9N2 virus? New Straits Times 2018.

26. Marchenko, V.Y.; Goncharova, N.I.; Evsseenko, V.A.; Susloparov, I.M.; Gavrilova, E.V.; Maksyutov, R.A.; Ryzhikov, A.B. Overview of the Epidemiological Situation on Highly Pathogenic Avian Influenza Virus in Russia in 2018. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections]. 2019, 1, 42-49, doi:10.21055/0370-1069-2019-1-42-49.

27. Park, K.J.; Kwon, H.I.; Song, M.S.; Pascua, P.N.; Baek, Y.H.; Lee, J.H.; Jang, H.L.; Lim, J.Y.; Mo, I.P.; Moon, H.J., et al. Rapid evolution of low-pathogenic H9N2 avian influenza viruses following poultry vaccination programmes. The Journal of general virology 2011, 92, 36-50, doi:10.1099/vir.0.024992-0.

28. Zhang, P.; Tang, Y.; Liu, X.; Peng, D.; Liu, W.; Liu, H.; Lu, S.; Liu, X. Characterization of H9N2 influenza viruses isolated from vaccinated flocks in an integrated broiler chicken operation in eastern China during a 5 year period (1998-2002). The Journal of general virology 2008, 89, 3102-3112, doi:10.1099/vir.0.005652-0.

29. Cameron, K.R.; Gregory, V.; Banks, J.; Brown, I.H.; Alexander, D.J.; Hay, A.J.; Lin, Y.P. H9N2 subtype influenza A viruses in poultry in pakistan are closely related to the H9N2 viruses responsible for human infection in Hong Kong. Virology 2000, 278, 36-41, doi:10.1006/viro.2000.0585.

30. Negovetich, N.J.; Feeroz, M.M.; Jones-Engel, L.; Walker, D.; Alam, S.M.; Hasan, K.; Seiler, P.; Ferguson, A.; Friedman, K.; Barman, S., et al. Live bird markets of Bangladesh: H9N2 viruses
and the near absence of highly pathogenic H5N1 influenza. *PLoS One* **2011**, *6*, e19311, doi:10.1371/journal.pone.0019311.

31. Tosh, C.; Nagarajan, S.; Behera, P.; Rajukumar, K.; Purohit, K.; Kamal, R.P.; Murugkar, H.V.; Gounalan, S.; Pattnaik, B.; Vamanayya, P.R., et al. Genetic analysis of H9N2 avian influenza viruses isolated from India. *Arch Virol* **2008**, *153*, 1433-1439, doi:10.1007/s00705-008-0131-9.

32. Hosseini, H.; Ghalyanchilangeroudi, A.; Fallah Mehrabadi, M.H.; Sedijian, M.S.; Shayeganmehr, A.; Ghafori, S.A.; Maghsoudloo, H.; Abdollahi, H.; Farahani, R.K. Phylogenetic analysis of H9N2 avian influenza viruses in Afghanistan (2016-2017). *Arch Virol* **2017**, 10.1007/s00705-017-3474-2, doi:10.1007/s00705-017-3474-2.

33. Parvin, R.; Heenemann, K.; Halami, M.Y.; Chowdhury, E.H.; Islam, M.R.; Vahlenkamp, T.W. Full-genome analysis of avian influenza virus H9N2 from Bangladesh reveals internal gene reassortments with two distinct highly pathogenic avian influenza viruses. *Arch Virol* **2014**, *159*, 1651-1661, doi:10.1007/s00705-014-1976-8.

34. Monne, I.; Hussein, H.A.; Fusaro, A.; Valastro, V.; Hamoud, M.M.; Khalefa, R.A.; Dardir, S.N.; Radwan, M.I.; Capua, I.; Cattoli, G. H9N2 influenza A virus circulates in H5N1 endemically infected poultry population in Egypt. *Influenza and other respiratory viruses* **2013**, *7*, 240-243, doi:10.1111/j.1750-1078.2012.00399.x.

35. Aamir, U.B.; Wernery, U.; Ilyushina, N.; Webster, R.G. Characterization of avian H9N2 influenza viruses from United Arab Emirates 2000 to 2003. *Virology* **2007**, *361*, 45-55, doi:10.1016/j.virology.2006.10.037.

36. Banet-Noach, C.; Perk, S.; Simanov, L.; Grebenyuk, N.; Rozenblut, E.; Pokamunski, S.; Pirak, M.; Tendler, Y.; Panshin, A. H9N2 influenza viruses from Israeli poultry: a five-year outbreak. *Avian diseases* **2007**, *51*, 290-296, doi:10.1637/7590-040206R1.1.

37. Body, M.H.; Alrarawahi, A.H.; Alhubsy, S.S.; Saravanan, N.; Rajmony, S.; Mansoor, M.K. Characterization of Low Pathogenic Avian Influenza Virus Subtype H9N2 Isolated from Free-Living Mynah Birds (Acridotheres tristis) in the Sultanate of Oman. *Avian diseases* **2015**, *59*, 329-334, doi:10.1637/10998-120414-ResNote.

38. Barbour, E.K.; Sagherian, V.K.; Sagherian, N.K.; Dankar, S.K.; Jaber, L.S.; Usayran, N.N.; Farran, M.T. Avian influenza outbreak in poultry in the Lebanon and transmission to neighbouring farmers and swine. *Vet Ital* **2006**, *42*, 77-85.

39. Monne, I.; Cattoli, G.; Mazzacan, E.; Amarin, N.M.; Al Maaitah, H.M.; Al-Natour, M.Q.; Capua, I. Genetic comparison of H9N2 AI viruses isolated in Jordan in 2003. *Avian diseases* **2007**, *51*, 451-454, doi:10.1637/7563-033106R.1.

40. Kraid, Q.A.; Madadgar, O.; Ghalyanchi Langeroudi, A.; Karimi, V. Genetic analysis of H9N2 avian influenza viruses circulated in broiler flocks: a case study in Iraq in 2014-2015. *Virus genes* **2017**, *53*, 205-214, doi:10.1007/s11262-016-1407-x.

41. Davidson, I.; Shkoda, I.; Golender, N.; Perk, S.; Lapin, K.; Khinich, Y.; Panshin, A. Genetic characterization of HA gene of low pathogenic H9N2 influenza viruses isolated in Israel during 2006-2012 periods. *Virus genes* **2013**, *46*, 255-263, doi:10.1007/s11262-012-0852-4.

42. Tombari, W.; Nsiri, J.; Larbi, I.; Guerin, J.L.; Ghram, A. Genetic evolution of low pathogeneity H9N2 avian influenza viruses in Tunisia: acquisition of new mutations. *Virol J* **2011**, *8*, 467, doi:10.1186/1743-422X-8-467.
43. Kammon, A.; Heidari, A.; Dayhum, A.; Eldaghayes, I.; Sharif, M.; Monne, I.; Cattoli, G.; Asheg, A.; Farhat, M.; Kraim, E. Characterization of Avian Influenza and Newcastle Disease Viruses from Poultry in Libya. *Avian diseases* 2015, 59, 422-430, doi:10.1637/11068-032215-ResNote.1.

44. El Houadfi, M.; Fellahi, S.; Nassik, S.; Guerin, J.L.; Ducatez, M.F. First outbreaks and phylogenetic analyses of avian influenza H9N2 viruses isolated from poultry flocks in Morocco. *Virol J* 2016, 13, 140, doi:10.1186/s12985-016-0596-1.

45. Zecchin, B.; Minoungou, G.; Fusaro, A.; Moctar, S.; Ouedraogo-Kabore, A.; Schivo, A.; Salvatia, A.; Marciano, S.; Monne, I. Influenza A(H9N2) Virus, Burkina Faso. *Emerging infectious diseases* 2017, 23, doi:10.3201/eid2312.171294.

46. Rubrum, A., Jeevan,T., Darnell,D., Webby,R., Derrar,F. and Gradi,E.-A. hemagglutinin [Influenza A virus]. Accession no. AZF86190.1. GenBank, 2018.

47. Byarugaba, D.K., Erima,B., Ukuli,Q.A., Atim,A., Tugume,T., Millard,M., Kibuuka,K., Mimbe,M., Mworozzi,E.A., Danner,A., McKenzie,P., Webby,R., Ducatez,M.F., Mancuso,J., Krauss,S. and Wabwire-Mangen,F. hemagglutinin [Influenza A virus]. Accession no. AVK87156.1. GenBank, 2018.

48. Awuni, J.A.; Bianco, A.; Dogbey, O.J.; Fusaro, A.; Yingar, D.T.; Salviato, A.; Ababio, P.T.; Milani, A.; Bonfante, F.; Monne, I. Avian influenza H9N2 subtype in Ghana: virus characterization and evidence of co-infection. *Avian pathology : journal of the W.V.P.A* 2019, 10.1080/03079457.2019.1624687, 1-65, doi:10.1080/03079457.2019.1624687.

49. Abolnik, C.; Cornelius, E.; Bisschop, S.P.; Romito, M.; Verwoerd, D. Phylogenetic analyses of genes from South African LPAI viruses isolated in 2004 from wild aquatic birds suggests introduction by Eurasian migrants. *Developments in biologicals* 2006, 124, 189-199.

50. Khan, S.U.; Anderson, B.D.; Heil, G.L.; Liang, S.; Gray, G.C. A Systematic Review and Meta-Analysis of the Seroprevalence of Influenza A(H9N2) Infection Among Humans. *The Journal of infectious diseases* 2015, 212, 562-569, doi:10.1093/infdis/jiv109.

51. Reid, S.M.; Banks, J.; Ceeraz, V.; Seeking, A.; Howard, W.A.; Puranik, A.; Collins, S.; Manvell, R.; Irvine, R.M.; Brown, I.H. The Detection of a Low Pathogenicity Avian Influenza Virus Subtype H9 Infection in a Turkey Breeder Flock in the United Kingdom. *Avian diseases* 2016, 60, 126-131, doi:10.1637/11356-122315-Case.1.

52. Alexander, D.J. Report on avian influenza in the Eastern Hemisphere during 1997-2002. *Avian diseases* 2003, 47, 792-797, doi:10.1637/0005-2086-47.s3.792.

53. Swieton, E.; Jozwiak, M.; Minta, Z.; Smietanka, K. Genetic characterization of H9N2 avian influenza viruses isolated from poultry in Poland during 2013/2014. *Virus genes* 2017, 10.1007/s11262-017-1513-4, doi:10.1007/s11262-017-1513-4.

54. Verhagen, J.H.; Lexmond, P.; Vuong, O.; Schutten, M.; Guldemeeister, J.; Osterhaus, A.D.; Elbers, A.R.; Slaterus, R.; Hornman, M.; Koch, G., et al. Discordant detection of avian influenza virus subtypes in time and space between poultry and wild birds; Towards improvement of surveillance programs. *PLoS One* 2017, 12, e0173470, doi:10.1371/journal.pone.0173470.

55. Coman, A.; Maftei, D.N.; Krueger, W.S.; Heil, G.L.; Friary, J.A.; Cereches, R.M.; Sirlincan, E.; Bria, P.; Dragnea, C.; Kasler, I., et al. Serological evidence for avian H9N2 influenza virus...
infections among Romanian agriculture workers. *Journal of infection and public health* **2013**, *6*, 438-447, doi:10.1016/j.jiph.2013.05.003.

56. Shu, Y.; McCauley, J. GISAID: Global initiative on sharing all influenza data - from vision to reality. *Eurosurveillance: Bulletin European sur les maladies transmissibles = European communicable disease bulletin* **2017**, *22*, doi:10.2807/1560-7917.ES.2017.22.13.30494.

57. Bao, Y.; Bolotov, P.; Dernovoy, D.; Kryutin, B.; Zaslavsky, L.; Tatusova, T.; Ostell, J.; Lipman, D. The influenza virus resource at the National Center for Biotechnology Information. *Journal of virology* **2008**, *82*, 596-601, doi:10.1128/JVI.02005-07.

58. Zhang, Y.; Aevermann, B.D.; Anderson, T.K.; Burke, D.F.; Dauphin, G.; Gu, Z.; He, S.; Kumar, S.; Larsen, C.N.; Lee, A.J., et al. Influenza Research Database: An integrated bioinformatics resource for influenza virus research. *Nucleic Acids Res* **2017**, *45*, D466-D474, doi:10.1093/nar/gkw857.

59. Wan, X.F.; Dong, L.; Lan, Y.; Long, L.P.; Xu, C.; Zou, S.; Li, Z.; Wen, L.; Cai, Z.; Wang, W., et al. Indications that live poultry markets are a major source of human H5N1 influenza virus infection in China. *Journal of virology* **2011**, *85*, 13432-13438, doi:10.1128/JVI.05266-11.

60. Fournie, G.; Guitian, J.; Desvaux, S.; Cuong, V.C.; Dung do, H.; Pfeiffer, D.U.; Mangtani, P.; Ghani, A.C. Interventions for avian influenza A (H5N1) risk management in live bird market networks. *Proceedings of the National Academy of Sciences of the United States of America* **2013**, *110*, 9177-9182, doi:10.1073/pnas.1220815110.

61. Thuy, D.M.; Peacock, T.P.; Bich, V.T.; Fabrizio, T.; Hoang, D.N.; Tho, N.D.; Diep, N.T.; Nguyen, M.; Hoa, L.N.; Trang, H.T., et al. Prevalence and diversity of H9N2 avian influenza in chickens of Northern Vietnam, 2014. *Infection, genetics and evolution: Journal of molecular epidemiology and evolutionary genetics in infectious diseases* **2016**, *44*, 530-540, doi:10.1016/j.meegid.2016.06.038.

62. Chen, L.J.; Lin, X.D.; Guo, W.P.; Tian, J.H.; Wang, W.; Ying, X.H.; Wang, M.R.; Yu, B.; Yang, Z.Q.; Shi, M., et al. Diversity and evolution of avian influenza viruses in live poultry markets, free-range poultry and wild wetland birds in China. *The Journal of general virology* **2016**, *97*, 844-854, doi:10.1099/jgv.0.00399.

63. Huang, Y.; Li, X.; Zhang, H.; Chen, B.; Jiang, Y.; Yang, L.; Zhu, W.; Hu, S.; Zhou, S.; Tang, Y., et al. Human infection with an avian influenza A (H9N2) virus in the middle region of China. *Journal of medical virology* **2015**, *87*, 1641-1648 doi:10.1002/jmv.24231.

64. Liu, R.; Zhao, B.; Li, Y.; Zhang, X.; Chen, S.; Chen, T. Clinical and epidemiological characteristics of a young child infected with avian influenza A (H9N2) virus in China. *J Int Med Res* **2018**, 10.1177/0300060518779959, 300060518779959, doi:10.1177/0300060518779959.

65. Guan, Y.; Shortridge, K.F.; Krauss, S.; Chin, P.S.; Dyrting, K.C.; Ellis, T.M.; Webster, R.G.; Peiris, M. H9N2 influenza viruses possessing H5N1-like internal genomes continue to circulate in poultry in southeastern China. *Journal of virology* **2000**, *74*, 9372-9380.
24.

67. Turner, J.C.; Feeroz, M.M.; Hasan, M.K.; Akhtar, S.; Walker, D.; Seiler, P.; Barman, S.; Franks, J.; Jones-Engel, L.; McKenzie, P., et al. Insight into live bird markets of Bangladesh: an overview of the dynamics of transmission of H5N1 and H9N2 avian influenza viruses. *Emerging microbes & infections* 2017, 6, e12, doi:10.1038/emi.2016.142.

68. Chaudhry, M.; Ahmad, M.; Rashid, H.B.; Sultan, B.; Chaudhry, H.R.; Riaz, A.; Shaheen, M.S. Prospective study of avian influenza H9 infection in commercial poultry farms of Punjab Province and Islamabad Capital Territory, Pakistan. *Tropical animal health and production* 2017, 49, 213-220, doi:10.1007/s11250-016-1159-6.

69. Chaudhry, M.; Rashid, H.B.; Angot, A.; Thrusfield, M.; Bronsvoort, B.M.D.; Capua, I.; Cattoli, G.; Welburn, S.C.; Eisler, M.C. Risk Factors for Avian Influenza H9 Infection of Chickens in Live Bird Retail Stalls of Lahore District, Pakistan 2009-2010. *Scientific reports* 2018, 8, 5634, doi:10.1038/s41598-018-23895-1.

70. Tolba, H.M.N.; Abou Elez, R.M.M.; Elsohaby, I.; Ahmed, H.A. Molecular identification of avian influenza virus subtypes H5N1 and H9N2 in birds and in respiratory patients. *PeerJ* 2018, 6, e5473, doi:10.7717/peerj.5473.

71. Killingley, B.; Nguyen-Van-Tam, J. Routes of influenza transmission. *Influenza Other Respir Viruses* 2013, 7 Suppl 2, 42-51, doi:10.1111/irv.12080.

72. Shortridge, K.F.; Zhou, N.N.; Guan, Y.; Gao, P.; Ito, T.; Kawaoka, Y.; Kodihalli, S.; Krauss, S.; Markwell, D.; Murti, K.G., et al. Characterization of avian H5N1 influenza viruses from poultry in Hong Kong. *Virology* 1998, 252, 331-342, doi:10.1006/viro.1998.9488.

73. Pu, J.; Wang, S.; Yin, Y.; Zhang, G.; Carter, R.A.; Wang, J.; Xu, G.; Sun, H.; Wang, M.; Wen, C., et al. Evolution of the H9N2 influenza genotype that facilitated the genesis of the novel H7N9 virus. *Proceedings of the National Academy of Sciences of the United States of America* 2015, 112, 548-553, doi:10.1073/pnas.1422456112.

74. Spekreijse, D.; Bouma, A.; Koch, G.; Stegeman, J.A. Airborne transmission of a highly pathogenic avian influenza virus strain H5N1 between groups of chickens quantified in an experimental setting. *Vet Microbiol* 2011, 152, 88-95, doi:10.1016/j.vetmic.2011.04.024.

75. Zhou, J.; Wu, J.; Zeng, X.; Huang, G.; Zou, L.; Song, Y.; Gopinath, D.; Zhang, X.; Kang, M.; Lin, J., et al. Isolation of H5N6, H7N9 and H9N2 avian influenza A viruses from air sampled at live poultry markets in China, 2014 and 2015. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2016, 21, doi:10.2807/1560-7917.ES.2016.21.35.30331.

76. Claes, G.; Welby, S.; Van Den Berg, T.; Van Der Stede, Y.; Dewulf, J.; Lambrecht, B.; Marche, S. The impact of viral tropism and housing conditions on the transmission of three H5/H7 low pathogenic avian influenza viruses in chickens. *Epidemiology and infection* 2013, 141, 2428-2443, doi:10.1017/S0950268813001025.

77. Banks, J.; Speidel, E.S.; Moore, E.; Plowright, L.; Piccirillo, A.; Capua, I.; Cordioli, P.; Fioretti, A.; Alexander, D.J. Changes in the haemagglutinin and the neuraminidase genes prior to the emergence of highly pathogenic H7N1 avian influenza viruses in Italy. *Arch Virol* 2001, 146, 963-973.

78. Sorrell, E.M.; Song, H.; Pena, L.; Perez, D.R. A 27-amino-acid deletion in the neuraminidase stalk supports replication of an avian H2N2 influenza A virus in the respiratory tract of chickens. *Journal of virology* 2010, 84, 11831-11840, doi:10.1128/JVI.01460-10.
782 79. Lv, J.; Wei, L.; Yang, Y.; Wang, B.; Liang, W.; Gao, Y.; Xia, X.; Gao, L.; Cai, Y.; Hou, P., et al. Amino acid substitutions in the neuraminidase protein of an H9N2 avian influenza virus affect its airborne transmission in chickens. *Veterinary research* 2015, 46, 44, doi:10.1186/s13567-014-0142-3.

783 80. Bonfante, F.; Mazzetto, E.; Zanardello, C.; Fortin, A.; Gobbo, F.; Maniero, S.; Bigolaro, M.; Davidson, I.; Haddas, R.; Cattoli, G., et al. A G1-lineage H9N2 virus with oviduct tropism causes chronic pathological changes in the infundibulum and a long-lasting drop in egg production. *Veterinary research* 2018, 49, 83, doi:10.1186/s13567-018-0575-1.

784 81. Lu, H.G.; Castro, A.E. Evaluation of the infectivity, length of infection, and immune response of a low-pathogenicity H7N2 avian influenza virus in specific-pathogen-free chickens. *Avian diseases* 2004, 48, 263-270, doi:Doi 10.1637/7064.

785 82. van der Goot, J.A.; de Jong, M.C.; Koch, G.; Van Boven, M. Comparison of the transmission characteristics of low and high pathogenicity avian influenza A virus (H5N2). *Epidemiology and infection* 2003, 131, 1003-1013.

786 83. Perez, D.R.; Lim, W.; Seiler, J.P.; Yi, G.; Peiris, M.; Shortridge, K.F.; Webster, R.G. Role of quail in the interspecies transmission of H9 influenza A viruses: molecular changes on HA that correspond to adaptation from ducks to chickens. *J Virol* 2003, 77, 3148-3156.

787 84. Yao, M.; Lv, J.; Huang, R.; Yang, Y.; Chai, T. Determination of infective dose of H9N2 Avian Influenza virus in different routes: aerosol, intranasal, and gastrointestinal. *Intervirology* 2014, 57, 369-374, doi:10.1159/000365925.

788 85. Seiler, P.; Kercher, L.; Feeroz, M.M.; Shanmuganatham, K.; Jones-Engel, L.; Turner, J.; Walker, D.; Alam, S.M.R.; Hasan, M.K.; Akhtar, S., et al. H9N2 influenza viruses from Bangladesh: Transmission in chicken and New World quail. *Influenza Other Respir Viruses* 2018, 12, 814-817, doi:10.1111/irv.12589.

789 86. Peacock, T.P.; Benton, D.J.; James, J.; Sadeyen, J.R.; Chang, P.; Sealy, J.E.; Bryant, J.E.; Martin, S.R.; Shelton, H.; Barclay, W.S., et al. Immune escape variants of H9N2 influenza viruses containing deletions at the haemagglutinin receptor binding site retain fitness in vivo and display enhanced zoonotic characteristics. *Journal of virology* 2017, 10.1128/JVI.00218-17, doi:10.1128/JVI.00218-17.

790 87. Liu, D.; Shi, W.; Gao, G.F. Poultry carrying H9N2 act as incubators for novel human avian influenza viruses. *Lancet* 2014, 383, 869, doi:10.1016/S0140-6736(14)60386-X.

791 88. Chen, H.; Yuan, H.; Gao, R.; Zhang, J.; Wang, D.; Xiong, Y.; Fan, G.; Yang, F.; Li, X.; Zhou, J., et al. Clinical and epidemiological characteristics of a fatal case of avian influenza A H10N8 virus infection: a descriptive study. *Lancet* 2014, 383, 714-721, doi:10.1016/S0140-6736(14)60111-2.

792 89. Shen, Y.Y.; Ke, C.W.; Li, Q.; Yuan, R.Y.; Xiang, D.; Jia, W.X.; Yu, Y.D.; Liu, L.; Huang, C.; Qi, W.B., et al. Novel Reassortant Avian Influenza A(H5N6) Viruses in Humans, Guangdong, China, 2015. *Emerging infectious diseases* 2016, 22, doi:10.3201/eid2208.160146.

793 90. Shanmuganatham, K.; Feeroz, M.M.; Jones-Engel, L.; Walker, D.; Alam, S.; Hasan, M.; McKenzie, P.; Krauss, S.; Webby, R.J.; Webster, R.G. Genesis of avian influenza H9N2 in Bangladesh. *Emerging microbes & infections* 2014, 3, e88, doi:10.1038/emi.2014.84.

794 91. Dong, G.; Xu, C.; Wang, C.; Wu, B.; Luo, J.; Zhang, H.; Nolte, D.L.; Deliberto, T.J.; Duan, M.; Ji, G., et al. Reassortant H9N2 influenza viruses containing H5N1-like PB1 genes isolated
from black-billed magpies in Southern China. *PLoS One* **2011**, *6*, e25808, doi:10.1371/journal.pone.0025808.

92. Tosh, C.; Nagarajan, S.; Kumar, M.; Murugkar, H.V.; Venkatesh, G.; Shukla, S.; Mishra, A.; Mishra, P.; Agarwal, S.; Singh, B., et al. Multiple introductions of a reassortant H5N1 avian influenza virus of clade 2.3.2.1c with PB2 gene of H9N2 subtype into Indian poultry. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases* **2016**, *43*, 173-178, doi:10.1016/j.meegid.2016.05.012.

93. Xu, H.; Meng, F.; Huang, D.; Sheng, X.; Wang, Y.; Zhang, W.; Chang, W.; Wang, L.; Qin, Z. Genomic and phylogenetic characterization of novel, recombinant H5N2 avian influenza virus strains isolated from vaccinated chickens with clinical symptoms in China. *Viruses* **2015**, *7*, 887-898, doi:10.3390/v7030887.

94. Monne, I.; Meseko, C.; Joannis, T.; Shittu, I.; Ahmed, M.; Tassoni, L.; Fusaro, A.; Cattoli, G. Highly Pathogenic Avian Influenza A(H5N1) Virus in Poultry, Nigeria, 2015. *Emerging infectious diseases* **2015**, *21*, 1275-1277, doi:10.3201/eid2107.150421.

95. Naguib, M.M.; Ulrich, R.; Kasbohm, E.; Eng, C.L.P.; Hoffmann, D.; Grund, C.; Beer, M.; Harder, T.C. Natural reassortants between potentially zoonotic avian influenza viruses H5N1 and H9N2 from Egypt display distinct pathogenic phenotypes in experimentally infected chickens and ferrets. *Journal of virology* **2017**, *10.1128/JVI.01300-17*, doi:10.1128/JVI.01300-17.

96. Peiris, M.; Yuen, K.Y.; Leung, C.W.; Chan, K.H.; Ip, P.L.; Lai, R.W.; Orr, W.K.; Shortridge, K.F. Human infection with influenza H9N2. *Lancet* **1999**, *354*, 916-917.

97. Guo, Y.; Li, J.; Cheng, X. [Discovery of men infected by avian influenza A (H9N2) virus]. Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese journal of experimental and clinical virology **1999**, *13*, 105-108.

98. International Centre for Diarrhoeal Disease Research (ICDDR,B). Outbreak of mild respiratory disease caused by H5N1 and H9N2 infections among young children in Dhaka, Bangladesh; Health and Science Bulletin, 2011; pp 5–12. .

99. Ali, M.; Yaqub, T.; Mukhtar, N.; Imran, M.; Ghafoor, A.; Shahid, M.F.; Naeem, M.; Iqbal, M.; Smith, G.J.D.; Su, Y.C.F. Avian Influenza A(H9N2) Virus in Poultry Worker, Pakistan, 2015. *Emerging infectious diseases* **2019**, *25*, 136-139, doi:10.3201/eid2501.180618.

100. *Influenza at the human-animal interface, Summary and assessment*, 23 June 2015; World Health Organisation: [www.who.int](http://www.who.int), 2015; pp 3-4.

101. *Influenza at the human-animal interface, Summary and assessment*, 10 April to 10 May 2019; World Health Organisation: [www.who.int](http://www.who.int), 2019; pp 2-3.

102. *Influenza at the human-animal interface, Summary and assessment*, 20 July to 3 October 2016; World Health Organisation: [www.who.int](http://www.who.int), 2016; pp 5-6.

103. Gou, Y.; Xie, J.; Wang, M. [A strain of influenza A H9N2 virus repeatedly isolated from human population in China]. Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese journal of experimental and clinical virology **2000**, *14*, 209-212.

104. Butt, K.M.; Smith, G.J.; Chen, H.; Zhang, L.J.; Leung, Y.H.; Xu, K.M.; Lim, W.; Webster, R.G.; Yuen, K.Y.; Peiris, J.S., et al. Human infection with an avian H9N2 influenza A virus in Hong Kong in 2003. *J Clin Microbiol* **2005**, *43*, 5760-5767, doi:10.1128/JCM.43.11.5760-5767.2005.
105. Hong Kong Department of Health. Gene sequencing of H9N2 virus shows avian origin.
Hong Kong Department of Health: http://www.dh.gov.hk/english/press/2009/090107-2.html, 2009.

106. Hong Kong Department of Health. CHP investigating case of influenza A (H9N2) infection.
Hong Kong Department of Health: http://www.dh.gov.hk/english/press/2009/091223-3.html, 2009.

107. Influenza at the human-animal interface, Summary and assessment, 24 January 2014; World Health Organisation: www.who.int, 2014; pp 2-3.

108. Xu, J.; Li, S.; Yang, Y.; Liu, B.; Yang, H.; Li, T.; Zhang, L.; Li, W.; Luo, X.; Zhang, L., et al. Human infection with a further evolved avian H9N2 influenza A virus in Sichuan, China. Sci China Life Sci 2017, 10.1007/s11427-017-9150-8, doi:10.1007/s11427-017-9150-8.

109. Influenza at the human-animal interface, Summary and assessment, 4 September 2015; World Health Organisation: www.who.int, 2015; p 2.

110. Influenza at the human-animal interface, Summary and assessment, 14 December 2015; World Health Organisation: www.who.int, 2015; p 3.

111. Influenza at the human-animal interface, Summary and assessment, 20 January 2016; World Health Organisation: www.who.int, 2016; pp 5.

112. Influenza at the human-animal interface, Summary and assessment, 21 January to 25 February 2016; World Health Organisation: www.who.int, 2016; pp 5-6.

113. Influenza at the human-animal interface, Summary and assessment, 5 April to 9 May 2016; World Health Organisation: www.who.int, 2016; pp 5-6.

114. Influenza at the human-animal interface, Summary and assessment, 13 June to 19 July 2016; World Health Organisation: www.who.int, 2016; p 5.

115. Yuan, R.; Liang, L.; Wu, J.; Kang, Y.; Song, Y.; Zou, L.; Zhang, X.; Ni, H.; Ke, C. Human infection with an avian influenza A/H9N2 virus in Guangdong in 2016. The Journal of infection 2017, 74, 422-425, doi:10.1016/j.jinf.2017.01.003.

116. Influenza at the human-animal interface, Summary and assessment, 20 December to 16 January 2017; World Health Organisation: www.who.int, 2017; pp 3-4.

117. Pan, Y.; Cui, S.; Sun, Y.; Zhang, X.; Ma, C.; Shi, W.; Peng, X.; Lu, G.; Zhang, D.; Liu, Y., et al. Human infection with H9N2 avian influenza in northern China. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2018, 24, 321-323, doi:10.1016/j.cmi.2017.10.026.

118. Influenza at the human-animal interface, Summary and assessment, 16 March to 20 April 2017; World Health Organisation: www.who.int, 2017; p 3.

119. Influenza at the human-animal interface, Summary and assessment, 21 April to 16 May 2017; World Health Organisation: www.who.int, 2017; pp 4-5.

120. Influenza at the human-animal interface, Summary and assessment, 16 June 2017 to 25 July 2017; World Health Organisation: www.who.int, 2017; pp 3-4.

121. Influenza at the human-animal interface, Summary and assessment, 25 July to 27 September 2017; World Health Organisation: www.who.int, 2017; pp 4-5.
123. Avian Influenza Report: Reporting period: January 7, 2018 – January 13, 2018 (Week 2); Hong Kong Centre for Health Protection: [http://www.chp.gov.hk](http://www.chp.gov.hk), 2018.

124. Influenza at the human-animal interface, Summary and assessment, 30 October 2017 to 7 December 2017; World Health Organisation: [www.who.int](http://www.who.int), 2017; p 4.

125. Influenza at the human-animal interface, Summary and assessment, 26 January to 2 March 2018; World Health Organisation: [www.who.int](http://www.who.int), 2018; p 2.

126. Influenza at the human-animal interface, Summary and assessment, 21 July to 21 September 2018; World Health Organisation: [www.who.int](http://www.who.int), 2018; p 2.

127. Influenza at the human-animal interface, Summary and assessment, 2 November to 13 December 2018; World Health Organisation: [www.who.int](http://www.who.int), 2018; p 2.

128. Influenza at the human-animal interface, Summary and assessment, 14 December 2018 to 21 January 2019; World Health Organisation: [www.who.int](http://www.who.int), 2018; p 2.

129. Influenza at the human-animal interface, Summary and assessment, 22 January to 12 February 2019; World Health Organisation: [www.who.int](http://www.who.int), 2019; p 2.

130. Influenza at the human-animal interface, Summary and assessment, 2 November to 13 December 2018; World Health Organisation: [www.who.int](http://www.who.int), 2018; p 2.

131. Hoa, L.N.M.; Tuan, N.A.; My, P.H.; Huong, T.T.K.; Hau Thu, T.T.; Carrique-Mas, J.; Duong, M.T.; Tho, N.D.; Hoang, N.D., et al. Assessing evidence for avian-to-human transmission of influenza A/H9N2 virus in rural farming communities in northern Vietnam. The Journal of general virology 2017, 98, 2011-2016, doi:10.1099/jgv.0.000877.

132. Imai, M.; Watanabe, T.; Hatta, M.; Das, S.C.; Ozawa, M.; Shinya, K.; Zhong, G.; Hanson, A.; Katsura, H.; Watanabe, S., et al. Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets. Nature 2012, 486, 420-428, doi:10.1038/nature10831.

133. Linster, M.; van Boheemen, S.; de Graaf, M.; Schrauwen, E.J.; Lexmond, P.; Manz, B.; Besteboer, T.M.; Baumann, J.; van Riel, D.; Rimmelzwaan, G.F., et al. Identification, characterization, and natural selection of mutations driving airborne transmission of A/H5N1 virus. Cell 2014, 157, 329-339, doi:10.1016/j.cell.2014.02.040.

134. Gambaryan, A.S.; Tuzikov, A.B.; Pazynina, G.V.; Desheva, J.A.; Bovin, N.V.; Matrosovich, M.N.; Klimov, A.I. 6-sulfo sialyl Lewis X is the common receptor determinant recognized by H5, H6, H7 and H9 influenza viruses of terrestrial poultry. Virol J 2008, 5, 85, doi:10.1186/1743-422X-5-85.

135. Peacock, T.P.; Benton, D.J.; Sadeyen, J.R.; Chang, P.; Sealy, J.E.; Bryant, J.E.; Martin, S.R.; Shelton, H.; McCauley, J.W.; Barclay, W.S., et al. Variability in H9N2 haemagglutinin receptor-binding preference and the pH of fusion. Emerging microbes & infections 2017, 6, e11, doi:10.1038/emeri.2016.139.

136. Teng, Q.; Xu, D.; Shen, W.; Liu, Q.; Rong, G.; Li, X.; Yan, L.; Yang, J.; Chen, H.; Yu, H., et al. A Single Mutation at Position 190 in Hemagglutinin Enhances Binding Affinity for Human Type Sialic Acid Receptor and Replication of H9N2 Avian Influenza Virus in Mice. Journal of virology 2016, 10.1128/JVI.01141-16, doi:10.1128/JVI.01141-16.

137. Li, X.; Shi, J.; Guo, J.; Deng, G.; Zhang, Q.; Wang, J.; He, X.; Wang, K.; Chen, J.; Li, Y., et al. Genetics, receptor binding property, and transmissibility in mammals of naturally isolated
H9N2 Avian Influenza viruses. *PLoS pathogens* 2014, 10, e1004508, doi:10.1371/journal.ppat.1004508.

138. Yuan, J.; Xu, L.; Bao, L.; Yao, Y.; Deng, W.; Li, F.; Lv, Q.; Gu, S.; Wei, Q.; Qin, C. Characterization of an H9N2 avian influenza virus from a Fringilla montifringilla brambling in northern China. *Virology* 2015, 476, 289-297, doi:10.1016/j.virol.2014.12.021.

139. Kaverin, N.V.; Rudneva, I.A.; Ilyushina, N.A.; Lipatov, A.S.; Krauss, S.; Webster, R.G. Structural differences among hemagglutinins of influenza A virus subtypes are reflected in their antigenic architecture: analysis of H9 escape mutants. *Journal of virology* 2004, 78, 240-249.

140. Wan, H.; Perez, D.R. Amino acid 226 in the hemagglutinin of H9N2 influenza viruses determines cell tropism and replication in human airway epithelial cells. *Journal of virology* 2007, 81, 5181-5191, doi:10.1128/JVI.02827-06.

141. Sang, X.; Wang, A.; Ding, J.; Kong, H.; Gao, X.; Li, L.; Chai, T.; Li, Y.; Zhang, K.; Wang, C., et al. Adaptation of H9N2 AIV in guinea pigs enables efficient transmission by direct contact and inefficient transmission by respiratory droplets. *Scientific reports* 2015, 5, 15928, doi:10.1038/srep15928.

142. Peacock, T.P.; Harvey, W.T.; Sadeyen, J.R.; Reeve, R.; Iqbal, M. The molecular basis of antigenic variation among A(H9N2) avian influenza viruses. *Emerging microbes & infections* 2018, 7, 176, doi:10.1038/s41426-018-0178-y.

143. Thangavel, R.R.; Bouvier, N.M. Animal models for influenza virus pathogenesis, transmission, and immunology. *Journal of immunological methods* 2014, 410, 60-79, doi:10.1016/j.jim.2014.03.023.

144. Wan, H.; Sorrell, E.M.; Song, H.; Hossain, M.J.; Ramirez-Nieto, G.; Monne, I.; Stevens, J.; Cattoli, G.; Capua, I.; Chen, L.M., et al. Replication and transmission of H9N2 influenza viruses in ferrets: evaluation of pandemic potential. *PLoS One* 2008, 3, e2923, doi:10.1371/journal.pone.0002923.

145. SJCEIRS H9N2 Working Group. Assessing the fitness of distinct clades of influenza A (H9N2) viruses. In *Emerging microbes & infections*, Emerg Microbes Infect, 2013; Vol. 2, p e75.

146. Shanmuganatham, K.K.; Jones, J.C.; Marathe, B.M.; Feeroz, M.M.; Jones-Engel, L.; Walker, D.; Turner, J.; Rabiu Alam, S.M.; Kamrul Hasan, M.; Akhtar, S., et al. The replication of Bangladeshi H9N2 avian influenza viruses carrying genes from H7N3 in mammals. *Emerging microbes & infections* 2016, 5, e35, doi:10.1038/emi.2016.29.

147. Sorrell, E.M.; Wan, H.; Araya, Y.; Song, H.; Perez, D.R. Minimal molecular constraints for respiratory droplet transmission of an avian-human H9N2 influenza A virus. *Proceedings of the National Academy of Sciences of the United States of America* 2009, 106, 7565-7570, doi:10.1073/pnas.0900877106.

148. Kimble, J.B.; Sorrell, E.; Shao, H.; Martin, P.L.; Perez, D.R. Compatibility of H9N2 avian influenza surface genes and 2009 pandemic H1N1 internal genes for transmission in the ferret model. *Proceedings of the National Academy of Sciences of the United States of America* 2011, 108, 12084-12088, doi:10.1073/pnas.1108058108.

149. Russier, M.; Yang, G.; Rehg, J.E.; Wong, S.S.; Mostafa, H.H.; Fabrizio, T.P.; Barman, S.; Krauss, S.; Webster, R.G.; Webby, R.J., et al. Molecular requirements for a pandemic influenza virus:
An acid-stable hemagglutinin protein. *Proceedings of the National Academy of Sciences of the United States of America* **2016**, *113*, 1636-1641, doi:10.1073/pnas.1524384113.

Zhong, L.; Wang, X.; Li, Q.; Liu, D.; Chen, H.; Zhao, M.; Gu, X.; He, L.; Liu, X.; Gu, M., et al. Molecular mechanism of the airborne transmissibility of H9N2 avian influenza A viruses in chickens. *Journal of virology* **2014**, *88*, 9568-9578, doi:10.1128/JVI.00943-14.

Xu, K.M.; Smith, G.J.; Bahl, J.; Duan, L.; Tai, H.; Vijaykrishna, D.; Wang, J.; Zhang, J.X.; Li, K.S.; Fan, X.H., et al. The genesis and evolution of H9N2 influenza viruses in poultry from southern China, 2000 to 2005. *Journal of virology* **2007**, *81*, 10389-10401, doi:10.1128/JVI.00979-07.

Wan, H.; Perez, D.R. Quail carry sialic acid receptors compatible with binding of avian and human influenza viruses. *Virology* **2006**, *346*, 278-286, doi:10.1016/j.virol.2005.10.035.

Kimble, B.; Nieto, G.R.; Perez, D.R. Characterization of influenza virus sialic acid receptors in minor poultry species. *Virol J* **2010**, *7*, 365, doi:10.1186/1743-422X-7-365.

Matrosovich, M.N.; Krauss, S.; Webster, R.G. H9N2 influenza A viruses from poultry in Asia associated genetic changes in a duck H9N2 influenza virus following adaptation in quail and chickens. *PLoS One* **2008**, *3*, e3170, doi:10.1371/journal.pone.0003170.

Peiris, J.S.; Guan, Y.; Markwell, D.; Ghose, P.; Webster, R.G.; Shortridge, K.F. Cocirculation of avian H9N2 and contemporary "human" H3N2 influenza A viruses in pigs in southeastern China: potential for genetic reassortment? *Journal of virology* **2001**, *75*, 9679-9686, doi:10.1128/JVI.75.20.9679-9686.2001.

Cong, Y.L.; Wang, C.F.; Yan, C.M.; Peng, J.S.; Jiang, Z.L.; Liu, J.H. Swine infection with H9N2 influenza viruses in China in 2004. *Virus genes* **2008**, *36*, 461-469, doi:10.1007/s11262-008-0227-z.

Ge, F.; Li, X.; Hu, Y.; Yang, D.; Liu, J.; Qi, X.; Wang, J.; Yang, X.; Qiu, Y.; Liu, P., et al. Genotypic evolution and antigenicity of H9N2 influenza viruses in Shanghai, China. *Arch Virol* **2016**, 10.1007/s00705-016-2767-1, doi:10.1007/s00705-016-2767-1.

Wang, J.; Wu, M.; Hong, W.; Fan, X.; Chen, R.; Zheng, Z.; Zeng, Y.; Huang, R.; Zhang, Y.; Lam, T.T., et al. Infectivity and Transmissibility of Avian H9N2 Influenza Viruses in Pigs. *Journal of virology* **2016**, *90*, 3506-3514, doi:10.1128/JVI.02605-15.

Mancera Gracia, J.C.; Van den Hoecke, S.; Saelens, X.; Van Reeth, K. Effect of serial pig passages on the adaptation of an avian H9N2 influenza virus to swine. *PLoS One* **2017**, *12*, e0175267, doi:10.1371/journal.pone.0175267.

Crawford, P.C.; Dubovi, E.J.; Castleman, W.L.; Stephenson, I.; Gibbs, E.P.; Chen, L.; Smith, C.; Hill, R.C.; Ferro, P.; Pompey, J., et al. Transmission of equine influenza virus to dogs. *Science* **2005**, *310*, 482-485, doi:10.1126/science.1117950.

Song, D.; Kang, B.; Lee, C.; Jung, K.; Ha, G.; Kang, D.; Park, S.; Park, B.; Oh, J. Transmission of avian influenza virus (H3N2) to dogs. *Emerging infectious diseases* **2008**, *14*, 741-746, doi:10.3201/eid1405.071471.

Sun, X.; Xu, X.; Liu, Q.; Liang, D.; Li, C.; He, Q.; Jiang, J.; Cui, Y.; Li, J.; Zheng, L., et al. Evidence of Avian-like H9N2 Influenza A Virus among Dogs in Guangxi, China. *Infection,
1038 genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases 2013, 10.1016/j.meegid.2013.10.012, doi:10.1016/j.meegid.2013.10.012.
1040 164. Zhou, H.; He, S.Y.; Sun, L.; He, H.; Ji, F.; Sun, Y.; Jia, K.; Ning, Z.; Wang, H.; Yuan, L., et al. Serological evidence of avian influenza virus and canine influenza virus infections among stray cats in live poultry markets, China. Vet Microbiol 2015, 175, 369-373, doi:10.1016/j.vetmic.2014.12.018.
1044 165. Su, S.; Zhou, P.; Fu, X.; Wang, L.; Hong, M.; Lu, G.; Sun, L.; Qi, W.; Ning, Z.; Jia, K., et al. Virological and epidemiological evidence of avian influenza virus infections among feral dogs in live poultry markets, china: a threat to human health? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2014, 58, 1644-1646, doi:10.1093/cid/ciu154.
1049 166. Lee, I.H.; Le, T.B.; Kim, H.S.; Seo, S.H. Isolation of a novel H3N2 influenza virus containing a gene of H9N2 avian influenza in a dog in South Korea in 2015. Virus genes 2016, 52, 142-145, doi:10.1007/s11262-015-1272-z.
1052 167. Yong-Feng, Z.; Fei-Fei, D.; Jia-Yu, Y.; Feng-Xia, Z.; Chang-Qing, J.; Jian-Li, W.; Shou-Yu, G.; Kai, C.; Chuan-Yi, L.; Xue-Hua, W., et al. Intraspecies and interspecies transmission of mink H9N2 influenza virus. Scientific reports 2017, 7, 7429, doi:10.1038/s41598-017-07879-1.
1055 168. Song, H.Q. Isolation and Whole Genome Sequence Analysis of Equine H9N2 Influenza Virus in Guang Xi. Guangxi University, Nanning, China, 2012.
1057 169. Akerstedt, J.; Valheim, M.; Germundsson, A.; Moldal, T.; Lie, K.I.; Falk, M.; Hungnes, O. Pneumonia caused by influenza A H1N1 2009 virus in farmed American mink (Neovison vindur). The Veterinary record 2012, 170, 362, doi:10.1136/vr.100512.
1060 170. Englund, L. Studies on influenza viruses H10N4 and H10N7 of avian origin in mink. Vet Microbiol 2000, 74, 101-107.
1062 171. Peng, L.; Chen, C.; Kai-yi, H.; Feng-xia, Z.; Yan-li, Z.; Zong-shuai, L.; Xing-xiao, Z.; Shi-jin, J.; Zhi-jing, X. Molecular characterization of H9N2 influenza virus isolated from mink and its pathogenesis in mink. Vet Microbiol 2015, 176, 88-96, doi:10.1016/j.vetmic.2015.01.009.
1065 172. Zhang, C.; Xuan, Y.; Shan, H.; Yang, H.; Wang, J.; Wang, K.; Li, G.; Qiao, J. Avian influenza virus H9N2 infections in farmed minks. Virol J 2015, 12, 180, doi:10.1186/s12985-015-0411-4.
1067 173. Capuano, A.M.; Miller, M.; Stallknecht, D.E.; Moriarty, M.; Plancarte, M.; Dodd, E.; Batac, F.; Boyce, W.M. Serologic Detection of Subtype-specific Antibodies to Influenza A Viruses in Southern Sea Otters (Enhydra lutris nereis). J Wildl Dis 2017, 10.7589/2017-01-011, doi:10.7589/2017-01-011.
1071 174. Yu, Z.; Cheng, K.; Sun, W.; Xin, Y.; Cai, J.; Ma, R.; Zhao, Q.; Li, L.; Huang, J.; Sang, X., et al. Lowly pathogenic avian influenza (H9N2) infection in Plateau pika (Ochotona curzoniae), Qinghai Lake, China. Vet Microbiol 2014, 173, 132-135, doi:10.1016/j.vetmic.2014.07.002.
1074 175. Yan, Y.; Gu, J.Y.; Yuan, Z.C.; Chen, X.Y.; Li, Z.K.; Lei, J.; Hu, B.L.; Yan, L.P.; Xing, G.; Liao, M., et al. Genetic characterization of H9N2 avian influenza virus in plateau pikas in the Qinghai Lake region of China. Arch Virol 2016, 10.1007/s00705-016-3176-1, doi:10.1007/s00705-016-3176-1.
1078 176. Li, Y.; Xiao, H.; Huang, C.; Sun, H.; Li, L.; Su, J.; Ma, J.; Liu, D.; Wang, H.; Liu, W., et al. Distribution of sialic acid receptors and experimental infections with different subtypes of
influenza A viruses in Qinghai-Tibet plateau wild pika. Virol J 2015, 12, 63, doi:10.1186/s12985-015-0290-8.

Kandeil, A.; Gomaa, M.R.; Shehata, M.M.; El Taweel, A.N.; Mahmoud, S.H.; Bagato, O.; Moatasim, Y.; Kutkat, O.; Kayed, A.S.; Dawson, P., et al. Isolation and characterization of a distinct influenza A virus from Egyptian bats. Journal of virology 2018, 10.1128/JVI.01059-18, doi:10.1128/JVI.01059-18.

Lee, D.H.; Song, C.S. H9N2 avian influenza virus in Korea: evolution and vaccination. Clinical and experimental vaccine research 2013, 2, 26-33, doi:10.7774/cevr.2013.2.1.26.

Naeem, K.; Siddique, N. Use of strategic vaccination for the control of avian influenza in Pakistan. Developments in biologicals 2006, 124, 145-150.

Kilany, W.H.; Ali, A.; Bazid, A.H.; El-Deeb, A.H.; El-Abideen, M.A.; Sayed, M.E.; El-Kady, M.F. A Dose-Response Study of Inactivated Low Pathogenic Avian Influenza H9N2 Virus in Specific-Pathogen-Free and Commercial Broiler Chickens. Avian diseases 2016, 60, 256-261, doi:10.1637/11143-050815-Reg.

Bahari, P.; Pourbakhsh, S.A.; Shoushtari, H.; Bahmaninejad, M.A. Molecular characterization of H9N2 avian influenza viruses isolated from vaccinated broiler chickens in northeast Iran. Tropical animal health and production 2015, 47, 1195-1201, doi:10.1007/s11250-015-0848-x.

Sealy, J.E.; Yaqub, T.; Peacock, T.P.; Chang, P.; Ermetal, B.; Clements, A.; Sadeyen, J.R.; Mehboob, A.; Shelton, H.; Bryant, J.E., et al. Association of Increased Receptor-Binding Avidity of Influenza A(H9N2) Viruses with Escape from Antibody-Based Immunity and Enhanced Zoonotic Potential. Emerging infectious diseases 2018, 25, 63-72, doi:10.3201/eid2501.180616.

Offeddu, V.; Cowling, B.J.; Malik Peiris, J.S. Interventions in live poultry markets for the control of avian influenza: a systematic review. One Health 2016, 2, 55-64, doi:10.1016/j.onehlt.2016.03.002.