

1 *Review*

## 2 **A Global Perspective on H9N2 Avian Influenza Virus**

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

24 **Keywords:** H9N2; avian influenza viruses; zoonotic; pandemic potential; poultry

## 25 1. Introduction

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

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

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

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

56

## 57 2. History and phylogeography of H9N2 virus in poultry

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

64 H9N2 viruses are nearly uniformly low pathogenicity in the laboratory when tested by IVPI  
65 [5,11], however in the field they often exhibit moderate-to-high morbidity and mortality. This is  
66 usually associated with confounding factors such as co-infection with bacterial or viral pathogens,

67 and other factors such as poor nutrition and housing [12-14]. However certain strains can show high  
68 morbidity and mortality in controlled *in vivo* experiments [5,15].

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

73

#### 74 **2.1. Phylogeography of H9N2 viruses**

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

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

92

##### 93 **2.1.1. East and Southeast Asia**

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

103

##### 104 **2.1.2. South Asia**

105 H9N2 viruses are considered endemic in Bangladesh and Pakistan and are likely endemic in  
106 regions of India, Afghanistan and Nepal [29-32]. G1 'Western' viruses constitute the majority of  
107 viruses found in poultry in South Asia, with a few Y439 viruses occasionally spilling over into poultry  
108 from wild birds (but apparently not maintaining sustained transmission). The predominant G1  
109 'Western' sub-lineage of viruses in this region (as well as in Iran) appears to have arisen from a

110 reassortment event between co-circulating HPAIV H7N3 and LPAIV H9N2 viruses, which replaced  
111 other local clades [11,33].

112

### 113 2.1.3. *The Middle East*

114 H9N2 is frequently isolated from, and therefore probably endemic in poultry in many Middle  
115 Eastern countries including Egypt, Iran, Israel, Saudi Arabia, and the United Arab Emirates [29,34-  
116 36]. Virus has also been isolated on occasion from Iraq, Jordan, Lebanon and Oman [37-40]. In Israel  
117 mass vaccination of poultry, which began in 2003, has had some success in limiting the endemicity  
118 of the virus. This vaccine regime has necessitated an update of the vaccine seed strain at least once  
119 due to antigenic drift [41]. Extensive surveillance in Israel between 2006 and 2012 has indicated that  
120 rather than there being a single *in situ* evolving strain, viruses appear to be periodically eradicated,  
121 then reintroduced into the country.

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

125

### 126 2.1.4. *Africa*

127 H9N2 viruses have been isolated from several African countries, the virus appears endemic in  
128 poultry in Egypt and has been repeatedly isolated from chickens in Libya and Tunisia [34,42,43].  
129 Additionally, since 2016 the virus has recently been isolated for the first time in countries across West  
130 Africa including Morocco, Burkina Faso, Ghana and Algeria as well as in East Africa in Uganda [44-  
131 48]. Morocco has subsequently undertaken a mass poultry vaccination programme [44]. All viruses  
132 isolated from poultry in Africa have been of the G1 'Western' sub-lineage, related to those circulating  
133 in the Middle East in Israel, Jordan, Lebanon and the United Arab Emirates.

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

138 Finally, there is a single study showing high seropositivity against H9N2 in Nigerian  
139 agricultural workers, however no virus has been isolated from this country and H9N2 serological  
140 studies are notorious for giving false positives due to cross-reactivity with human influenza viruses  
141 [50]. Although surveillance for HPAIVs is ongoing in Nigeria it is unclear whether protocols are used  
142 that would pick up presence (or absence) of H9N2 viruses, therefore it remains unclear whether the  
143 virus is/was present in this region.

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

148

### 149 2.1.5. *Europe*

150 There is currently no evidence of endemic H9N2 in poultry in Europe, despite rigorous sampling  
151 (especially within the European Union). There is, however, good evidence for the virus in wild birds  
152 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 20<sup>th</sup> 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

169 **Table 1 – List of countries with laboratory confirmed H9 infections in domestic gallinaceous**  
 170 **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 <sup>3</sup> , 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 <sup>1</sup>	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 <sup>2</sup>	2009	n/a	Potentially endemic	No
Lebanon	2004, 2010, 2017-18	G1-W	Potentially endemic	No
Libya	2013	G1-W	Potentially endemic	No

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	<i>2010-11</i>	Y439	H9N2-free	No
Nigeria <sup>2</sup>	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	<i>2013-2014</i>	Y439	H9N2-free	No
Portugal	<i>2004</i>	Y439	H9N2-free	No
Qatar	2008	G1	Potentially endemic	No
Romania <sup>2</sup>	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	<i>1995, 2008-09</i>	Y439	H9N2-free	No
South Korea	1996, 1999-2012	Y439	Potentially endemic	No
Thailand <sup>2</sup>	n/a	n/a	Potentially endemic	Serology only
Tunisia	2010-12, 2014	G1-W	Potentially endemic	No
USA	<i>1966, 1978, 1981, 1983, 1985, 1988-89, 1993, 1995, 1997, 1999</i>	USA	H9N2-free	No
UAE	1999-2003, 2005-08, 2011, 2015	G1-W	Potentially endemic	No
Uganda	2017	G1-W	Potentially endemic	No
UK	<i>1970, 2010, 2013</i>	Y439	H9N2-free	No
Vietnam	2009, 2012-17	BJ94, G1-W, Y439	Likely endemic	Serology only

171 <sup>1</sup>Potential endemicity of Israel is based on apparent recurring epidemics, it is unclear how much is *in*  
172 *situ* circulation and how much is incursions from surrounding countries. <sup>2</sup>Evidence for H9N2 virus  
173 in Nigeria, Romania, Thailand and Laos comes solely from sero-surveys. No viruses have been  
174 isolated from poultry/humans in these countries (though it is unclear whether any active surveillance  
175 has been performed that would detect H9N2). <sup>3</sup>Years where only viruses most likely transmitted  
176 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



220 in the field and experimentally poultry adapted H9N2 viruses are mostly detected from buccal rather  
221 than cloacal swabs [15,67,86]. Additionally inoculation of some H9N2 viruses into the respiratory  
222 tract is 40 times more effective than gastrointestinal inoculation at initiating infection [84]. However,  
223 many of these routes appear to be environmentally contextual, for example, at LBMs communal  
224 water sources have been implicated as the major route of transmission of endemic H5N1 and H9N2  
225 viruses [67]. Together these studies indicate that for H9N2 and other enzootic poultry adapted H9N2  
226 viruses, respiratory and contact transmission are likely the primary routes of transmission and that  
227 respiratory transmission may partly arise initially as an adaptation to poultry.

228

### 229 3. H9N2 reassortment and evolution

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

233

#### 234 3.1. H9N2 viruses as gene donors

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

243

#### 244 3.2. H9N2 viruses as a gene recipients

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

253

#### 254 3.3. H9N2 Intrasubtypic reassortment

255 Overall, considering the large overlap and frequent coinfections between different influenza  
256 subtypes in chickens, *intersubtypic* reassortments remain rare, when such reassortants are found, or  
257 experimentally generated, they rarely outcompete the currently circulating parental viruses to  
258 become the predominant genotypes (with the rare exceptions of the examples in the previous  
259 paragraphs) [11,94,95]. However phylogenetic analysis suggests *intrasubtypic* reassortment (between  
260 different H9N2 viruses) occurs at a very high rate and has been shown to greatly contribute to the  
261 increasing fitness seen in these viruses in recent years [11,61,73]. This is likely due to the more similar

262 host ranges, tropisms, and geographic spreads found between H9N2 viruses, as well as the  
263 fundamental greater compatibility between gene segments that are more closely related to each other.

264

#### 265 **4. H9N2 virus in Humans**

##### 266 *4.1. History of human infections with H9N2*

267 H9N2 viruses are fairly regularly isolated from humans, the first reported human cases came  
268 from two children in Hong Kong in 1999 who exhibited flu-like symptoms, retrospectively several  
269 H9N2 infections on the Chinese mainland were also found to have occurred in 1998 [96,97].  
270 Subsequent human infections have been reported from Egypt, Bangladesh, Pakistan and Oman [98-  
271 101]. Human H9N2 infections are generally mild; there has only been a single reported death due to  
272 the virus, likely due to an underlying health problems [102]. Human H9N2 cases are more often  
273 isolated during periods where other more pathogenic zoonotic influenza viruses are being surveyed  
274 for; many H9N2 cases have been found recently in China, most likely due to the ongoing screening  
275 for zoonotic H7N9 [75], and in Egypt and Bangladesh due to ongoing screening for zoonotic H5N1  
276 infections [34,98]. As of June 2019, there have been a total of 57 laboratory-confirmed human H9N2  
277 infections with half of those being recorded since 2016 (see Table 2). The majority of those infected  
278 were young children (36 of 54 cases were aged 7 years or below) and in many of the infections contact  
279 with poultry was confirmed as the likely source of the infection (28 with confirmed poultry exposure  
280 compared to 9 without any known poultry exposure). There remains no confirmed human-to-human  
281 transmission of H9N2 viruses. Virus sequencing indicates the majority of human H9N2 isolates  
282 contain HA genes from the G1 or BJ94 lineages with virus isolates highly related to local poultry  
283 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 <sup>a</sup>	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 <sup>c</sup>	Yes	[105]
2008	Guangdong province, China	2-month-old, female	ILI <sup>b</sup>	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 <sup>d</sup>	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]

	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]
2019	Jiangsu province, China	9-year-old, male	Severe pneumonia	ND	Yes	[130]
	Oman	13-month-old, female	ILI	G1 'Western'	Yes	[101]

285 <sup>a</sup>ARI – acute respiratory infection. <sup>b</sup>ILI – influenza-like illness. <sup>c</sup>ND – strain lineage not reported.

286 <sup>d</sup>Underlying health conditions were cited as contributing factor.

287

#### 288 4.2. Seropositivity rates

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

302

#### 303 4.3. Haemagglutinin and receptor binding

304 Receptor binding preference of HA protein is a well-established determinant of zoonotic and  
 305 pandemic potential [132,133]. Multiple studies have therefore attempted to evaluate this property of  
 306 H9N2 AIVs. Initial studies showed that some H9N2 virus lineages, particularly the G1 and BJ94  
 307 lineages, appeared to possess a preference towards human-like  $\alpha$ 2,6-linked SA over avian-like  $\alpha$ 2,3-  
 308 linked SA. Subsequent studies utilised synthetic receptor analogues, including sulphated and  
 309 fucosylated variants of the classically avian-like 3SLN receptor analogue, to show that H9N2 viruses,  
 310 particularly those of the G1 'Eastern' sub-lineage and BJ94 lineage viruses, displayed high binding  
 311 towards analogues sulphated on the antepenultimate sugar though a few viruses of the G1 'Eastern'  
 312 sub-lineage also displayed moderate 'human-like' 6SLN binding [134,135]. A further study utilising  
 313 purified recombinant H9 HA and glycan arrays found binding to  $\alpha$ 2,3-linked sialosides, as well as  
 314 some binding to  $\alpha$ 2,6-, and  $\alpha$ 2,8- or  $\alpha$ 2,9- linked receptors. Furthermore, several studies have looked  
 315 at the receptor binding of BJ94 lineage viruses using ELISA based methods, these have unanimously

316 showed that contemporary H9N2 viruses show a preference for the 'human-like' receptor analogue  
317 6SLN over 'avian-like' 3SLN [136-138].

318

#### 319 *4.3.1. Molecular basis of receptor binding*

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

327

#### 328 *4.4. Ferret experiments*

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

348

#### 349 *4.5. Other factors involved in zoonotic and pandemic potential in H9N2 viruses*

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

## 358 5. H9N2 infection in other species

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

361

### 362 5.1. *Minor poultry species*

363 Although chickens appear to be the primary host for most poultry adapted H9N2 lineages,  
364 the virus is also endemic in minor poultry in many regions and appears to have evolved and adapted  
365 separately to members of these species, for example; quail, guinea fowl, partridge, and pheasants  
366 [75,151]. The G1 'Eastern' sub-lineage, in particular, appears to occupy a niche within these species  
367 [75,151]. Quail have been shown to possess a more 'human-like' receptor repertoire than chickens,  
368 containing a higher amount of  $\alpha$ 2,6-linked sialic acids [152,153], indicating that viruses adapted to  
369 these species may have a greater zoonotic potential than viruses circulating in chickens. This  
370 hypothesis is supported by the higher relative binding of viruses from this lineage to  $\alpha$ 2,6 linked  
371 receptor analogues, the higher replicative ability of these viruses in human primary tissues, and also  
372 by the higher than expected rate of zoonotic infections caused by these viruses, relative to their  
373 limited prevalence and geographical distribution [10,72,96,135,145,154]. Further, it has been shown  
374 that passage of a duck-origin H9N2 virus in quail leads to an expanded host range, with a virus that  
375 can more readily infect mice compared to the parental duck virus [155]. Poultry are also included in  
376 this host range expansion, which may explain the initial detection of an H9N2 virus in Japanese quail  
377 which preceded H9N2 establishment in poultry in endemic regions [83].

378 Due to the co-circulation G1 'Eastern' sub-lineage and G57/H7N9 viruses we hypothesise  
379 that a potential reassortment event between a naturally  $\alpha$ 2,6-binding G1 'Eastern' virus and the  
380 naturally mammalian pre-adapted internal gene cassette of a G57-lineage virus could result in a virus  
381 with higher pandemic and zoonotic potential than either parental virus, therefore continuous full  
382 genome surveillance of viruses, particularly in minor poultry, is vital in this region of Southern China.

383

### 384 5.2. *Swine*

385 Swine are often said to represent a potential 'mixing vessel' for human and avian viruses, a  
386 fact supported by semi-regular establishment of human and avian virus lineages in these hosts. There  
387 have been many recorded outbreaks of H9N2 virus in farmed pigs, mostly in Hong Kong and China  
388 [156-159]. As swine carry viruses closely related to human seasonal influenza viruses it has been  
389 hypothesised a swine influenza/H9N2 reassortant could emerge with high pandemic potential [156].  
390 Un-adapted, H9N2 viruses do not transmit efficiently between pigs, and swine H9N2 isolates show  
391 little evidence of mammalian adaption suggesting repeated reintroduction from avian hosts rather  
392 than continuous within-species circulation [159,160]. Repeated serial passage through pigs can lead  
393 to partial adaptation allowing for modest replication and transmission [160]. Although H9N2 viruses  
394 don't appear to actively circulate in pigs, there remains a possibility that these viruses could spill  
395 over into these hosts due to the proximity between poultry and pigs in many smallholding farms  
396 leading to the potential for reassortment with currently circulating swine influenza viruses.

397

### 398 5.3. *Canids*

399 Dogs play host to several lineages of canine influenza viruses (CIV), the most common being  
400 equine-origin H3N8 and avian-origin H3N2 [161,162]. H9N2 viruses of the BJ94 lineage have been

401 isolated in China several times from dogs with CIV-like illness [163], furthermore a pair of studies  
402 have shown high seropositivity against H9 HA in stray dogs at LBMs in China, potentially due to  
403 feeding upon infected birds [164,165]. In 2016 a single avian-origin H3N2 CIV isolate was found that  
404 contained a PA gene closely related to that of circulating avian H9N2 viruses suggesting the  
405 possibility of active reassortment between AIV and CIV viruses in canine hosts [166]. Furthermore,  
406 there is serological evidence for H9N2 infection of foxes and racoon dogs in China, further indicating  
407 canids may be a potential host for these viruses [167].

408

#### 409 5.4. Horses

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

416

#### 417 5.5. Mustelidae

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

431

#### 432 5.6. Lagomorpha

433 Pikas are small rodent-like mammals of the order lagomorpha (which also includes rabbits.)  
434 There is evidence from serosurveys and from direct virus isolation that H9N2 viruses naturally infect  
435 pikas in China [174,175]. HA phylogeny of the pika isolates show these viruses are of the American  
436 lineage, known to occasionally infect wild birds in Asia [175]. As pikas are known to be able to be  
437 experimentally infected with avian influenza viruses, and due to the lack of any signature of  
438 mammalian adaptation (i.e. PB2 E627K), it appears more likely these infections are due to direct  
439 contact with infected birds or virus contaminated water sources rather than continuously circulating,  
440 mammalian adapted viruses (as may be the case with the H9N2 infected minks described previously)  
441 [175,176].



## 442 5.7. *Chiroptera*

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

449

## 450 6. Vaccination and control

451 Due to the economic damage caused by enzootic H9N2, many countries including China,  
452 Israel, South Korea, Morocco, Pakistan, Egypt and Iran have adopted vaccination at either a  
453 national or local level as a key approach for preventing H9N2 disease in poultry [28,36,44,178-181].  
454 The most common vaccines in use are traditional inactivated vaccines, similar to those used in human  
455 seasonal vaccines. H9N2 viruses exhibit a wide antigenic variability, both between, and within  
456 lineages [10,73,142]. Unlike human vaccines, H9N2 vaccines are generally not as regularly assessed  
457 for their efficacy against antigenically drifted viruses and consequently are far less often updated.  
458 Therefore, in many regions H9N2 viruses continue to infect and cause disease in vaccinated poultry  
459 with tentative evidence suggesting that sub-optimal use of vaccination may be driving antigenic drift  
460 and/or clade replacement, and theoretically zoonotic potential and pathogenesis  
461 [27,28,41,73,86,181,182]. Because of this there is a real need for i) better understanding of the  
462 molecular determinants of H9 antigenicity, ii) better understanding of antigenic drift and the  
463 consequences upon viral fitness and zoonotic potential and iii) next generation vaccines that protect  
464 better against multiple strains and antigenically drifted variants.

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

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

## 485 7. Conclusions and perspectives

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

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

503

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509

## 510 Conflict of Interest

511 The authors declare they have no conflict of interest.

512

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