Avian Influenza A(H9N2): Human Infections, Epidemiology, and Public Health Implications

Jadhav Roshani*, Rutuja Pagare *, Charushila C. Bhangale.[1]
Pravara Rural Education Society's College Of Pharmacy, (For Women's) Chincholi, Nashik-422102.

Abstract: A subtype of the influenza A virus known as avian influenza A (H9N2) primarily affects birds, while occasional human infections have also been observed. This overview highlights the mild clinical manifestations commonly associated with H9N2 infections in humans and covers the latest case that was reported to the WHO from India in May 2024. The virus co-circulates with more dangerous strains and is endemic in domestic poultry throughout Eurasia, making surveillance efforts more difficult. Its emergence in the 1960s and subsequent global spread, especially in Asia, are revealed by the historical context. To lower infection rates in poultry and safeguard the public's health, preventive measures have been put in place, such as vaccination and biosecurity procedures. The WHO stresses the necessity of ongoing monitoring and awareness in order to track any potential effects of H9N2 on human health.

Key words: Human Infections with Avian Influenza A H9N2, Clinical Signs and Vaccination, Measures, Bird Disease Vaccination, Biosecurity, Monitoring of Public Health, Zoonotic Infection

INTRODUCTION

A case of human infection with avian influenza A(H9N2) virus was reported to WHO on May 22, 2024, by the National Focal Point (NFP) for India under the International Health Regulations (IHR) after a child living in West Bengal state in India was found to have the virus. After the first case in 2019, this is the second case of avian influenza A(H9N2) in humans that the WHO has been informed of from India. After making a full recovery, the child was released from the hospital. A human infection brought on by a novel influenza A virus subtype, according to the IHR (2005), is considered an occurrence with the potential to have a significant impact on public health and has to be reported to the WHO. The majority of human instances of avian influenza A(H9N2) virus infection occur via contact with contaminated surroundings or diseased animals. A human infection typically causes a minor form of clinical disease.[1]

Influenza A virus's segmented, negative-sense RNA genome encodes 10 core proteins and an arbitrary number of auxiliary proteins. Viruses belong to the Orthomyxoviridae family. Influenza Haemagglutinin (HA) and neuraminidase (NA), two surface proteins that are regularly combined to form viruses, give rise to a variety of subtypes known by names like H1N1, H5N6, or H9N2 With the exception of H17N10 and H18N11, which have only been seen in bats, practically all known subtypes of influenza are naturally present in wild waterfowl and seabirds, making them the natural hosts of influenza viruses. Every now and again, viruses that are meant for wild birds can spread to domestic chickens. Avian influenza viruses (AIVs) can be divided into two groups according to the combination of their molecular markers in the HA protein and their pathogenicity in chickens.[2]

Compared to H5N1 and H7N9 human infections, the public and clinic physicians give significantly less attention to H9N2 cases because the majority of these cases had mild and self-limited symptoms. Therefore, part of the laboratory confirmed cases were detected with heightened active surveillance during emergency responses period There have been no reports of H9N2 virus transmission from person to person to date. In China, around 40 cases of human infection have been reported in the last thirty years.[3]

H9N2 viruses, which cause avian influenza, are mostly found in wild birds in North America and are extensively endemic in domestic poultry across Eurasia [4,5]. H9N2 viruses naturally occur in wild birds, just like all other influenza A viruses do. A growing body of research revealed that H9N2 viruses had become well adapted and were widespread in Asia in gallinaceous poultry as early as the 1990s [6]. Different genotypes emerged from different reassortments among distinct H9N2 strains or lineages.

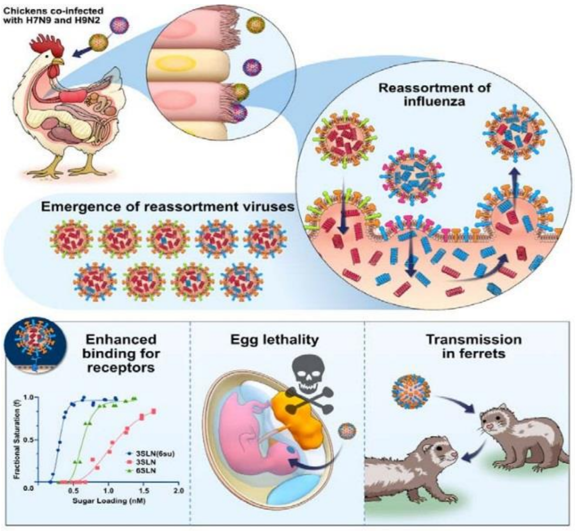


Figure.1 In vivo experimental design of H9N2 infection

In 1998, Southern China recorded the first five laboratory-confirmed cases of avian influenza A (H9N2) infections. The patients experienced severe respiratory distress before ultimately making a full recovery [7]. In the four years that followed, three more human instances were recorded in Hong Kong [8,9]. These patients were all children who had a simple influenza-like sickness and had recovered completely. Two further H9N2 cases were reported in 2008 and 2009 [10]. A human case of avian influenza A (H9N2) in 2011 was discovered in Bangladesh; the virus has several genetic traits with mammals [11].

HISTORY AND PHYLOGEOGRAPHY OF H9N2 VIRUS

In 1966, the US state of Wisconsin saw the first isolation of H9N2 viruses from turkeys [12]. Over the ensuing decades, the virus was periodically isolated during rare outbreaks in domestic ducks and wild birds across Eurasia, as well as in poultry in the Northern USA [13]. The virus was initially discovered in Chinese chickens in the early 1990s. Over the ensuing decades, viruses linked to this Chinese progenitor have spread over most of Asia, the Middle East, and North and West Africa in farmed poultry [14].

Figure 2. Phylogeographic distribution of H9N2 lineages suited to poultry. Whereas only G1-W viruses are found in blue, only BJ94 lineage viruses are found in red, mixtures of BJ94 and G1-E sub-lineage viruses are found in orange, mixtures of BJ94 and G1-W sub-lineage viruses are found in purple, and only Y439-lineage viruses that have been adapted for poultry are found in light pink. H9N2-positive nations with unknown H9N2 ancestry are shown in grey.

Co-circulating 9N2 viruses with other AIV subtypes, namely H5 and H7 HPAIVs, are frequently observed in chicken. Strong evidence suggests that concurrent or past H9N2 infection may conceal the high death rate caused by these viruses, enabling the "silent" spread of HPAIVs and impeding surveillance and follow-up intervention efforts [15,16].

2.1. Phylogeography of H9N2 Viruses

The H9N2 virus's HA gene can be roughly divided into two primary branches based on phylogenetic analysis: an American branch and a Eurasian branch. The majority of American H9N2 viruses are found in wild birds, but they can also infect farmed turkeys and remain in the bloodstream without becoming stable in poultry. The A/quail/Hong Kong/G1/1997, A/chicken/Beijing/1/94, and A/chicken/Hong Kong/Y439/1997 viruses, which are named after their prototypic viruses, are the result of Eurasian H9N2 viruses. These lineages are therefore referred to as the G1, BJ94 (also known as the Y280 or G9 lineage), and Y439 (also sometimes known as the Korean lineage) lineages [17]. The G1 lineage can further be separated into two phylogenetic and geographical sub-lineages referred to as the ‘Western’ and ‘Eastern’ sub-lineage.

Compared to HPAIV viruses, LPAIV viruses like H9N2 provide a challenge to global surveillance since they are not considered notifiable pathogens and produce very few overt human illnesses. Many areas with inadequate resources either rarely or never conduct surveillance. H9N2 viruses are probably more widespread than what is shown below, especially in low- and middle-income nations in Asia and Africa. In fact, they may even be endemic in more nations. Since poultry-adapted strains of the virus, for instance, tend to spread over short distances rather than long distance flyways, the fact that the virus was isolated in Uganda, West Africa, and that it was most closely related, albeit not very closely, to viruses from the Arabian Peninsula, which is about 2000 km away, suggests that the countries in between also likely contain H9N2 viruses that are intermediately related but have not yet been isolated [18].

2.1.1. South Asia

In addition to being thought to be endemic in Bangladesh and Pakistan, H9N2 viruses are also probably endemic in parts of India, Afghanistan, and Nepal [19,20,21,22,23,24,25]. The majority of viruses in poultry in South Asia are classified as G1 or "Western" viruses. Occasionally, Y439 viruses from wild birds infect poultry, but they do not seem to spread over time. This region's (as well as Iran's) predominant G1 "Western" sub-lineage of viruses appears to have emerged from a reassortment event involving co-circulating HPAIV H7N3 and LPAIV H9N2 viruses, which supplanted other regional clades [26,27].

2.1.2 Africa

Though H9N2 viruses have been isolated from farmed ostriches in South Africa on multiple occasions, it appears these viruses most likely represent dead-end spillover events from wild migratory birds due to their homology to wild bird virus isolates (of the Y439 lineage) and subsequent sampling that found no further evidence of virus circulation [28]. Lastly, two investigations indicate that Nigerian poultry and agricultural labourers have significant seropositivity against H9N2, but no virus has been detected from this nation [29,30]. It is uncertain whether protocols are being utilized to detect the presence (or absence) of H9N2 viruses, despite the fact that surveillance for HPAIVs is underway in Nigeria. As a result, it is still unknown whether the virus is or was prevalent in this area.

As was previously mentioned, the fact that the H9N2 virus is present in poultry in non-contiguous regions of Africa raises the possibility that other nations may also be infected. But there's no proof because the virus isn't being actively searched for, and if it is, it's not being reported because LPAIs, like H9N2 infections, aren't illnesses that have to be reported to the World Organization for Animal Health (OIE).

2.1.3 The Americas

Throughout the second half of the 20th century, H9N2 viruses have been periodically isolated from poultry in the USA; in fact, it was during this time that the classic H9N2 isolate (A/turkey/Wisconsin/1/1966) was discovered. The viruses that have been isolated are all of American descent and seem to have spread from wild birds, likely sea birds, who are known to carry viruses that are closely linked genetically in this area. Despite routine surveillance and abundant evidence of other non-H9N2 viruses in poultry, there has been no evidence of the virus in North America since 2001 [31,32,33,34,35].

Serological evidence of H9N2 infections in Colombia dates back to 2005 in South America; however, no virus was isolated, and no further evidence has been reported subsequently [33].

Sampling and Testing

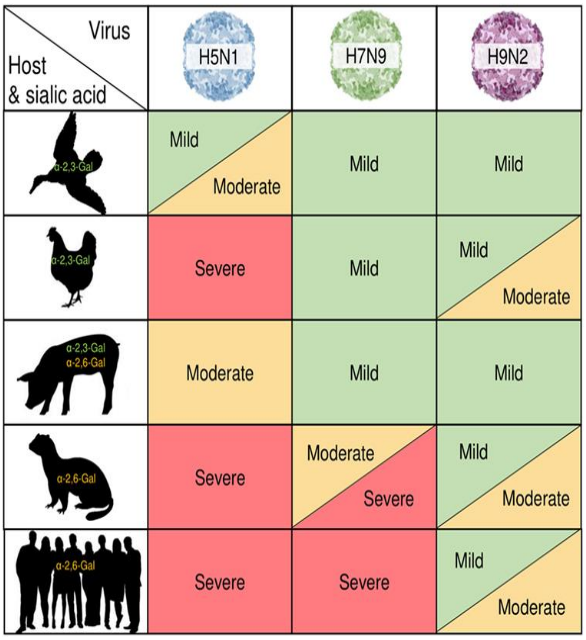
On the first day after the disease began, a throat swab was taken from the patient at Yongzhou City Central

Hospital. 742 environmental samples, including sewage, poultry faces, cage swabs, and chopping board swabs, were collected from 12 live poultry trade and slaughter markets between November 2013 and May 2014 in order to identify the potential source of infection. These samples were epidemiologically linked to a human H9N2 infection case in Yongzhou city. Real-time RT-PCR assays were used to analyse the samples for influenza A and its subtypes H5, H7, and H9. Primers and probe sequences are available upon request.

H9N2 Virus in Humans

The majority of H9N2 infections in humans are moderate, and the virus has only been linked to one recorded fatality, which was probably caused by an underlying medical condition [36]. When other, more dangerous zoonotic influenza viruses are being searched for, human H9N2 cases are more frequently isolated at those times. Recently, a large number of H9N2 cases have been discovered in Egypt and Bangladesh as a result of continuing screening for zoonotic H5N1 illnesses and in China most likely as a result of screening for zoonotic H7N9 [37,38]. There have been 59 laboratory-confirmed cases of H9N2 infection in humans as of June 2019, with more than half of those cases occurring since 2015. The majority of individuals with confirmed infections were young children (39 out of 56 cases), with a median infection age of 4 years old and a mean infection age of 14. It seems that the rates of infection in both sexes were comparable. The distribution of ages and sexes is quite different from the first wave of H7N9, which largely affected men and the elderly, and the H5N1 viruses, which mostly affected young people [39,40]. Contact with poultry was identified as the most probable source of infection in the majority of cases (29 with confirmed poultry exposure compared to 11 with no known poultry exposure). But unlike H7N9, no verified reports of H9N2 viral transmission from person to person exist [41]

Although they typically infect animals, animal influenza viruses can also infect people. Human infections have mostly been transmitted by indirect contact with contaminated settings or direct contact with infected animals. Influenza can vary depending on its original host. One can categorize viruses as animal influenza viruses, swine influenza viruses, or avian influenza viruses. Human infections with the avian influenza virus can range in severity from mild upper respiratory tract infections to more serious illnesses that are potentially lethal. There have also been reports of encephalitis, encephalopathy, conjunctivitis, and gastrointestinal problems. It takes laboratory testing to diagnose influenza in humans. The World Health Organization (WHO) regularly updates technical advice protocols for molecular approaches of zoonotic influenza diagnosis. [1]



Virus / Host & sialic acid	H5N1	H7N9	H9N2
α-2,3-Gal	Mild Moderate	Mild	Mild
α-2,3-Gal	Severe	Mild	Mild Moderate
α-2,3-Gal α-2,6-Gal	Moderate	Mild	Mild
α-2,6-Gal	Severe	Moderate Severe	Mild Moderate
α-2,6-Gal	Severe	Severe	Mild Moderate

Figure 3. Avian Influenza a(h9n2) Virus.

Vaccination and Control

Many nations, including China, Israel, South Korea, Morocco, Pakistan, Egypt, Iran, and the United Arab Emirates, have implemented vaccination programs at the national or municipal level as a crucial measure in reducing H9N2 disease in poultry due to the economic harm caused by the enzootic virus [42,43,44,45,46,47,48,49]. Conventional inactivated vaccines, which resemble the vaccines used in human seasonal vaccinations, are the most widely used vaccines. H9N2 viruses demonstrate a wide antigenic diversity, both between, and within lineages [14,50,51]. H9N2 vaccinations are updated significantly less frequently than human vaccines because they are typically not evaluated as frequently for their effectiveness against viruses that have antigenically drifted. As a result, H9N2 viruses continue to infect and sicken vaccinated poultry in many regions. Some evidence indicates that this may be due to suboptimal vaccination practices, which may also be causing antigenic drift and/or clade replacement, as well as theoretically increased zoonotic potential and pathogenicity [50,52,42,53,54,48,49]. This means that: (i) a deeper comprehension of the molecular factors that determine H9 antigenicity; (ii) a deeper comprehension of antigenic drift and its effects on viral fitness and zoonotic potential; and (iii) the development of next-generation vaccines that offer protection against multiple strains and antigenically drifted variants.

In nations where H9N2 has never before been reported, stamping out—which entails eliminating possibly infected birds and birds exhibiting influenza-related morbidity—has occasionally been employed as a first line of defence against the virus. This was true in the past for the outbreaks in Ghana and Russia, as well as the early ones in Korea [55,56,45]. Vaccination is frequently employed once the virus becomes endemic in a nation since it becomes impractical and uneconomic to eradicate at that time. Regardless of a nation's previous experience with outbreaks or endemicity, stamping out is more frequently employed during HPAIV epidemics because of their status as notifiable diseases.

In addition to vaccination and eradication, a number of other strategies have been effectively implemented in the field to prevent or lessen the spread of the avian influenza virus in poultry and the ensuing zoonotic infection. As was previously mentioned, the convergence of a high density of several poultry species from a wide geographic range makes LBMs a hotspot for influenza infection. LBMs were first recognized as the primary causes of AIV outbreaks in China and Hong Kong in the late 1990s. A number of interventions, including temporary closures, recurring rest days, depopulation of the overnight market, and fundamental improvements in biosecurity and hygiene practises, were employed. Offeddu and colleagues conducted a thorough analysis of the efficacy of these practices in the past and came to the conclusion that LBM closure in particular was effective in stopping the spread of AIV among birds and in lowering the number of zoonotic AIV cases [57]. According to a second thorough assessment by Fournié and colleagues, human behaviour that exposes people to AIVs and increases their risk of contracting zoonotic infections is very diverse and may call for control measures that are specific to each community [58].

Sr. No	Year	Location	Age	Sex	Clinical signs
1	1998	Guangdone province, China	14-year-old	Male	ARI[1]
			75-year-old	Male	ARI
			4-year-old	Male	ARI
			1 year - old	Female	ARI
			36-year-old	Female	ARI
2	1999	Guangdone province, China	22-month-old	Female	Fever, Cough
		Hong Kong	13-month-old	Female	Fever
			4-year-old	Female	Fever, malaise
3	2003	Hong Kong	5-year-old	Male	Fever, Cough
4	2007	Hong Kong	9-month-old	Female	Mild illness
5	2008	Guangdone province, China	2-month-old	Female	ILI[2]
6	2009	Hong Kong	35-month-old	Female	Fever, Cough
			47-year-old	Female	Fever, Cough
7	2011	Dhaka Bangladesh	4-year-old	Female	Fever, Cough
8	2013	Guangdone province, China	86-year-old	Male	Cough
		Hunan province, China	7-year-old	Male	Fever
9	2014	Sichuan province, China	2.5-year-old	Male	Mild illness

		Guangdone province, China	Unknown	Unknown	Mild illness
10	2015	Aswan, Egypt	3year-old	Male	Unknown
		Cairo, Egypt	7year-old	Female	ILI
			9-month-old	Female	ILI
		Guangdone province, China	Unknown	Male	Unknown
		Bangladesh	3.5-year-old	Female	Mild illness
		Anhui province, China	4-year-old	Female	Mild illness
		Hunan province, China	2-year-old	Male	Mild illness
		Anhui province, China	6-year-old	Male	Unknown
		Hunan province, China	15-year-old	Female	Mild illness
			11-year-old	Female	Mild illness
		Dhaka Bangladesh	46- year-old	Male	Fever
		Hunan province, China	2-year-old	Male	Mild illness
		Guangdone province, China	84-year-old	Female	Unknown
		Punjab district Pakistan	36-year-old	Male	Non-symptomatic
11	2016	Sichuan province, China	57-year-old	Female	ARI, Died
		Cairo, Egypt	18-month-old	Male	ILI
		Guangdone province, China	4-year-old	Female	ARI
			29-year-old	Female	ARI
		Yunnan province, China	10-month-old	Male	ILI
		Jiangxi province, China	4-year-old	Female	Mild illness
		Guang done province, China	7-month-old	Female	Mild illness
		Beijing, China	4-month-old	Male	Mild illness
12	2017	Gansu province, China	11-month-old	Male	Mild illness

		Beijing, China	32-year-old	Male	Mild illness
		Guang done province, China	2-month-old	Female	ILI
		Hunan province, China	20-month-old	Female	n/a
			9-month-old	Male	ILI
		Anhui province, China	9-year-old	Female	Mild illness
13	2018	Guang done province, China	3-year-old	Female	Mild illness
		Beijing, China	51-year-old	Female	Mild illness
		Guangxi province, China	3-year-old	Male	n/a
		Guang done province, China	32-year-old	Female	Pneumonia
14	2019	Yunnan province, China	8- year-old	Female	Mild illness
		Jiangsu province, China	9-year-old	Male	Severe pneumonia
		Oman	13-month-old	Female	ILI

[1] ARI—acute respiratory infection. [2] ILI—influenza-like illness.

WHO advice

The current WHO guidelines for public health precautions and influenza surveillance at the interface of humans, animals, and the environment are unaffected by this instance. Every human infection must be thoroughly investigated. Unprotected contact with live poultry, high-risk locations like live animal markets or farms, and surfaces that could be contaminated by chicken droppings should all be avoided by the general public. Along with routinely cleaning and disinfecting the environment, infection prevention and control (IPC) methods should be used. These include practicing frequent hand hygiene, which involves washing hands with soap and water or using alcohol-based hand rub solutions to ensure that the hands are visibly clean. The World Health Organization (WHO) recommends the following actions to prevent the disease from spreading nosocomial—that is, from starting in a healthcare setting—early infection control and preventive measures:

1. Inform healthcare professionals about suspicious cases.
2. Hospitals should put in place a screening and triaging (patient categorization) system.
3. While conducting aerosol-generating procedures on suspected cases, observe standard, droplet, and airborne precautions (N95/FFP2/FFP3).
4. Keep an eye out for fever and influenza-like symptoms in healthcare personnel.
5. Assign personal protective equipment and provide the necessary instruction for using it

According to the IHR (2005), all human infections brought on by a novel influenza virus subtype must be reported. State Parties to the IHR (2005) shall promptly report to WHO any case of influenza A virus of pandemic potential (IVPP) that has been laboratory-confirmed as a recent human infection. Based on the information that is currently available regarding this event, WHO recommends against imposing any travel or trade restrictions. The WHO does not advise any particular precautions for travellers[1]

CONCLUSION

The avian influenza A(H9N2) virus continues to pose a significant threat to public health, especially in areas where poultry are endemic. Even though the majority of infections in people are usually minor, recent human cases—including the one that was reported in India—highlight the possibility of zoonotic transmission. Risks must be reduced by vigorous biosecurity protocols and ongoing surveillance, particularly in live poultry markets where the virus is prevalent. Many nations have adopted poultry vaccination programs, but issues including antigenic drift and inconsistent efficacy still need to be resolved. Ultimately, even though there is currently little immediate risk of H9N2 to human health, it is nevertheless important to exercise caution to stop outbreaks and guarantee public safety.

REFERENCES

[1] https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON523#:~:text=On%2022%20May%202024%2C%20the,West%20Bengal%20state%20in%20India

[2] Wu, Y.; Wu, Y.; Tefsen, B.; Shi, Y.; Gao, G.F. Bat-derived influenza-like viruses H17N10 and H18N11. Trends Microbiol. 2014, 22, 183–191. [Google Scholar] [CrossRef] [PubMed]

[3] Huang, Y., Li, X., Zhang, H., Chen, B., Jiang, Y., Yang, L., … Gao, L. (2015).

[4] Alexander DJ. 2007. An overview of the epidemiology of avian influenza. Vaccine 25:5637–5644

[5] Hossain MJ, Hickman D, Perez DR. 2008

[6] Alexander DJ. 2000. A review of avian influenza in different bird species. Vet Microbiol 74:3–13.

[7] Guo Y, Li J, Cheng X. 1999. [Discovery of men infected by avian influenza A (H9N2) virus].

[8] Guo Y, Li J, Cheng X. 1999. [Discovery of men infected by avian influenza A (H9N2) virus].

[9] Butt KM, Smith GJ, Chen H, Zhang LJ, Leung YH, Xu KM, Lim W, Webster RG, Yuen KY, Peiris JS, Guan Y. 2005

[10] Cheng VC, Chan JF, Wen X, Wu WL, Que TL, Chen H, Chan KH, Yuen KY. 2011

[11] Shanmuganatham K, Feeroz MM, Jones-Engel L, Smith GJ, Fourment M, Walker D, McClenaghan L, Alam SM, Hasan MK Seiler P, Franks J, Danner A, Barman S, McKenzie P, Krauss S, Webby RJ, Webster RG. 2013. Antigenic and molecular characterization of avian influenza A(H9N2) viruses, Bangladesh.Emerg Infect Dis 19:13931402

[12] Homme, P.J.; Easterday, B.C. Avian influenza virus infections. I. Characteristics of influenza A-turkey-Wisconsin-1966 virus. Avian Dis. 1970, 14, 66–74. [Google Scholar] [CrossRef]

[13] Shortridge, K.F. Pandemic influenza: A zoonosis? Semin Respir Infect 1992, 7, 11–25. [Google Scholar]

[14] Guan, Y.; Shortridge, K.F.; Krauss, S.; Webster, R.G. Molecular characterization of H9N2 influenza viruses: Were they the donors of the “internal” genes of H5N1 viruses in Hong Kong? Proc. Natl. Acad. Sci. USA 1999, 96, 9363–9367. [Google Scholar] [CrossRef]

[15] Khalenkov, A.; Perk, S.; Panshin, A.; Golender, N.; Webster, R.G. Modulation of the severity of highly pathogenic H5N1 influenza in chickens previously inoculated with Israeli H9N2 influenza viruses. Virology 2009, 383, 32–38. [Google Scholar] [CrossRef] [PubMed] [Green Version]

[16] Naguib, M.M.; Grund, C.; Arafa, A.S.; Abdelwhab, E.M.; Beer, M.; Harder, T.C. Heterologous post-infection immunity against egyptian avian influenza virus (AIV) H9N2 modulates the course of subsequent infection by highly pathogenic AIV H5N1, but vaccination immunity does not. J. Gen. Virol. 2017, 98, 1169–1173. [Google Scholar] [CrossRef] [PubMed]

[17] Guo, Y.J.; Krauss, S.; Senne, D.A.; Mo, I.P.; Lo, K.S.; Xiong, X.P.; Norwood, M.; Shortridge, K.F.; Webster, R.G.; Guan, Y. Characterization of the pathogenicity of members of the newly established H9N2 influenza virus lineages in Asia. Virology 2000, 267, 279–288. [Google Scholar] [CrossRef]

[18] Byarugaba, D.K.; Erima, B.; Ukuli, Q.A.; Atim, A.; Tugume, T.; Millard, M.; Kibuuka, K.; Mimbe, M.; Mworozi, E.A.; Danner, A.; et al. Hemagglutinin [Influenza A Virus]. Accession no. Avk87156.1. GenBank 2018.Available online: https://www.ncbi.nlm.nih.gov/protein/Avk87156.1 (accessed on 3 July 2019

[19] Alexander, D.J. Report on avian influenza in the eastern hemisphere during 1997–2002. Avian Dis. 2003, 47, 792–797. [Google Scholar] [CrossRef]

[20] Cameron, K.R.; Gregory, V.; Banks, J.; Brown, I.H.; Alexander, D.J.; Hay, A.J.; Lin, Y.P. H9N2 subtype influenza A viruses in poultry in pakistan are closely related to the H9N2 viruses responsible for human infection in Hong Kong. Virology 2000, 278, 36–41. [Google Scholar] [CrossRef] [PubMed]

[21] Negovetich, N.J.; Feeroz, M.M.; Jones-Engel, L.; Walker, D.; Alam, S.M.; Hasan, K.; Seiler, P.; Ferguson, A.; Friedman, K.; Barman, S.; et al. Live bird markets of Bangladesh: H9N2 viruses and the near absence of highly pathogenic H5N1 influenza. PLoS ONE 2011, 6, e19311. [Google Scholar] [CrossRef] [PubMed]

[22] Tosh, C.; Nagarajan, S.; Behera, P.; Rajukumar, K.; Purohit, K.; Kamal, R.P.; Murugkar, H.V.; Gounalan, S.; Pattnaik, B.; Vanamayya, P.R.; et al. Genetic analysis of H9N2 avian influenza viruses isolated from India. Arch. Virol. 2008, 153, 1433–1439. [Google Scholar] [CrossRef]

[23] Hosseini, H.; Ghalyanchilangeroudi, A.; Fallah Mehrabadi, M.H.; Sediqian, M.S.; Shayeganmehr, A.; Ghafouri, S.A.; Maghsoudloo, H.; Abdollahi, H.; Farahani, R.K. Phylogenetic analysis of H9N2 avian influenza viruses in Afghanistan (2016–2017). Arch. Virol. 2017, 162, 3161–3165. [Google Scholar] [CrossRef] [PubMed]

[24] Alexander, D.J. Summary of avian influenza Activity in Europe, Asia, Africa, and Australasia, 2002–2006. Avian Dis. 2007, 51, 161–166. [Google Scholar] [CrossRef]

[25] Brown, I.H. Summary of avian influenza Activity in Europe, Asia, and Africa, 2006–2009. Avian Dis. 2010, 54, 187–193. [Google Scholar] [CrossRef]

[26] Iqbal, M.; Yaqub, T.; Reddy, K.; McCauley, J.W. Novel genotypes of H9N2 influenza A viruses isolated from poultry in Pakistan containing ns genes similar to highly pathogenic H7N3 and H5N1 viruses. PLoS ONE 2009, 4, e5788. [Google Scholar] [CrossRef]

[27] Parvin, R.; Heenemann, K.; Halami, M.Y.; Chowdhury, E.H.; Islam, M.R.; Vahlenkamp, T.W. Full-genome analysis of avian influenza virus H9N2 from Bangladesh reveals internal gene reassortments with two distinct highly pathogenic avian influenza viruses. Arch. Virol. 2014, 159, 1651–1661. [Google Scholar] [CrossRef]

[28] Abolnik, C.; Cornelius, E.; Bisschop, S.P.; Romito, M.; Verwoerd, D. Phylogenetic analyses of genes from South African LPAI viruses isolated in 2004 from wild aquatic birds suggests introduction by Eurasian migrants. Dev. Biol. 2006, 124, 189–199. [Google Scholar] [PubMed]

[29] Oluwayelu, D.O.; Omolanwa, A.; Adebiyi, A.I.; Aiki-Raji, C.O. Flock-based surveillance for low pathogenic avian influenza virus in commercial breeders and layers, southwest nigeria. Afr. J. Infect. Dis. 2016, 11, 44–49. [Google Scholar] [CrossRef]

[30] Okoye, J.; Eze, D.; Krueger, W.S.; Heil, G.L.; Friary, J.A.; Gray, G.C. Serologic evidence of avian influenza virus infections among Nigerian agricultural workers. J. Med. Virol. 2013, 85, 670–676. [Google Scholar] [CrossRef]

[31] Panigrahy, B.; Senne, D.A.; Pedersen, J.C. Avian influenza virus subtypes inside and outside the live bird markets, 1993–2000: A spatial and temporal relationship. Avian Dis. 2002, 46, 298–307. [Google Scholar] [CrossRef]

[32] Senne, D.A. Avian influenza in north and South America, the Caribbean, and Australia, 2006–2008. Avian Dis. 2010, 54, 179–186. [Google Scholar] [CrossRef] [PubMed]

[33] Senne, D.A. Avian influenza in north and South America, 2002–2005. Avian Dis. 2007, 51, 167–173. [Google Scholar] [CrossRef] [PubMed]

[34] Senne, D.A. Avian influenza in the western hemisphere including the pacific islands and Australia. Avian Dis. 2003, 47, 798–805. [Google Scholar] [CrossRef] [PubMed]

[35] Pasick, J.; Pedersen, J.; Hernandez, M.S. Avian influenza in north America, 2009–2011. Avian Dis. 2012, 56, 845–848. [Google Scholar] [CrossRef] [PubMed]

[36] Influenza At the human-animal interface, summary and assessment, 20 July to 3 October 2016; World Health Organisation: Geneva, Switzerland, 2016; pp. 5–6.

[37] Monne, I.; Hussein, H.A.; Fusaro, A.; Valastro, V.; Hamoud, M.M.; Khalefa, R.A.; Dardir, S.N.; Radwan, M.I.; Capua, I.; Cattoli, G. H9N2 influenza A virus circulates in H5N1 endemically infected poultry population in

Egypt. Influenza Other Respi. Viruses 2013, 7, 240–243. [Google Scholar] [CrossRef] [PubMed]

[38] International Centre for Diarrhoeal Disease Research (ICDDRB). Outbreak of mild respiratory disease caused by H5N1 and H9N2 infections among young children in Dhaka, Bangladesh; Health and Science Bulletin, ICDDRB: Dhaka, Bangladesh, 2011; Volume 9, pp. 5–12. [Google Scholar]

[39] Li, Q.; Zhou, L.; Zhou, M.; Chen, Z.; Li, F.; Wu, H.; Xiang, N.; Chen, E.; Tang, F.; Wang, D.; et al. Epidemiology of human infections with avian influenza A(H7N9) virus in China. N. Engl. J. Med. 2014, 370, 520–532. [Google Scholar] [CrossRef] [PubMed]

[40] Smallman-Raynor, M.; Cliff, A.D. Avian influenza A (H5N1) age distribution in humans. Emerg. Infect. Dis. 2007, 13, 510–512. [Google Scholar] [CrossRef] [PubMed]

[41] Zhou, L.; Chen, E.; Bao, C.; Xiang, N.; Wu, J.; Wu, S.; Shi, J.; Wang, X.; Zheng, Y.; Zhang, Y.; et al. Clusters of human infection and human-to-human transmission of avian influenza A(H7N9) virus, 2013–2017. Emerg. Infect. Dis. 2018, 24, 397. [Google Scholar] [CrossRef] [PubMed]

[42] Zhang, P.; Tang, Y.; Liu, X.; Peng, D.; Liu, W.; Liu, H.; Lu, S.; Liu, X. Characterization of H9N2 influenza viruses isolated from vaccinated flocks in an integrated broiler chicken operation in eastern China during a 5 year period (1998–2002). J. Gen. Virol. 2008, 89, 3102–3112. [Google Scholar] [CrossRef] [PubMed]

[43] Banet-Noach, C.; Perk, S.; Simanov, L.; Grebenyuk, N.; Rozenblut, E.; Pokamunski, S.; Pirak, M.; Tendler, Y.; Panshin, A. H9N2 influenza viruses from Israeli poultry: A five-year outbreak. Avian Dis. 2007, 51, 290–296. [Google Scholar] [CrossRef] [PubMed]

[44] El Houadfi, M.; Fellahi, S.; Nassik, S.; Guerin, J.L.; Ducatez, M.F. First outbreaks and phylogenetic analyses of avian influenza H9N2 viruses isolated from poultry flocks in Morocco. Virol. J. 2016, 13, 140. [Google Scholar] [CrossRef] [PubMed]

[45] Lee, D.H.; Song, C.S. H9N2 avian influenza virus in Korea: Evolution and vaccination. Clin. Exp. Vaccine Res. 2013, 2, 26–33. [Google Scholar] [CrossRef] [PubMed]

[46] Naeem, K.; Siddique, N. Use of strategic vaccination for the control of avian influenza in Pakistan. Dev. Biol. 2006, 124, 145–150. [Google Scholar] [PubMed]

[47] Kilany, W.H.; Ali, A.; Bazid, A.H.; El-Deeb, A.H.; El-Abideen, M.A.; Sayed, M.E.; El-Kady, M.F. A dose-response study of inactivated low pathogenic avian influenza H9N2 virus in specific-pathogen-free and commercial broiler chickens. Avian Dis. 2016, 60, 256–261. [Google Scholar] [CrossRef] [PubMed]

[48] Bahari, P.; Pourbakhsh, S.A.; Shoushtari, H.; Bahmaninejad, M.A. Molecular characterization of H9N2 avian influenza viruses isolated from vaccinated broiler chickens in northeast Iran. Trop. Anim. Health Prod. 2015, 47, 1195–1201. [Google Scholar] [CrossRef] [PubMed]

[49] Lau, S.Y.; Joseph, S.; Chan, K.H.; Chen, H.; Patteril, N.A.; Elizabeth, S.K.; Muhammed, R.; Baskar, V.; Lau, S.K.; Kinne, J.; et al. Complete genome sequence of influenza virus H9N2 associated with a fatal outbreak among chickens in Dubai. Genome Announc. 2016, 4, e00752-16. [Google Scholar] [CrossRef]

[50] Pu, J.; Wang, S.; Yin, Y.; Zhang, G.; Carter, R.A.; Wang, J.; Xu, G.; Sun, H.; Wang, M.; Wen, C.; et al. Evolution of the H9N2 influenza genotype that facilitated the genesis of the novel H7N9 virus. Proc. Natl. Acad. Sci. USA 2015, 112, 548–553. [Google Scholar] [CrossRef] [PubMed]

[51] Peacock, T.P.; Harvey, W.T.; Sadeyen, J.R.; Reeve, R.; Iqbal, M. The molecular basis of antigenic variation among a(H9N2) avian influenza viruses. Emerg. Microbes Infect. 2018, 7, 176. [Google Scholar] [CrossRef]

[52] Park, K.J.; Kwon, H.I.; Song, M.S.; Pascua, P.N.; Baek, Y.H.; Lee, J.H.; Jang, H.L.; Lim, J.Y.; Mo, I.P.; Moon, H.J.; et al. Rapid evolution of low-pathogenic H9N2 avian influenza viruses following poultry vaccination programmes. J. Gen. Virol. 2011, 92, 36–50. [Google Scholar] [CrossRef] [PubMed]

[53] Davidson, I.; Shkoda, I.; Golender, N.; Perk, S.; Lapin, K.; Khinich, Y.; Panshin, A. Genetic characterization of ha gene of low pathogenic H9N2 influenza viruses isolated in israel during 2006–2012 periods. Virus Genes 2013, 46, 255–263. [Google Scholar] [CrossRef]

[54] Peacock, T.P.; Benton, D.J.; James, J.; Sadeyen, J.R.; Chang, P.; Sealy, J.E.; Bryant, J.E.; Martin, S.R.; Shelton, H.; Barclay, W.S.; et al. Immune escape variants of H9N2 influenza viruses containing deletions at the haemagglutinin receptor binding site retain fitness in vivo and display enhanced zoonotic characteristics. J. Virol. 2017, 91, e00218-17. [Google Scholar] [CrossRef]

[55] Marchenko, V.Y.; Goncharova, N.I.; Evseenko, V.A.; Susloparov, I.M.; Gavrilova, E.V.; Maksyutov, R.A.; Ryzhikov, A.B. Overview of the epidemiological situation on highly pathogenic avian influenza virus in Russia in 2018. Problemy Osobo Opasnykh Infektsii [Problems of Particularly Dangerous Infections] 2019, 1, 42–49. [Google Scholar] [CrossRef]

[56] Awuni, J.A.; Bianco, A.; Dogbey, O.J.; Fusaro, A.; Yingar, D.T.; Salviato, A.; Ababio, P.T.; Milani, A.; Bonfante, F.; Monne, I. Avian influenza H9N2 subtype in Ghana: Virus characterization and evidence of co-infection. Avian Pathol. 2019, 1–7. [Google Scholar] [CrossRef] [PubMed]

[57] Offeddu, V.; Cowling, B.J.; Malik Peiris, J.S. Interventions in live poultry markets for the control of avian influenza: A systematic review. One Health 2016, 2, 55–64. [Google Scholar] [CrossRef] [Green Version]

[58] Fournie, G.; Hog, E.; Barnett, T.; Pfeiffer, D.U.; Mangtani, P. A systematic review and meta-analysis of practices exposing humans to avian influenza viruses, their prevalence, and rationale. Am. J. Trop. Med. Hyg. 2017, 97, 376–388. [Google Scholar] [CrossRef]