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Review

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

153 turkeys), for example in the UK, the Netherlands, Poland, Hungary, Germany, Italy, and Ireland [51-
154 54]. There is a single report of a G1 lineage H9N2 virus in Germany, however due to no subsequent
155 reports of this virus, it appears likely this was an anomalous spillover event from wild birds.
156 Finally, there is a single study showing sero-prevalence of H9N2 antibodies in Romanian
157 agriculture workers [55], similarly to the Nigerian study, H9N2 virus has not been isolated from
158 poultry in this country, therefore it remains to be seen if the virus is truly present here.
159
160 ***2.1.6. The Americas***
161 H9N2 viruses have been isolated from poultry in the USA periodically throughout the second
162 half of the 20th Century, in fact the prototypic H9N2 isolate (A/turkey/Wisconsin/1/1966) was isolated
163 in this period [8]. All isolated viruses have been of the American lineage and appear to be spillover
164 events from wild birds, possibly sea birds which carry genetically closely related viruses in this region.
165 Since the turn of the Century, there has been no evidence of the virus in poultry in the Americas,
166 despite routine surveillance and extensive evidence of other non-H9N2 viruses in poultry
167 (particularly in North America).
168

Table 1 – List of countries with laboratory confirmed H9 infections in domestic gallinaceous poultry

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*[3], *2015*	Wild bird, G1-W	H9N2-free	No
Ghana	2017-18	G1-W	Potentially endemic	No
Hong Kong SAR	*1988*, *1992*, *1994*, 1997, 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	Serology only
Iraq	2005, 2008, 2014-2016	G1-W	Potentially endemic	No
Israel	2000-2014, 2016-2017	G1-W	Potentially endemic[1]	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
Laos[2]	2009	n/a	Potentially endemic	No
Lebanon	2004, 2010, 2017-18	G1-W	Potentially endemic	No
Libya	2013	G1-W	Potentially endemic	No

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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[2]	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[2]	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[2]	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 in Nigeria, Romania, Thailand and Laos comes solely from sero-surveys. No viruses have been 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

177 references used in this paper supplemented with sequences from GISAID, NCBI influenza virus
178 resource and FluDB databases as of June 2019 [56-58].
179
180 ***2.2. Hyper-Prevalence of H9N2 viruses in poultry***
181 Whenever H9N2 virus prevalence has been investigated in lower- and middle-income countries,
182 either by poultry sero-surveys or by passive sampling (i.e. random sampling of apparently healthy
183 birds), the virus has been found to be present at extremely high rates, particularly in live bird markets
184 (LBMs). LBMs act as hubs for poultry traders and their birds and are a major component of the disease
185 transmission pathway, shown to maintain AIV dissemination among poultry as well as facilitate
186 zoonotic infection [59,60]. In recent surveys in Vietnam, prevalence of the virus exceeded 3.5% in
187 chickens in LBMs [61,62]; in various Chinese provinces prevalence was found to be upwards of 10%
188 [63-66]. Several separate studies have shown that the prevalence in Bangladesh and Pakistan of H9
189 viruses in chickens at LBMs and farms was almost 10% [30,67-69]. Another recent study has shown
190 prevalence of upwards of 10% at LBMs in Egypt [70]. Overall, these studies imply a degree of hyper-
191 endemicity not seen for other influenza virus subtypes, potentially due to the low pathogenicity
192 phenotype of the virus allowing repeated re-infections of the same birds (in the case of longer-lived
193 layers and breeders) and silent spread between farms and smallholdings.
194
195 ***2.3. H9N2 virus transmission and host tropism in poultry***
196 Four routes of transmission are widely accepted for influenza viruses; droplet, aerosol, faecal-
197 oral, and direct contact [71]. Droplet transmission describes exhaled particles >10 μm which are
198 deposited into the upper respiratory tract, whereas aerosol droplets are typically less than 5 μm and
199 can reach the lower respiratory tract [71]. Contact transmission relies on the transfer of particles to
200 mucous membranes directly, or via a fomite intermediate. For a successful transmission event to
201 occur, enough virus must persist long enough in the external environment to reach the target tissue.
202 Transmission is therefore determined via several viral, host, and environmental aspects, including;
203 (i) the major site of viral replication and viral titres shed. (ii) The distance and frequency between
204 contacts. (iii) Environmental conditions and virus stability. In wild aquatic birds such as ducks and
205 gulls AIVs generally exhibit gastrointestinal tropism and are thought to be spread primarily through
206 the oral-faecal route. In poultry adapted AIVs there exists some heterogeneity in tropism and
207 transmission routes; HPAIV, such as H5N1, have a systemic distribution and are probably
208 transmitted by a combination of the oral-faecal route and airborne transmission, whereas, LPAIVs in
209 chickens tend to show more respiratory tropism, though some strains also show gastrointestinal
210 tropism [15,71-76]. One of the key molecular markers that facilitates adaptation of an AIV from wild
211 aquatic birds to poultry is the deletion of amino acids from the stalk domain of NA, which have been
212 shown to mediate the switch to respiratory tropism in chickens [77,78]. There is good evidence to
213 suggest that many LPAIV strains transmit by the airborne route, the oral-faecal route and the
214 waterborne route [15,75,79]. However, the favoured mechanism of transmission between individuals
215 varies by host species and viral strain.
216 Many studies have implicated direct contact as an important transmission route for H9N2
217 viruses in chickens, although indirect routes such as aerosol and faecal-oral have been shown to be
218 important for some strains and many viruses show primarily a respiratory tropism. Although some
219 H9N2 strains have been shown to have an extended tropism in the kidneys or oviducts [80-85]. Both

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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, *inter*subtypic 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 *intra*subtypic 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].

284 **Table 2 – Laboratory confirmed human cases of H9N2 infection.**

Year	Location	Patient	Clinical signs	Viral Lineage	Poultry Exposure?	Reference
1998	Guangdong province, China	14-year-old, male	ARI[a]	BJ94	Yes	[97]
		75-year-old, male	ARI	BJ94	Yes	[97]
		4-year-old, male	ARI	BJ94	Unknown	[97]
		1-year-old, female	ARI	BJ94	Unknown	[97]
		36-year-old, female	ARI	BJ94	Yes	[97]
1999	Guangdong province, China	22-month-old, female	Fever, cough	BJ94	No	[103]
	Hong Kong	13-month-old, female	Fever	G1 'Eastern'	Yes	[96]
		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[c]	Yes	[105]
2008	Guangdong province, China	2-month-old, female	ILI[b]	ND	Unknown	[105]
2009	Hong Kong	35-month-old, female	Fever, cough,	G1 'Eastern'	Unknown	[106]
		47-year-old, female	Fever, cough	G1 'Eastern'	No	[107]
2011	Dhaka, Bangladesh	4-year-old, female	Fever, cough	G1 'Western'	Yes	[98]
2013	Guangdong province, China	86-year-old, male	Cough	BJ94	No	[108]
	Hunan province, China	7-year-old, male	Fever	BJ94	Yes	[64,108]
2014	Sichuan Province, China	2.5-year-old, male	Mild illness	BJ94	Unknown	[100,109]
	Guangdong province, China	Unknown	Mild illness	BJ94	Unknown	[100]
2015	Aswan, Egypt	3-year-old, male	Unknown	ND	Yes	[100]
	Cairo, Egypt	7-year-old, female	ILI	ND	Yes	[100]
		9-month-old, female	ILI	ND	Yes	[100]
	Bangladesh	3-year-old, female	Mild illness	ND	Yes	[110]
	Anhui province, China	4-year-old, female	Mild illness	BJ94	Yes	[111]
	Hunan province, China	2-year-old, male	Mild illness	BJ94	Unknown	[65,111]

		15-year-old, female	Mild illness	ND	No	[65,111]
		1-year-old, female	Mild illness	ND	Unknown	[111]
	Dhaka, Bangladesh	46-year-old, male	Fever	ND	Yes	[112]
	Guangdong province, China	84-year-old, female	Unknown	ND	Yes	[102]
	Punjab district, Pakistan	36-year-old	Non-symptomatic	G1 'Western'	Yes	[99]
	Sichuan Province, China	57-year-old, female	ARI, Died[d]	ND	Unknown	[113]
	Cairo, Egypt	18-month-old, male	ILI	ND	Yes	[114]
	Guangdong province, China	4-year-old, female	ARI	BJ94	Yes	[115,116]
		29-year-old, female	ARI	ND	Unknown	[102]
2016	Yunnan province, China	10-month-old, male	ILI	ND	Unknown	[102]
	Jiangxi province, China	4-year-old, female	Mild illness	ND	Unknown	[102]
	Henan 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]
	Guangdong province, China	2-month-old, female	ILI	ND	Yes	[121]
2017	China	Child	Mild illness	ND	No	[122]
	Hunan province, China	20-month-old, female	n/a	BJ94	Unknown	[123]
		9-month-old, male	ILI	BJ94	Unknown	[65,123]
	China	Child	Mild illness	ND	Yes	[124]
	Anhui province, China	9-year-old, female	Mild illness	BJ94	Unknown	[125]
	Guangdong province, China	3-year-old, female	Mild illness	ND	Yes	[125]
2018	Beijing, China	51-year-old, female	Mild illness	ND	Yes	[125]
	Guangdong province, China	24-year-old, female (pregnant)	Mild illness	ND	Yes	[126]

2019	Guangdong province, China	10-month-old, female	Mild illness	ND	Yes	[127]
	Guangxi province, China	3-year-old, male	n/a	BJ94	No	[127]
	Guangdong province, China	32-year-old, female	Mild illness	ND	Unknown	[128]
	Hunan province, China	2-year-old, male	Mild illness	BJ94	No	[129]
	Yunnan province, China	8-year-old, female	Mild illness	ND	No	[129]
	Jiangsu province, China	9-year-old, male	Severe pneumonia	ND	Yes	[130]
	Oman	13-month-old, female	ILI	G1 'Western'	Yes	[101]

[a]ARI – acute respiratory infection. [b]ILI – influenza-like illness. [c]ND – strain lineage not reported. [d]Underlying 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 [10,72,96,135,145,154]. 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 racoon 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.

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