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Pathobiological Origins and Evolutionary History of Highly Pathogenic Avian Influenza Viruses

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High-pathogenicity avian influenza (HPAI) viruses have arisen from low-pathogenicity avian influenza (LPAI) viruses via changes in the hemagglutinin proteolytic cleavage site, which include mutation of multiple nonbasic to basic amino acids, duplication of basic amino acids, or recombination with insertion of cellular or viral amino acids. Between 1959 and 2019, a total of 42 natural, independent H5 ($n = 15$) and H7 ($n = 27$) LPAI to HPAI virus conversion events have occurred in Europe ($n = 16$), North America ($n = 9$), Oceania ($n = 7$), Asia ($n = 5$), Africa ($n = 4$), and South America ($n = 1$). Thirty-eight of these HPAI outbreaks were limited in the number of poultry premises affected and were eradicated. However, poultry outbreaks caused by A/goose/Guangdong/1/1996 (H5Nx), Mexican H7N3, and Chinese H7N9 HPAI lineages have continued. Active surveillance and molecular detection and characterization efforts will provide the best opportunity for early detection and eradication from domestic birds.

Avian influenza (AI) viruses have their ancestry within the ecological niches occupied by aquatic birds, predominately of the orders Anseriformes and Charadriiformes, and these aquatic birds are the primordial reservoir of genes for all Influenzavirus A strains with the exception of the genetic material of H17N11 and H18N12 influenza A viruses, which have been detected only in bats (Webster et al. 1992; Mehle 2014). Currently, AI viruses have surface proteins of any of the 16 different hemagglutinin (H1–16) and nine different neuraminidase (N1–9) subtypes (Swayne et al. 2020). Based on their pathogenicity in chickens, most

H1–H16 AI viruses cause mild respiratory, enteric, or reproductive diseases (i.e., low-pathogenicity avian influenza [LPAI]), whereas some of the H5 and H7 AI viruses cause deadly, systemic disease (high-pathogenicity avian influenza [HPAI]).

Historically, the first identification of an AI virus in birds was an HPAI virus, termed fowl plague virus, which was initially identified in Northern Italy during the 1880s (Kaleta and Rulke 2008). Most fowl plague cases were in gallinaceous poultry, principally chicken and turkeys, but some cases also affected geese (Kaleta and Rulke 2008). The affected poultry

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were housed close to migratory waterfowl on river banks such as the River Po. The initial clinical presentation in poultry had a mild course with an abrupt change to highly lethal, rapidly spreading disease very similar to our contemporary understanding of the origins of a HPAI virus through changes in the hemagglutinin (HA) proteolytic cleavage site of a H5 or H7 LPAI virus (Bosch et al. 1979; Kawaoka and Webster 1985; Perdue et al. 1996; Kaleta and Rulke 2008). The fowl plague cases from the 1880s to 1959 were exclusively H7N7 and H7N1 HPAI viruses, but in 1959, the first H5 HPAI virus appeared in chickens in Scotland, H5N1 (Kaleta and Rulke 2008; Swayne et al. 2020). From the 1880s to 1959, fowl plague spread throughout Europe, Asia, and Africa and was reported from North and South America. However, it is unclear if these fowl plague cases were a single HPAI virus lineage that was maintained and widely spread geographically among poultry populations or if there were multiple local occurrences of LPAI viruses giving rise to HPAI viruses, but with a more restricted geographic spread. The lack of knowledge related to uniqueness of virus isolates prior to 1959 severely limited the maintenance of diverse and unique fowl plague isolates, which are available today for genetic analysis (Swayne 2008a). However, since 1959, with well-maintained unique virus isolates in archives, outbreaks caused by HPAI viruses have mostly arisen from virulence shifts by LPAI viruses with limited spread and eradication from poultry via stamping out programs. The major exception has been the A/goose/Guangdong/1/1996 (Gs/GD) lineage of H5, which arose in 1996 and has spread and been maintained in poultry and wild aquatic bird reservoirs until the current date, producing infections in poultry, wild birds, or humans in 84 countries in Asia, Africa, Europe, and North America (Röhm et al. 1995; Swayne et al. 2020). The first LPAI virus from poultry was identified in chickens in Germany in 1949 (Dinter virus, H10N7) (Swayne 2008a), and the first LPAI viruses in wild waterfowl (Slemons et al. 1974) and pelagic seabirds (Downie and Laver 1973) were identified in 1972, although antibodies to Influenza-

virus A had been detected in migratory waterfowl as early as 1968 (Easterday et al. 1968).

This review will discuss the mechanisms and genetic changes in the HA gene that are responsible for the shift from LPAI to HPAI viruses and analyze the genetic information, demonstrating that HPAI viruses belong to distinct lineages (Table 1).

MECHANISMS OF THE EMERGENCE OF H5 AND H7 HPAI VIRUSES

The phenotype classification of avian influenza into LPAI (H1–16) and HPAI (H5 and H7) viruses is based on in vivo testing (i.e., the ability to produce severe lethal disease in chickens on intravenous inoculation) and molecular characteristics of the HA protein, more specifically as changes in the proteolytic cleavage site (OIE 2019b). According to the 12th Organisation for Animal Health (OIE) Terrestrial Animal Health Code, the H5 and H7 AI viruses classified as HPAI virus should have an intravenous pathogenicity index (IVPI) in 6-wk-old chickens of >1.2 (OIE 2002). Beginning with the 13th edition of the Terrestrial Animal Health Code (OIE 2004), H5 and H7 AI viruses with IVPI of ≤1.2 or lethality of <75% should be sequenced to determine whether multiple basic amino acids are present at the cleavage site of the HA. If similar sequences of the cleavage site have been observed for other previously reported HPAI viruses, the virus should be classified as HPAI virus. These regulatory definitions are still in place in 2019 (OIE 2019b). However, the presence of any insertion that lengthens the cleavage site but has not been previously reported should be discussed with an OIE Avian Influenza Reference Laboratory or Collaborating Centre before classifying the virus as LPAI or HPAI virus (OFFLU 2019). Although most of the HPAI chicken viruses emerged from LPAI precursors in aquatic wild birds, the emergence of HPAI viruses does not always occur in gallinaceous host (Swayne et al. 2020). The detailed steps of how LPAI viruses evolve into HPAI viruses are not completely understood, but molecular techniques such as next-generation sequencing and reverse genetics have helped to identify the HA

Table 1. Forty-two documented pandemics, epidemics, or limited outbreaks of HPAI since discovery of AI viruses as cause of fowl plague in 1955

No.	Year	Country	Host species	Prototype AI virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
1	1959	Scotland	Domestic poultry	A/chicken/Scotland/1959	H5N1	GU052518	PQRKKR/GLF	Aberdeen: 1 premise, unknown number of chickens (<i>Gallus gallus domesticus</i>) affected (Pereira et al. 1965; Alexander et al. 2008)
2	1961	South Africa	Wild bird	A/tern/South Africa/1961	H5N3	GU052822	PQRETRRQKR/GLF	Western and Eastern Cape provinces (coastline from Port Elizabeth to Lambert's Bay): 1300 common terns (<i>Sterna hirundo</i>) (Rowan 1962; Becker 1966; Alexander et al. 2008)
3	1963	England	Domestic poultry	A/turkey/England/1963	H7N3	AF202238	PETPKRRRR/GLF	Norfolk County: 2 farms; 29,000 breeder turkeys (<i>Meleagris gallopavo</i>) in outdoor and indoor pens (Wells 1963; Alexander et al. 2008)
4	1966	Canada	Domestic poultry	A/turkey/Ontario/7732/1966	H5N9	CY107859	PQRRRRKKR/GLF	Ontario province: 2 indoor farms; 8,100 breeder turkeys (Lang et al. 1968; Swayne 2008b)
5	1976	Australia	Domestic poultry	A/chicken/Victoria/1976	H7N7	CY024786	PEIPKKREKR/GLF	Victoria province: 2 farms; 25,000 indoor laying chickens, 17,000 indoor broilers, and 16,000 indoor and outdoor ducks (<i>Anas platyrhynchos</i>) (Anonymous 1976; Turner 1976; Bashiruddin et al. 1992; Sims and Turner 2008b)
6	1979	Germany	Domestic poultry	A/chicken/Germany/01/1979 A/goose/Leipzig/187_7/1979 A/goose/Leipzig/137/8/1979 A/chicken/Leipzig/79	H7N7	CY107844 L43914 L43913 U20459 L43915	PEIPKKKKKKR/GLF PETPKKKKKR/GLF PEIPKKKKR/GLF PEIPKKKKR/GLF PEIPKKKKR/GLF	Saxony: 2 farms: 600,000 chickens, 80 geese (Röhm et al. 1996; Harder and Werner 2006; Alexander et al. 2008)
7	1979	England	Domestic poultry	A/goose/Leipzig/192/7/1979 A/turkey/England/199/1979	H7N7	N/A	PEIPKKRRR/GLF, PEIP KKRRR/GLF, PEIP KKRRR/GLF	Norfolk county: 3 commercial farms, 9262 turkeys (Alexander et al. 2008)
8	1983–84	USA	Domestic poultry	A/chicken/Pennsylvania/1/1983 (LP) A/chicken/Pennsylvania/1370/ 1983 (HP)	H5N2	J04325 GU052771	PQKKR/GLF (LP) PQKKR/GLF (HP) – lost a glycosylation site on amino acid 13	Pennsylvania, Maryland, and Virginia: 452 flocks, 17 million birds; mostly chickens or turkeys, a few chukar partridges (<i>Alectoris chukar</i>) and guinea fowl (<i>Numida meleagris</i>) (Kawaoka and Webster 1985; USAHA 1985; Eckroade and Silverman-Bachin 1986; Easterday et al. 1997)
9	1983	Ireland	Domestic poultry	A/turkey/Ireland/1378/1983	H5N8	M18451	PQRRKKR/GLF	Monaghan County: 4 farms; 8,120 turkeys, 28,020 chickens, and 270,000 ducks (McNulty et al. 1985; Alexander et al. 2008)
10	1985	Australia	Domestic poultry	A/chicken/Victoria/1/1985	H7N7	M17735	PEIPKKREKR/GLF	Victoria province: 1 farm; 24,000 broiler breeders, 27,000 laying chickens, and 61,000 broilers (Barr et al. 1986; Cross 1987; Senne et al. 1996a; Sims and Turner 2008b)

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Table 1. Continued

No.	Year	Country	Host species	Prototype A1 virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
11	1991	England	Domestic poultry	A/turkey/England/50-92/1991	H5N1	GU052510	PQRKRKTR/GLF	Norfolk County: 1 farm; 8000 turkeys (Alexander et al. 1993; Alexander and Wood 1993; Wood et al. 1993; Senne et al. 1996)
12	1992	Australia	Domestic poultry	A/chicken/Victoria/1/1992	H7N3	AF202227	PEIPKPKKR/GLF	Victoria province: 2 farms, 1 backyard flock and 1 hatchery; 17,000 broiler breeders, 5,700 ducks, 105,000 day-old chicks, 540,000 hatching eggs (Selleck et al. 1997; Westbury 1998; Sims and Turner 2008b)
13	1994–95	Australia	Domestic poultry	A/chicken/Queensland/1994 A/chicken/Queensland/667/1995	H7N3	CY022685 AF202231	PEIPRKRKR/GLF	Queensland province: 1 farm; 22,000 laying chickens (Westbury 1998; Perdue et al. 1999)
14	1994–95	Mexico	Domestic poultry	A/chicken/Mexico/31381-7/1994 (LP) A/chicken/Puebla/8623-607/1994 (HP)	H5N2	GU186573 AB558473	PQRETR/GLF (LP) PQRKRKTR/GLF (HP)	Puebla and Queretaro: Chickens—concurrent circulation of LP (1993–) and HPAI virus (late 1994 to mid-1995) strains. 360 commercial chicken flocks “depopulated” (1995) via vaccination and controlled marketing. Unknown number of HP-infected birds (Garcia et al. 1996; Easterday et al. 1997; Perdue et al. 1997; Villareal and Flores 1998; Smith 2006)
15	1994–95, 2004	Pakistan	Domestic poultry	A/chicken/Queretaro/14588_19/1995 A/chicken/Queretaro/7653_20/1995	H5N2	AB558474 U85390	PQRKRKTR/GLF PQRKRKTR/GLF	Two incursions: (1) 3.2 million broilers and broiler breeder chickens (northern part of country, 1994–1995), and (2) 2.52 million layers (Karachi, 2004). Vaccination and controlled marketing (Naeem and Hussain 1995; Easterday et al. 1997; Naeem 1998; Banks et al. 2000)
16	1996–cont.	84 countries in Asia, Africa, Europe and North America	Domestic poultry and wild bird	A/goose/Guangdong/1/1996 (Gs/GD)	H5Nx	NC_007362	PQRRRRKR/GLF (majority), Variations: 1) Clade 1, PQREGRRKR/GLF; 2) Clade 2.1, PQRESRRKR/GLF; 3) Clade 2.2, QGERRRKR/GLF; 4) Clade 2.3, PQRRRRKR/GLF; 5) Clade 7, PQEGRRKR/GLF	Unknown number of commercial and noncommercial flocks (principally village poultry); more than 400 million birds dead or culled from 2003 to early 2012, mostly chickens, but also ducks, geese, Japanese quail, and some wild birds (Sims et al. 2003a; Sims et al. 2003b; FAO 2006; Sims and Brown 2008a; Sims and Brown 2017). Largest HPAI outbreak since 1959 with more birds and countries affected than the other 41 outbreaks since 1959.

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Table 1. Continued

No.	Year	Country	Host species	Prototype A1 virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
17	1997	Australia	Domestic poultry	A/chicken/NSW/1/1997 A/chicken/New_South_Wales/ 327/1997	H7N4	AY943924 CY022701	PEIPRRKR/GLF PEIPRRRRR/GLF	New South Wales province: 3 farms; 160,000 indoor broiler breeders and 261 outdoor emu (<i>Dromaius novaehollandiae</i>) (Perdue et al. 1999; Sims and Turner 2008b)
18	1997	Italy	Domestic poultry	A/poultry/Italy/330/1997	H5N2	CY017403	PQRRRRKR/GLF	Veneto and Friuli–Venezia–Giulia Regions: 8 flocks (hobby/backyard only); 2116 chickens, 1501 turkeys, 731 guinea fowl, 2322 ducks, 204 quail (species unknown), 45 pigeons (<i>Columbia livia</i>), 45 geese (species unknown), 1 pheasant (species unknown) (Capua et al. 1999; Alexander et al. 2008)
19	1999–2000	Italy	Domestic poultry	A/turkey/Italy/977/1999 (LP) A/turkey/Italy/4580/1999 (HP)	H7N1	GU052999 CY021405	PEIPKGR/GLF (LP) PEIPKGSRRR/GLF (HP, majority), PEIPKGSRRR/GLF (HP, minor), PEIPKRSRRR/GLF (HP, minor)	Veneto and Lombardia Regions: 413 farms, 8.1 million laying chickens; 2.7 million meat and breeder turkeys; 2.4 million broiler breeders and broilers; 247,000 guinea fowl; 260,000 quail, ducks, and pheasants; 1,737 backyard poultry and 387 ostriches (Banks et al. 2001; Capua et al. 2003; Alexander et al. 2008)
20	2002	Chile	Domestic poultry	A/chicken/Chile/176822/2002 (LP) A/chicken/Chile/4322/2002 (HP) A/chicken/Chile/4957/2002 (HP)	H7N3	AY303630 AY303631 AY303632	PEKPKTR/GLF (LP) PEKPKTCSPLSRCRTTR/GLF (HP) PEKPKTCSPLSRCRTTR/GLF (HP)	Valparaíso region: Two farms of one company, multiple houses; 617,800 broiler breeders, 18,500 turkey breeders (2 houses) (Rojas et al. 2002; Suarez et al. 2004; Max et al. 2007; Swayne 2008b)
21	2003	Netherlands Belgium Germany	Domestic poultry	A/chicken/Netherlands/1/03	H7N7	AY338458	PEIPKRRRR/GLF	(1) Netherlands, Gelderse Vallei and Limburg region: 255 infected flocks, and 1381 commercial and 16,521 backyard/smallholder flocks depopulated—30 million affected, mostly chickens. (2) Belgium (Limburg and Antwerp provinces), 8 farms, 2.3 million chickens. (3) Germany (Nordrhein–Westfalen State), 1 farm, 419,000 chickens (Elbers et al. 2004; Harder and Werner 2006; Alexander et al. 2008)

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Table 1. *Continued*

No.	Year	Country	Host species	Prototype A1 virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
22	2004	Canada	Domestic poultry	A/chicken/Canada/AVFV1/2004 (LP) A/chicken/Canada/AVFV2/ 2004 (HP)	H7N3	AY650270 AY648287	LP: PENPKQAYRKRMTR/GLF HP: PENPKQAYRKRMTR/GLF PENPKQAYQKRMTR/GLF, PENPKQAYKRMTR/GLF, PENPKQAYHKKRMTR/GLF, PENPKQAHQKRMTR/GLF, PENPKQAYRKRMTR/GLF, PENPKQACQKRMTR/GLF PQRKKR/GLF	British Columbia province: 42 commercial and 11 backyard flocks infected (1.2 million poultry)— approximately 16 million commercial poultry depopulated, most were chickens (Hirst et al. 2004; Pasick et al. 2005)
23	2004	USA	Domestic poultry	A/chicken/Texas/298313/2004	H5N2	AY849793	PQRRKR/GLF	Texas state: 1 noncommercial farm (6608 chickens), 2 LPM affected; 3 dangerous LPM contacts culled (Lee et al. 2005)
24	2004	South Africa	Domestic poultry	A/ostrich/South Africa/N227/ 2004	H5N2	FJ519983	PQREKRKR/GLF	East Cape province: 2004–2008 farms, culled. 23,625 ostriches, 3,550 other poultry (chickens, turkeys, geese, ducks, and pigeons), 1594 ostrich eggs and 1707 other farmed bird eggs (Abolnik 2007; Alexander et al. 2008; Abolnik et al. 2009)
25	2006	South Africa	Domestic poultry	A/ostrich/South_Africa/A11160/ 2006 (LP) A/ostrich/South Africa/ A11091/2006 (HP)	H5N2	EF591757 EF591749	PQRRKR/GLF	Western Cape province: 24 farms, 7334 ostriches culled (Abolnik 2007; Alexander et al. 2008; Brown et al. 2017)
26	2005	North Korea	Domestic poultry	A/chicken/North Korea/1/2005	H7N7	N/A	PEIPKGRHRRPKR/GLF	3 farms, 218,882 layer chickens culled; number dead unknown (Alexander et al. 2008)
27	2007	Canada	Domestic poultry	A/chicken/Saskatchewan/HR- 00011/2007	H7N3	EU500860	PENPKTTKPRPR/GLF	Saskatchewan province: 1 farm, 10 barns, 49,500 broiler breeder hens and roosters (Swayne 2008; Berhane et al. 2009)
28	2008	England	Domestic poultry	A/chicken/England/1158-114061/ 2008	H7N7	FJ476173	PEIPKRRK/GLF	Oxfordshire county: 1 farm, 25,000 free-range layer chickens (Brown et al. 2017)
29	2009	Spain	Domestic poultry	A/chicken/Spain/6279-2/2009	H7N7	GU121458	PELPKGTTPRPR/GLF	Guadalajara province: 1 farm, 5 barns; 308,640 layer chickens (Iglesias et al. 2010; Brown et al. 2017)
30	2011–2013	South Africa	Domestic poultry	A/ostrich/SA/A12114/2011 A/ostrich/SA/A12512/2011	H5N2	JX069081 JX069097	PQRRKR/GLF PQRRKR/GLF	Western Cape province: 45,343 ostriches on 50 premises (Brown et al. 2017)
31	2012–2013	Taiwan	Domestic poultry	A/chicken/Taiwan/A1997/2012 A/chicken/Taiwan/1680/2013	H5N2	KF193394 KJ162620	PQRRKR/GLF PQRRKR/GLF	Chang-Hua, Pingtung, Yunlin, and Penghu counties: 6 premises (4 native chickens, 1 broiler breeder, 1 layer chicken); 47,151 chickens (Lee et al. 2014; Brown et al. 2017)

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Table 1. Continued

No.	Year	Country	Host species	Prototype AI virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
32	2012-present	Mexico	Domestic poultry	A/chicken/Jalisco/12283/2012	H7N3	JX908509	PENPKDRKSRHRRTR/GLF	Jalisco, Aguascalientes, Guanajuato, Tlaxcala, and Puebla states: 110 premises, 18,906,702 poultry. Two waves of disease: (1) 6/13/2012–9/29/2012, and (2) 1/3/2013–ongoing (Maurer-Stroh et al. 2013; Brown et al. 2017)
33	2012	Australia	Domestic poultry	A/chicken/New South Wales/12-3121-1/2012	H7N7	N/A	PEIPKRRKRR/GLF	New South Wales province: 1 premise, free-range layers, 50,000 chickens (Brown et al. 2017)
34	2013	Italy	Domestic poultry	A/chicken/Italy/13VIR4527-11/2013	H7N7	KF569186	PETPKRRRR/GLF	Emilia-Romagna Region: 6 premises, layers, 952,658 chickens (Brown et al. 2017)
35	2013	Australia	Domestic poultry	A/chicken/New South Wales/13-02811-1/2013	H7N2	N/A	PEIPKRRKRR/GLF	New South Wales province: 2 premises, free-range and caged layers, 490,000 chickens (Brown et al. 2017)
36	2015	England	Domestic poultry	A/chicken/England/26352/2015 (H7N7)	H7N7	EPI623939	PEIPRHRKGR/GLF	Lancashire county: 1 premise, colony and free-range laying chickens, 179,865 affected (Brown et al. 2017)
37	2015	Germany	Domestic poultry	A/chicken/Germany/AR1385/2015 (H7N7)	H7N7	EPI634885	PEIPKRRRR/GLF	Lower Saxony state: 1 premise, laying chickens, 10,104 affected (Brown et al. 2017)
38	2015–2016	France	Domestic poultry	A/chicken/France/150169a/2015 A/duck/France/150233/2015 A/duck/France/150236/2015	H5N1 H5N2 H5N9	KU310447 KX014878 KX014886	HQRRKR/GLF	8 southwest/southeast Departments: 81 premises, 155,415 poultry affected; primarily affected fattening ducks, and some guinea fowl, geese, and layer and meat chickens in small farms and backyard operations. H5N1 virus reassorted with Eurasian LPAI viruses to produce H5N2 and H5N9 HPAI viruses (OIE 2016b; Briand et al. 2017)
39	2016	USA	Domestic poultry	A/turkey/Indiana/16-001403-1/2016	H7N8	KU558906	PENPKRRKTR/GLF	Indiana state, Dubois county: 1 premise, 43,500 meat turkeys. 1 dangerous contact layer farm (156,158 layers), and 9 LP-affected turkey farms (195,937 birds) in control zone depopulated (ISBOAH 2016; Lee et al. 2017b; Swayne et al. 2017)
40	2016	Italy	Domestic poultry	A/chicken/Italy/16VIR-1873/2016	H7N7	EPI756028*	PELPKGRKRR/GLF	Emilia-Romagna region: 1 premise, 17,500 organic/free range layers (OIE 2016a; OIE 2016b)

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Table 1. *Continued*

No.	Year	Country	Host species	Prototype AI virus	Subtype	Accession No. (NCBI GenBank or GISAID Epiflu database)	HA cleavage site	Number affected with high mortality or depopulated ^a
41	2016–2019	China	Domestic poultry	A/chicken/Huizhou/HZ-3/2016 A/chicken/Huizhou/HZ04/ 2016 A/chicken/Heyuan/16876/ 2016	H7N9	EP1917102 EP1918826 EP1919533	PEVPRKRRTAR/GLF; PEVPRKGKRTAR/GLF	Initially Guangdong province: Since 10 January 2017, HP H7N9 virus was reported in a total of 58 poultry or environmental samples (46 chickens, 2 duck, and 10 environmental samples); H7N9 virus isolates from 32 human cases were found to be HP virus (as of 07 August 2019). HP derived from LP virus circulating in live poultry market system since early 2013 (OIE 2017a; Qi et al. 2018) Tennessee, Lincoln county: 2 premise, 128,000 chicken broiler breeders with HPAI virus. LPAI precursor virus on 12 premises (6 backyard and 6 commercial, 125,000 birds) in Tennessee, Alabama, Kentucky and Georgia (Lee et al. 2017a; OIE 2017b; USDA 2017)
42	2017	USA	Domestic poultry	A/chicken/Tennessee/17-007147- 1/2017	H7N9	MF357740	PENPKTDKRSRRHRIR/GLF	

Data modified from Alexander (2000), Swayne and Suarez (2000), Swayne (2017), OFFLU (2019), and Swayne et al. (2020).

(AI) Avian influenza, (GISAID) Global Initiative on Sharing All Influenza Data, (HA) hemagglutinin, (HP) high pathogenicity, (LP) low pathogenicity, (LPM) live poultry market, (N/A) not available, (NCBI) National Center for Biotechnology Information.

^aMost outbreaks were controlled by “stamping-out” or depopulation policies for infected and/or exposed populations of poultry. Chickens, turkeys, and poultry in the order Galliformes had clinical signs and mortality patterns consistent with HPAI, whereas ducks, geese, and other aquatic poultry lacked or had low mortality rates or infrequent presence of clinical signs.

cleavage site changes associated with high virulence. In addition, changes in other AIV gene segments can affect the phenotype, usually through increased replication efficiency and virus particle release.

The mechanisms by which H5/H7 LPAI viruses change into HPAI virus include mutation, insertion, and recombination in the proteolytic cleavage site of the HA. The HA is the AI virus surface glycoprotein responsible to attach the virus to the host cell receptor to initiate the infection life cycle. After the virus enters the cell the new viruses start to be produced, including the inactive precursor HA protein (HA0). The HA0 is cleaved at the proteolytic cleavage site by cellular proteases of the host to form the functional subunits HA1 and HA2, resulting in an infectious virus. The cleavage site region in the HA0 consists of an arginine (R) residue adjacent to a conserved glycine (G) (Garten and Klenk 1983; Swayne et al. 2020). The number of basic amino acids at the HA cleavage site plays a critical role in virulence by determining which proteases cleave the HA0 and consequently in which cell types and tissues in the host the AI viruses can replicate (Bosch et al. 1981; Kawaoka et al. 1987; Horimoto and Kawaoka 1994; Swayne et al. 2020). First, the AI virus HA cleavage site can be classified as a monobasic (e.g., PEKQTR/GLF) or multibasic (e.g., PQRKKR/GLF). The monobasic cleavage site usually contains one or two nonconsecutive basic amino acids, arginine (R) or lysine (K), in the critical position and is cleaved by trypsin or trypsin-like proteases that confines virus replication in the epithelial cells of the respiratory and gastrointestinal tracts (Suarez 2016; Swayne et al. 2020). The H5/H7 LPAI viruses maintain the general principle of monobasic cleavage site, although in the wild birds, these subtypes have varying patterns of amino acids at the cleavage site (Suarez 2016). The H5 LPAI viruses usually encode the QRETR/G sequence, whereas H7 LPAI viruses typically possess the NPKTR/G sequence at the cleavage site. An increased number of basic amino acids and/or a lengthening of the proteolytic cleavage site to a minimum motif of four basic amino acids change the virus to high virulence by allowing the HA0 to be cleaved

by several ubiquitous cellular proteases (furin-like proteases), which permit the virus to replicate in cells of multiple tissues, increasing the potential to cause a systemic disease and lethal infection in gallinaceous host (OIE 2019b; Swayne et al. 2020). More specifically, the changes observed in the HA cleavage site of HPAI viruses occurred because of (a) substitutions of nonbasic with basic amino acids and in some situations accompanied by loss of a shielding glycosylation site, (b) insertions of multiple basic amino acids from codons duplicated, (c) short inserts of basic and nonbasic amino acids from unknown source, or (d) nonhomologous recombination with cellular (e.g., host 28S RNA) or viral RNAs (e.g., RNA coding NP or M protein) that lengthen the proteolytic cleavage site. The changes (a), (b), and (c) have been observed in the H5/H7 HPAI viruses, whereas (d) has only been observed in H7 HPAI viruses (Suarez et al. 2004; Pasick et al. 2005; Maurer-Stroh et al. 2013; Swayne et al. 2020).

As illustrated in Table 1, the length of the multibasic cleavage site varies between different HPAI viruses within or between different outbreaks. Analysis of naturally occurring H5 HPAI viruses shows a preference of the cleavage site to harbor two additional basic amino acids residues for a total of four basic amino acids (Table 1), but additional basic amino acids do not increase the pathogenicity in chickens (Alexander et al. 1986; Suarez 2016). Experiments by reverse genetics confirmed that five or more basic amino acids in the cleavage site are preferentially selected with high viral fitness in chicken over those with fewer insertions (Luczo et al. 2018). Some studies suggest that the potential role of the polymerase slippage facilitates the incorporation of additional basic residues into the HA cleavage site (Perdue et al. 1997; Abolnik 2017; Nao et al. 2017). Other studies indicate that increased spacing in the cleavage site loop appears to play an important role in the virulence instead of just adding basic amino acids (Suarez 2016). Furthermore, in silico analysis suggests that potential RNA secondary structures in the cleavage site regions of HA segments, having conserved stem-loop structures with cleavage site codons in the hairpin

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loops, may facilitate evolution toward an multi-basic cleavage site, although future experimental studies should be done to clarify the structure–function relationships in these domains for H5 and H7 subtypes compared to other subtypes that have not had LPAI to HPAI phenotype changes (Gultyaev et al. 2019). Interestingly, reverse genetic approaches show that the virus loses the ability to cause severe disease when the multibasic antigenic site motif or specific basic residues of HPAI viruses are removed (Kawaoka and Webster 1988; Walker and Kawaoka 1993; Horimoto and Kawaoka 1994, 1997; Walker et al. 1994; Lu et al. 2006; Bogs et al. 2010; Gohrbandt et al. 2011). In general, the mechanisms for amino acid insertions in the cleavage site appear to be different in many cases, and for this reason the genetic basis to predict which LPAI viruses will result in the emergence of a HPAI virus remains unclear.

Other important mechanisms that alter the AI virus phenotype include the presence or absence of N-linked glycans and changes in histidine 184 residue or the adjacent E216(R/K) in HA. The glycosylation sites, especially in the HA stalk, can influence the protease accessibility to the cleavage site. Apart from the important glycosylation site at the position 10–12 (Asn-Asn-Ser) in the HA of the H5N2 HPAIV outbreak in Pennsylvania in 1983 (Kawaoka et al. 1984), other potential glycosylation sites have been demonstrated to affect the AI viruses' pathogenicity (Kawaoka and Webster 1989; Hulse et al. 2004; Zhang et al. 2015). The glycosylation sites in the HA are also shown to contribute to the virus replication and chicken-to-chicken transmission, which consequently affect the AI virus virulence (Abdelwhab et al. 2016; Swayne et al. 2020). The presence of critical key histidine residues in the HA can affect the conformational changes postcleavage. Reports show that mutations at or close to histidine 184 at the HA1–HA1 interface modulate the pH dependence and consequently the HA conformation (Mair et al. 2014). Alignments of the HA sequences from H5N1 HPAI viruses show that a Glu-to-Arg mutation at position 216 close to His184 can possibly contribute to AI virus adaptation to hosts (Mair et al. 2014). Other studies

demonstrated that mutations altering the pH of fusion modulate H5N1 virus pathogenicity in avian and mammalian host (Reed et al. 2010; DuBois et al. 2011; Zaraket et al. 2013a,b; Russell 2014).

Although the HA is the major determinant of virulence in AI viruses, the modulation of pathogenesis from LPAI to HPAI virus in domestic chickens may involve multiples genes. Comparison of the genetic changes between LPAI virus precursors and HPAI viruses in outbreaks between 1966 and 2016 show that, even though mutations were observed in other genes, changes mainly occur in the HA and polymerase (e.g., PA) gene (Richard et al. 2017). The number of changes varies from 7 to 68 substitutions without any association as a prerequisite of HPAI virus emergence (Richard et al. 2017). It is still unknown if the changes naturally observed in the evolution from LPAI to HPAI viruses in the field are only a selection of viruses adapted to replicate in several tissues. Most of the time, specific selection procedures (i.e., virus isolation without exogenous trypsin, etc.) are necessary to recover HPAI virus, which likely represent minority variants present in the field. Moreover, experimental studies show that mutation in the carboxy terminal at the nonstructural 1 (NS1) protein and neuraminidase (NA) stalk deletion during the change from LPAI to HPAI virus may contribute to virulence, increasing virus shedding and poultry adaptation (Senne et al. 1996; Keiner et al. 2010; Munier et al. 2010).

Therefore, besides all the available data, further studies are still necessary to better understand the modulation of virulence from LPAI to HPAI virus.

UNIQUE GENETIC LINEAGES ASSOCIATED WITH AVIAN HPAI OUTBREAKS

Table 1 lists the summaries and references of HPAI outbreaks between 1959 and 2017 based on epidemiological data, peer-reviewed publication, and published OIE reports. As of August 2019, a total of 42 independent H5 and H7 LPAI to HPAI conversion events have been documented since the discovery of AI viruses as the

cause of fowl plague in 1955 (i.e., HPAI [Swayne 2017; Dhingra et al. 2018; Swayne et al. 2020]). More specifically, for these 42 conversion events, 27 were H7 subtype (11 in Europe, seven in Oceania, five in North America, three in Asia, and one in South America) and 15 were H5 subtype (five in Europe, four in Africa, four in North America, and two in Asia) (Fig. 1). The highest number of conversions were documented in Europe ($n = 16$), followed by North

Figure 1. Geographic origin of H5 and H7 high-pathogenicity avian influenza viruses by country from 1959 to 2019. (A) Map based on average of longitude and average of latitude. Color shows details about subtype. Size shows sum of number of records. The marks are labeled by sum of number of records. Details are shown for each country. (B) Year for each country broken down by continent. Color shows details about subtype. Size shows number of records.

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America ($n=9$), Oceania ($n=7$), Asia ($n=5$), Africa ($n=4$), and South America ($n=1$). Among these 42 conversions, 40 outbreaks involved domestic poultry (principally chickens and turkeys), the South Africa outbreak (1961) involved exclusively wild birds, and the outbreak of Gs/GD lineage of H5 (1996–present) involved both domestic poultry and wild birds.

Genome sequencing data has been used to determine the pathogenicity based on the genetic sequences of the HA cleavage site and to trace the origin of viruses using a molecular epidemiological approach. Particularly, phylogenetic analysis and the use of direct sequence comparisons between isolates have provided important clues about the ancestry of outbreak strains. We were able to obtain all HA gene sequences of LPAI to HPAI conversions events, except three H7 outbreaks: 1979 H7N7 outbreak in England, and 2012 and 2013 H7N7 outbreaks in Australia. All available recorded conversions of the H5 and H7 HPAI viruses since 1959 were phylogenetically analyzed. All H7 and non-Gs/GD H5 nucleotide sequences from avian species were downloaded from the Influenza Research Database (www.fludb.org). We then removed identical nucleotide sequences with $\geq 98\%$ (H7) and 98.5% (non Gs/Gs H5) identity using the Cluster Database at High Identity with Tolerance (CD-HIT) (Li and Godzik 2006), resulting in representative strains that form the final set of nonredundant sequences. Representative Gs/GD H5 nucleotide sequences were added in the H5 data set. Sequences (H5: $n=298$, H7: $n=250$) were aligned using multiple alignment with fast Fourier transformation (MAFFT) in the Geneious v8.1.2 program and trimmed to remove nucleotides that were outside the coding region. The Bayesian relaxed clock phylogenetic analysis of the HA gene was conducted using BEAST v1.10.4. with an uncorrelated lognormal distribution relaxed clock method, the HKY nucleotide substitution model and the Gaussian Markov random field (GMRF) Bayesian skyride coalescent prior (Minin et al. 2008). All 39 documented HPAI outbreaks were phylogenetically different from each other (Fig. 2A,B). Each branch of documented HPAI virus reflects the

independent conversion from a LPAI ancestor to HPAI virus.

In Europe, the emergence of HPAI viruses was recorded on 16 occasions in England ($n=5$; H5 in 1991, H7 in 1963, 1979, 2008, 2015), Italy ($n=4$; H5 in 1997, H7 in 1999, 2013, 2016), Germany ($n=2$; H7 in 1979, 2015), Scotland ($n=1$; H5 in 1959), Ireland ($n=1$; H5 in 1983), Netherlands ($n=1$; H7 in 2003), Spain ($n=1$; H7 in 2009), and France ($n=1$; H5 in 2015) between 1959 and 2015. It has been suggested that the two outbreaks in 1979, in Germany and England, may have represented a single emergence of H7N7 HPAI virus that was spread by wild birds (Alexander and Brown 2009). It was not possible to genetically compare the two outbreaks in Germany and England during 1979 because the genetic sequence of 1979 H7N7 viruses in England was not available in public databases. The phylogenetic tree in a previous study suggested that they have emerged from a same close LPAI common ancestor (Banks and Plowright 2003). However, the HA cleavage sites of the Germany and England viruses have a slightly different multibasic cleavage site as shown in Table 1. These findings suggest that these viruses were converted from LPAI to HPAI viruses independently from the same close common ancestor circulating in Western Europe during 1979.

In North America, the emergence of HPAI viruses was recorded on nine occasions during 1966–2017, including the United States ($n=4$; H5 in 1983, 2004; H7 in 2016, 2017), Canada ($n=3$; H5 in 1966; H7 in 2004, 2007), and Mexico ($n=2$; H5 in 1994, H7 in 2012). On the other hand, there was only one occasion in South America (Chile, H7 in 2002). All of these HPAI outbreaks were eradicated from poultry, except the Mexican HPAI H7N3 outbreak. The Mexican HPAI H7N3 has continued to cause outbreaks in commercial chickens in Mexico since the first case in 2012 (OIE 2019a).

In Oceania, only Australia has had seven emergences of HPAI in poultry during 1976–2013, all of them the H7 subtype (H7N7 in 1976 and 1985, H7N3 in 1992 and 1994, H7N4 in 1997, H7N7 in 2012, and H7N2 in 2013). In addition, the devastating Gs/GD

A H5

Figure 2. Bayesian relaxed clock phylogenetic analysis of the H5 (A) and H7 (B) HA genes for 39 high-pathogenicity avian influenza viruses that emerged since 1959.

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B H7

Fig. 2. Continued.

H5Nx HPAI viruses have not been detected in Oceania. All H7 HPAI strains identified in Australia belong to the Australian lineage (Fig. 2). The two recent outbreaks in Australia were not included in the phylogenetic analysis because the HA gene sequences of the 2012 H7N7 and 2013 H7N2 strains were not available in public databases. It has been documented that H7 LPAI viruses similar to that found in the H7N7 outbreak in 2012 and the H7N2 outbreak in 2013 were unrelated samples from Australian wild waterfowl that have been circulating in Australia for many years (Wong and Daniels 2013).

In Asia, a total of five conversions have been recorded, including China ($n = 2$; Gs/GD H5N1 in 1996 and H7N9 in 2016), Pakistan ($n = 1$; H7N3 in 1994), North Korea ($n = 1$; H7N7 in 2005), and Taiwan ($n = 1$; H5N2 in 2012). Phylogenetic analysis shows that all HPAI strains that were identified in Asia emerged from Eurasian LPAI viruses, except the H5N2 HPAI identified in Taiwan during 2012, which clustered with Mexican H5N2 viruses (Fig. 2). The high similarity of the Taiwanese H5N2 viruses to the Mexican H5N2 vaccine strain suggests that the Mexican H5N2 viruses might have been introduced to Taiwan by using inadequately inactivated or attenuated Mexican H5N2 vaccines (Lee et al. 2014).

Unlike most previous HPAI virus epizootics that have been geographically limited, involving sporadic interfarm transmissions, and were eradicated from poultry by stamping-out programs, the Gs/GD lineage has caused deaths in wild birds, poultry, and mammals including humans and has spread to 84 countries in Asia, Europe, Africa, and North America as of August 2019. The first Gs/GD lineage H5N1 HPAI virus was identified in a domestic goose in southern Guangdong province of China in 1996 and this lineage has evolved into 10 genetically distinct virus clades (0–9) and multiple subclades (WHO/OIE/FAO_H5N1_Evolution_Working_Group 2008, 2014). There have been four waves of intercontinental transmission of Gs/GD lineage H5Nx virus (Figs. 3A–C; Sims et al. 2017). Briefly, the first intercontinental wave in 2005–2006 caused by a clade 2.2 H5N1 HPAI virus

involved China, Mongolia, Russia, Central Asia, Europe (widespread: over 20 European countries), Middle East, West Africa, Japan, and Republic of Korea (Fig. 3A). The second intercontinental wave in 2009–2010 caused by a clade 2.3.2.1c H5N1 HPAI virus involved mostly East Asia (China, Mongolia, Japan, and Republic of Korea), but was also found in Eastern Europe (Russia, Romania, and Bulgaria) and Nepal (Fig. 3B). The third intercontinental wave in 2014–2015 involved two separate viral lineages, clade 2.3.4.4a H5Nx (wave 3a) (Fig. 3C) and clade 2.3.2.1c H5N1 that differed from the 2009–2010 isolate (wave 3b) (Fig. 3B). The wave 3a was caused by a clade 2.3.4.4a H5N8 HPAI virus originated from East Asia that had spread rapidly and globally through wild birds and evolved through reassortment with prevailing local LPAI viruses to produce multiple H5Nx viruses. The wave 3b caused by a clade 2.3.2.1c H5N1 involved Russia, China, Middle East, West Africa, Cameroon, Romania, Bulgaria, and Central Asia. The fourth intercontinental wave in 2016–2017 caused by a clade 2.3.4.4b H5Nx involved Asia (East, Central, and South), Middle East, Europe (widespread), and Africa (West Central, East, and Southern) (Fig. 3C). The Gs/GD lineage has not been eradicated and still poses a serious threat to the poultry industry and public health as well. Additionally, LPAI H7N9 viruses have been a threat to public health since their emergence in 2013 in China (see Chen 2019). It has mutated into HPAI and caused human infections and outbreaks among poultry since 2016 (Yang et al. 2017).

In Africa, only South Africa has had four emergences of HPAI during 1961–2013, which were caused by viruses of the H5 subtype (H5N3 in 1961 and H5N2 in 2004, 2006, and 2011). The phylogenetic tree suggests that the H5N2 identified in 2004 and 2006 have emerged from the same close LPAI common ancestor. In a previous study, molecular and phylogenetic characterization was performed to determine whether the 2006 outbreak strain was supposedly derived from the eradicated 2004 H5N2 strain (Abolnik 2007). It was demonstrated that although the 2004 and 2006 H5N2 strains shared a common ancestor, the two outbreaks

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Figure 3. Four waves of intercontinental transmission of Gs/GD lineage H5Nx virus: (A) Clade 2.2, 2005-2006, wave 1. (B) Clade 2.3.2.1c, 2009-2010, wave 2; Clade 2.3.2.1c, 2014-2015, wave 3b. (C) Clade 2.3.4.4a, 2014-2015, wave 3a; Clade 2.3.4.4b, 2016-2017, wave 4. (Maps modified, with permission, from https://d-maps.com/carte.php?num_car=3503&lang=en.)

Fig. 3. Continued.

were not related. Not only were extensive reassortments with wild bird viruses involved in the evolution of the 2006 strains, but also the HA cleavage site sequence of the 2006 H5N2 virus contained fewer monobasic amino acid insertions (Abolnik 2007).

CONCLUDING REMARKS

Historically, the first AI virus in birds was identified in the 1880s as an HPAI virus (i.e., fowl plague virus). Forty-two documented epidemics or limited outbreaks of HPAI have occurred since the discovery of AI viruses as the cause of fowl plague in 1955. Since 1959 with well-maintained virus archives, most HPAI virus have arisen from changes in LPAI viruses with limited spread of outbreaks and eradication from poultry. However, the Gs/GD H5Nx, Mexican H7N3, and Chinese H7N9 HPAI viruses are concerning because these strains have not been eradicated and still cause poultry outbreaks. In particular, the Gs/GD H5Nx and Chinese H7N9 viruses pose a significant pandemic threat to human health. The Gs/GD lineage of H5 has a broad One Health impact as it con-

tinues to cause infections, disease, and death in poultry, wild birds, and humans. Furthermore, the Gs/GD lineage outbreak has affected more poultry and countries than the other 41 HPAI outbreaks combined.

Although chicken HPAI viruses are derived from LPAI viruses of aquatic wild birds, the emergence of HPAI virus does not always happen. The mechanisms by which H5/H7 HPAI virus has emerged is via mutation, insertion, or recombination within the HA—more specifically changes in the proteolytic cleavage site. The number of basic amino acids in the HA cleavage site plays a critical role in virulence determining which proteases can cleave HA and in which tissues the AI viruses can replicate. In general, the mechanisms for amino acid insertions in the cleavage site appear to be different in many cases, and for this reason the genetic basis to predict which LPAI viruses will result in the emergence of a HPAI virus remains unclear. The presence or absence of the N-linked glycans and key histidine residues in the HA are reported to influence the AI virus phenotype. In addition, changes in other AIV gene segments can increase or decrease the max-

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imal phenotypic expression of the HA usually through increasing replication efficiency and release. In general, molecular techniques such as next-generation sequencing and reverse genetics have helped to identify changes associated with high virulence. However, significant emphasis on basic research is needed to understand why changes occur only in certain LPAI precursors that increase their pathogenicity, which, once understood, could enhance our ability to predict and subsequently prevent conversion events and potentially lead to a reduced number of HPAI outbreaks. With the ultimate goal of eradication, enhanced active surveillance, education, biosecurity, rapid molecular, and characterization efforts will provide the best opportunity for early detection and elimination of HPAI in domestic poultry.

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