



Collaborators

- A collaborative project between the U.S. Centers for Disease Control and Prevention (CDC), National Association of State Public Health Veterinarians (NASPHV), and the Council of State and Territorial Epidemiologists (CSTE).
- Roles of contributors and representative organizations included:
 - CDC Influenza Division Veterinarian and SME
 - State Public Health Veterinarians
 - State Veterinarians
 - CDC One Health
 - USDA APHIS Veterinarians
 - State Epidemiologists

Intended Use

This reference guide was created to provide state and local animal and public health officials with an accessible, easy-to-use resource for understanding and managing novel and emerging situations involving animal and zoonotic influenza viruses. The content was obtained through an extensive textbook, journal article, and web source review along with subject matter interviews from veterinarians, epidemiologists, and other animal health and public health professionals.

The guide was organized by both animal species and by influenza virus subtypes to facilitate search by either, depending on the situation. General information on all known influenza virus strains was included as background for potential situations, whether zoonotic transmission resulting in human illness or suspected infection or where a zoonotic event simply occurred. Where possible direct links to resources were provided.



Major Sections: Background

- Influenza virology
 - Strains
 - · Genetic sequencing
- · Influenza in humans
 - · Burden of disease, prevention, treatment
 - Dominant influenza subtypes
 - Human pandemics
- Zoonotic influenza nomenclature
- · Emerging threats to human health
- Influenza Risk Assessment Tool

Influenza in Humans

Influenza in Humans

Burden of Disease, Clinical Symptoms, Transmission, and Risk Factors

Human influenza is a major respiratory disease-causing illness in 1 billion people globally every year with approximately 290,000-650,000 deaths^{33,34}. In the U.S., the Centers for Disease Control and Prevention (CDC) estimates between 9-41 million illnesses, 140,000-710,000 hospitalizations, and 12,000-52,000 deaths annually ^{35,36}. An average of 8% of the U.S. population experiences influenza illness every year, ranging from 3-11% ³⁷. Influenza A and B strains circulate seasonally, with A typically causing more severe illness. In temperate countries, the virus circulates in winter months, while tropical and subtropical countries experience year-round infections, though at a lower rate than temperate countries. Influenza follows a hemispheric and seasonal pattern where fall and winter seasons during the months of June-August in the southern hemisphere align with increased influenza activity in this region, while in the northern hemisphere, December-March are the dominant months for influenza activity ²³⁸

1957 - H2N2 (Asian Flu)

First identified in East Asia in 1957, this H2N2 strain was comprised of three different avian influenza genes including those for hemagglutinin and neuraminidase ⁵⁰. This strain demonstrated similar patterning to the H1N1 Spanish Flu with a late October wave and second peak in February. Total excess mortality, while substantial in exceeding one million, was one tenth of the Spanish Flu pandemic ⁴⁷. This virus continue to circulate for 10 years after the pandemic, producing one major epidemics before the next pandemic in 1968 ⁴⁷. With the arrival of this strain, H1N1 disappeared from human infections until 1977 ⁵⁷.

1968 - H3N2 (Hong Kong Flu)

H3N2 arose from the genetic reassortment of low pathogenicity avian influenza viruses (LPAI) and human influenza A viruses. One of the two avian-origin genes contained in this virus was a new H3 hemagglutinin; the N2 was from the 1957 Asian Flu virus ^{48,53}. The virus circulated in the U.S. as early as September 1968, but did not surge until December. This pandemic affected persons over 65 most severely and caused approximately one million total deaths ^{47,48}. This is one of the two human seasonal influenza A viruses still circulating today.

1976 – Ft. Dix (the pandemic that was not) – notable outbreak

A novel H1N1 virus was detected in 230 military recruits resulting in one death. In anticipation of the potential for a widespread epidemic, 40 million people were vaccinated resulting in 532 cases of Guillain-Barre syndrome and 32 deaths ⁵⁴. The transmissibility of this virus was substantially lower than previous pandemics, and due to the "tight social-contact structure of the military training base", transmission was not sufficient to reach epidemic proportions ^{57,58}.

1977 – H1N1 (Russian Flu) – notable epidemic

Russian Flu, a reemergent H1N1 strain, caused severe human infections in those under 26 years of age and a 50% fatality rate among children ^{53,55,59}. Case rates were estimated at <5 per 100,00, which was far less than any preceding pandemic or interpandemic event ⁴⁷. In 1977, those under age 26 had not been exposed to an H1N1 strain as its last wide circulation was

Influenza Risk Assessment Tool

Identification of situations of interest - International situations - Tool for Pandemic Risk Assessment and Influenza Risk Assessment Tool (CDC)

Domestic situations

The CDC Influenza Risk Assessment Tool (IRAT) is used to evaluate the risk posed by animal influenza viruses with the potential to spread to humans. The tool assesses pandemic potential based on "emergence" and "public health impact" factors. The IRAT is managed by CDC, but most of the viruses assessed have been animal influenza viruses detected internationally and assessed by subject matter experts in other countries ⁷⁰. The IRAT criteria were reviewed and updated in 2018 ⁸⁵.

According to CDC,

"Emergence" refers to the risk of a novel (i.e., new in humans) influenza virus acquiring the ability to spread easily and efficiently in people. "Public health impact" refers to the potential severity of human disease caused by the virus (e.g., deaths and hospitalizations) as well as the burden on society (e.g., missed workdays, the strain on hospital capacity and resources, and interruption of basic public services) if a novel influenza virus were to begin spreading efficiently and sustainably among people.

Influenza Risk Assessment Tool (IRAT)

To provide a frame of reference for the potential threat of various zoonotic influenza strains, findings for the Influenza Risk Assessment Tool are provided. The IRAT is used to evaluate the risk posed by animal influenza viruses potentially capable of spreading to humans. The risk of "emergence" and "public health impact" factors are assessed by federal, state, and local agencies involved in influenza incident investigations, and are coordinated by CDC. The "Summary Score" provides the category of cumulative pandemic potential with higher scores in "Potential Emergence" and "Potential Impact" indicating higher risk 85.242, <u>Additional information on IRAT</u> in a later section of this document.

Four H7N9 strains, both Asian and North American lineages, were evaluated using the CDC IRAT $^{\rm 85}.$ Their findings are displayed in Table 1.

Table 1. H7N9 avian influenza virus strains and their threat to human health as evaluated by the CDC IRAT®

Influenza Strain	Date	Potential Emergence	Potential Impact	Summary Score
H7N9 [A/chicken/Tennessee/17-007431-3/2017]	2017	3.1	3.5	Low
H7N9 [A/ chicken/Tennessee /17-007147-2/2017]	2017	2.8	3.5	Low
H7N9 [A/Hong Kong/125/2017]	2017	6.5	7.5	Moderate-High
H7N9 [A/Shanghai/02/2013]	2016	6.4	7.2	Moderate-High

Major Sections: Species and Strain Overview

- Influenza in Avian
 - Species differentiation
 - Highly pathogenic (HPAI) and low pathogenicity (LPAI)
 - · Lineage distinctions
 - LPAI subtype summaries
 - HPAI subtype summaries

- Influenza in Swine
- Influenza in Equine
- Influenza Canine & Feline
- Influenza in Bats
- Influenza in Other Animals

Influenza in Avian

Highly Pathogenic and Low Pathogenic Avian Influenza

Avian influenza viruses are categorized into two groups: low pathogenic influenza A (LPAI) viruses and highly pathogenic influenza A (HPAI) viruses. The differentiation of highly pathogenic and low pathogenicity is related to the virus's ability to cause illness and death in domestic poultry and does not refer to the severity of illness in humans. Both HPAI and LPAI have caused serious illnesses in humans ² (CDC, 2020c).

Wild waterfowl are known to be the reservoir for all avian influenza viruses, HPAI is thought to evolve in domestic poultry after transmission of LPAI from wild birds to poultry ^{99,109-105}. After domestic birds are infected, a change in the HA gene can occur allowing the virus to mature in the respiratory tract and cause systemic infection ^{92,99,105}. The virus can also infect the gastrointestinal tract of birds with minimal issues ⁷⁰. Once developed in poultry, HPAI can be transmitted back to wild birds. At present, HPAI is limited to H5 and H7 subtypes ^{31,99}. Most avian influenza viruses cause a gastrointestinal infection in birds with minimal clinical signs and are classified as low pathogenic.

H5N6

HPAI H5N6 has circulated in China since 2013 mainly in chickens and ducks. Outbreaks in 2014-2015 resulted in three human cases and two deaths with all cases reporting direct contact with infected poultry in live bird markets ^{177,178}. One study confirmed the presence of H5N6 (along with H7N9 and H9N2) in air samples in affected markets ⁹⁵. The 2013 Eurasian lineage HPAI H5N6 virus was a reassortant of H5N2 and H6N6 ¹⁷⁹.

In 2017, H5N6 was identified in three deceased cats in China proximal to outbreak-affected poultry flocks ¹⁸⁰. In 2020, an outbreak was reported in migratory swans in China as the strain continued to circulate in chickens and ducks ¹⁸¹.

In 2016, a CDC <u>IRAT</u> of HPAI H5N6 determined the virus posed "moderate risk" in terms of pandemic potential, though in light of the increase in cases reported by China in 2021, the <u>IRAT</u> was repeated, again scoring in the moderate risk category. Of the 51 cases reported globally since 2014, 25 occurred in 2021. Most human cases had exposure to infected birds before becoming ill ¹²⁷.

Key articles

Influenza in Swine

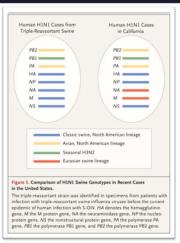


Figure 11. Comparison of human H1N1 cases from triple reassortant swine to human H1N1 cases in California (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team 2009)

reassortant consisted of four genes from classical swine influenza viruses (including HA and NA), two from AIV (North American lineage), and one from human IAV. Triple reassortant swine virus was first identified in the U.S. in 1998 ⁶⁴.

The A(H1N1)pdm09 eight genome had four primary origins. The NA and M genes were sourced from H3N2 Eurasian swine lineage viruses. The HA, NP, and NS genes were from classical swine influenza viruses, of the North American lineage. The PB2 and PA genes were from North American lineage avian influenza viruseland the PB1 gene originated from human seasonal H3N2 (Figure 9) ⁶³.

To summarize, the A(H1N1)pdm09 genome contained six gene segments (PB2, PB1, PA, HA, NP, and NS) previously found in triple-reasorants wine viruses circulating in pigs in North America ²²³. The remaining two genes, NA and M, were closely related to SIV circulating in Eurasia. This combination was completely new. Before A(H1N1)pdm09, the triple

Figure 12. U.S. novel influenza A infections in humans³¹⁶

Human infections continue to occur in people usually resulting from prolonged exposure to pigs at agricultural fairs. Sustained human transmission has not yet occurred ^{229,232-236}.

Major Sections: Surveillance, Epidemiology, Prevention & Control

- U.S. and international humans and animal surveillance
- Human surveillance and epidemiology
 - Seasonal
 - Novel influenza
 - International surveillance
 - · Surveillance of other respiratory pathogens
 - Epidemiology and transmission dynamics
 - Forecasting
 - · Prevention and control

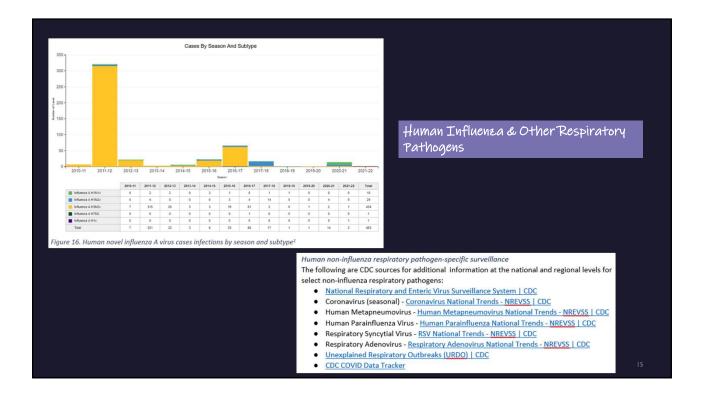
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Human, Avian, and Swine Surveillance Report Resources

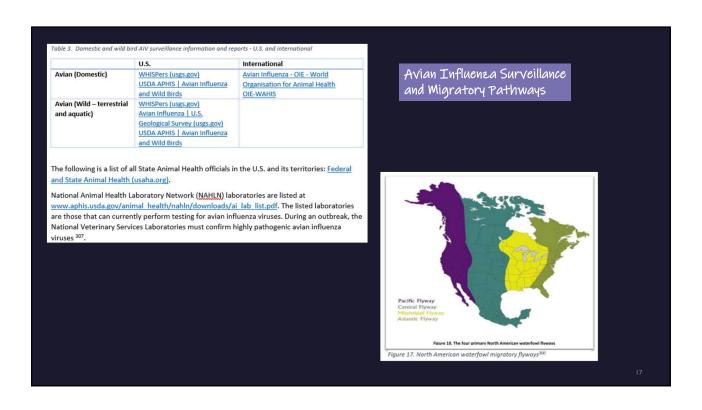
Table 2. Surveillance report references for human, avian, and swine influenza viruses by U.S. and internationa sources

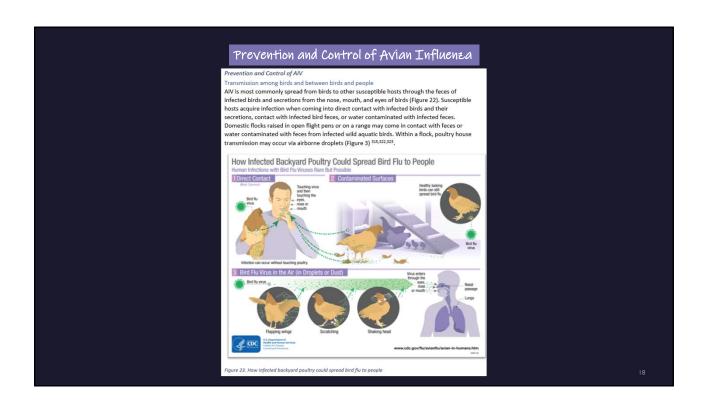
Influenza Virus	U.S.	International		
Human seasonal	Weekly U.S. Influenza	Flunet (who. int)		
	Surveillance Report CDC	WHO Biweekly Global Influenza Update		
Human novel (and variant)*	Novel Influenza A Virus Infections (cdc.gov)	WHO FluMart Outputs Monthly human-animal interface reports Global Influenza Programme (who.int) Cumulative number of human A(H5N1) cases Global Influenza Programme (who.int)		
Swine**				
Avian (Poultry)	USDA APHIS Highly Pathogenic Avian Influenza (HPAI)	Avian Influenza - OIE - World Organisation for Animal Health OIE-WAHIS		
Avian (Wild – Terrestrial & Aquatic)	WHISPers (usgs.gov) USDA APHIS Avian Influenza and Wild Birds USDA APHIS Highly Pathogenic Avian Influenza (HPAI)			
Outbreak reports	USDA APHIS Highly Pathogenic Avian Influenza (HPAI)	Disease Outbreak News (who.int) Influenza Research Database - Influenza genome database with visualization and analysis tools (fludb.org) The Weekly Epidemiological Record (WER) (who. int)		

*"Variant" influenza in the U.S. refers to human infection with a swine influenza virus. Internationally, "novel" influenza refers to any influenza virus that undergoes molecular, antigenic, or genetic changes from the original virus, regardless of species, *"Influenza is endemic in swine and not actively surveyed at the national or international levels. Some national outbreaks are tracked by State and local health agencies and the USDA APHIS.



Major Sections: Surveillance, Epidemiology, Avian influenza virus • Swine influenza virus • International surveillance Epidemiology • U.S. surveillance in domestic poultry Surveillance • Surveillance in wild birds • Transmission Migratory flyways • Marketing and production systems · Infections of AIV in humans · Prevention and control · Prevention and control • Equine influenza virus · Canine, feline, and Other Animal Influenza Viruses





Human outbreaks of SIV through 2012

The most significant outbreak of SIV in humans in the U.S. occurred between 2011-2012 and was caused by an H3N2v. A total of 315 cases were reported with 16 hospitalizations and one death. A total of 13 states reported cases, with the majority of cases split between Indiana and Ohio (Table 5). All cases reported direct or indirect contact with swine primarily at agricultural

U.S. State	Case Count		
Hawaii	1		
Illinois	4		
Indiana	138		
Iowa	1		
Maryland	12 6		
Michigan			
Minnesota	5		
Ohio	107		
Pennsylvania	11		
Utah	1		
West Virginia	3		
Wisconsin	20		

able 5. Human infections with SIV,

fairs. The median case age was seven years. This outbreak reinforced previous serologic study findings that children are less likely to have cross-reactive antibodies against a novel flu strain compared to adults. Evidence of limited person-to-person spread was documented. Rapid antigen point-of-care assays were unable to accurately detect these cases, reinforcing the need for confirmatory PCR testing, especially when influenza is suspected outside of typical seasonal prevalence periods $^{\rm 289}\!.$

Before 2012, cases of novel influenza A averaged only one case every 1-2 years and primarily in those with direct or indirect contact with swine 83. SIV poses no risk of infection when properly cooked swine meat is consumed by humans 83.

The FluView novel influenza dashboard only extends 10 years into the past. This CDC site contains detailed case reports of

novel infections before 2013 - Reports of Human Infections with Variant Viruses | CDC.

Human Novel Influenza Infections & Management Resources

esources for managing suspected and confirmed outbreaks of SIV

Responding to outbreaks of SIV where swine morbidity and mortality exceeds that of ender influenza activity requires the coordination of USDA APHIS VS and state animal health officials. The following is a list of contacts for USDA and state health officials, testing guidelines and forms, testing algorithms, laboratory contacts, and notification plans for a novel influenza A virus laboratory finding.

- Swine influenza OIE World Organisation for Animal Health
- VS District Offices Points of Contact and the State Animal Health Official Directory
- Testing Guidelines, Forms, Submission Instructions
- Influenza A in Swine Testing Algorithm Instructions
- Participating NAHLN labs
- Notification plan for novel influenza A virus in swine laboratory finding
- Guidance for State and Local Health Departments for the Investigation of Hunan Infections with Novel Influenza A Viruses at the Animal-Human Interface

Major Sections: Resources

- Future considerations for zoonotic influenza
- Public health resources
 - · General influenza
 - · Swine influenza
 - · Avian influenza
 - · Other animals
- Appendix A: LPAI & HPAI cases and outbreaks by world region and country, 2005-2021
- Appendix B: Contact list for state, tribal, local, and territorial health departments
- Appendix C: Influenza viruses evaluated using IRAT since 2010, CDC

Public Health Resources

General Influenza

- Pandemic Influenza | Pandemic Influenza (Flu) | CDC
- Influenza (Flu) | CDC
- Weekly U.S. Influenza Surveillance Report | CDC
- Understanding Flu Viruses | CDC
- What's New on this Site | CDC
- Influenza in Animals | Seasonal Influenza (Flu) | CDC
- What CDC Does About Novel Flu: Outbreak Investigations | CDC
- Nonpharmaceutical Interventions (NPIs) | CDC

Swine Influenza

- Information on Swine/Variant Influenza | CDC
- Variant Influenza Viruses in Humans | CDC
- Swine Influenza (Influenza in Swine) | CDC

Animal exhibitors and event organizers

- Measures to Minimize Influenza Transmission at Swine Exhibitions, 2018 NASAHO and NASPHV
- Information for Fair Organizers and People Exhibiting Pigs | CDC
- Video Podcast: CDC Recommendations to Reduce the Risk of H3N2v Flu Virus Infection for Fairgoers and Swine Exhibitors
- Swine Health Information Center
- Pork Checkoff

Key Facts for People Exhibiting at Fairs

- Key Facts for People Exhibiting Pigs at Fairs | CDC
- What People Who Raise Pigs Need to Know

Public Health Resources

Genera

- Find a state extension service
- Pandemic Influenza Overview | Occupational Safety and Health Administration (osha.gov)
- Foreign Animal Diseases: "The Gray Book"
- World Organization for Animal Health (OIE)
- National Assembly of State Animal Health Officials (NASAHO) (nasda.org)
- NASPHV Zoonotic Influenza
- Measures to Minimize Influenza Transmission at Swine Exhibitions, 2018 NASAHO and NASPHV
- Guidance for State and Local Health Departments for the Investigation of Human Infections with Novel Influenza A Viruses at the Animal-Human Interface

Other Animals

Equine

- Equine Disease Communication Center
- Universal Equine Microchip Lookup: www.horselookup.org
- Equine Health Resources (2016 Equine Health Forum)
- USDA APHIS | Equine Information

Canine, Feline, and Bats

- Key Facts about Canine Influenza (Dog Flu) | Seasonal Influenza (Flu) | CDC
- Influenza in Cats | Seasonal Influenza (Flu) | CDC
- Bat Influenza (Flu) | Seasonal Influenza (Flu) | CDC

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Appendix A: Avian LPAI and HPAI Cases and Outbreaks by World Region and Country, 2005 - 2021

Year	World region	Subtype	Cases	New outbreaks
2005	Africa	H5N2		2
	Asia	-	164325	32
		H5	400	0
		H5N1	571150	1208
		H7N7	20336	3
	Europe	-	4	3
		H5N1	23234	117
2006	Africa	-	4	1
		H5N1	112663	1179
		H5N2	16	76
	Asia	-	55	5
		H5	148086	4
		H5N1	1508132	653
		H7N1		1
		other	15486	53
	Europe	-	987	10
		H5N1	1434627	723
		H5N2	0	1
		H5N3		2
2007	Africa	-	2	2
		H5N1	29320	465
	Americas	H5N1		1
		H5N2	3	4
		H7N3	540	1
		H7N9		1
		not typed		1

Grand Total			177744250	37889
		H7N7	34	1
		H5N8	887498	377
		H5N5	84	3
		H5N3	12344	4
		H5N1	7383	6
		H5	31	2
	Europe		1241	7
		other	18218	26
		H5N8	1147509	114
		H5N6	28281	35
	Asia	H5N1	995	4
2021	Africa	H5N1	1268	3
		H7N7	255012	3
		H7N6	2000	1
	Oceania	H5N2		2
		H7N1	14300	2
		H5N8	925043	509
		H5N5	104	3
		H5N3	4	1
		H5N1	150	2
	Europe	H5	198254	38
		not typed	123595	14
		H5N8	380441	110
		H5N6	47633	60
		H5N5	53222	49
		H5N2	39711	27
		H5N1	22885	24
	Asia	H5	69828	19

Appendix B. Contact list CDC Influenza Division The CDC Influenza Division has an emergency contact line is staffed 24/7. CDC INFO: Contact CDC-INFO; 800-CDC-INFO (800-232-4636), TTY: 888-232-6348 CDC Influenza Division: 404-639-3747 National Veterinary Services Laboratories (USDA APHIS District Offices) NVSL FADDL NVSL AMES MAIn Office (631) 323-3256 NVSL Director

AFTER HOURS AND WEEKENDS

Diagnostic Services Section Head (631) 375-5312 Patholology

Acting Diagnostic Services Section Head (631) 450-2018 Diagnostic Bacteriology

Courier (631) 566-0073 AFTER HOURS AND WEEKENDS (515) 337-7301 (515) 337-7551 (515) 337-7568 NPIC (M-F, 8:00 AM - 4:30 PM ET)
 NPIC (M++, 8:00 AM - 4:30 PM ET)
 NaT1 (Centers for Animal Health Dispatch Jon Zack

 Jon Zack
 (240) 252-8074

 Julie Gauthier
 (919) 219-8433

 Barbara Potre-Spalding
 (919) 937-4409

 District Two
 Nathan Birnbaum

 Label Company
 (240) 508-9888

 District True
 District Four
 (508) 363-2290 (517) 337-4700 (512) 383-2400 (800) 940-6524 District Five (970) 494-7400 NPIC/NVS 24/7 Emergency Answering Service (916) 854-3950 NASPHV State Public Health Veterinarians Contact List StatePublicHealthVeterinariansByState.pdf (nasphv.org) National Assembly of State Animal Health Officials National Assembly of State Animal Health Officials (NASAHO) (nasda.org) United States Animal Health Association (USAHA) State Animal Health Officials State Contact Representatives and Key Contacts (National Poultry Improvement Plan) OfficialStateAgencies.pdf (poultryimprovement.org) U.S. Agencies United States Agency for International Development (USAID) United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service Food Safety and Inspection Service United States Department of the Interior

Influenza Virus	Month and Year of Risk Assessment	Potential Emergence Estimate	Potential Impact Estimate	Risk Score Category
H5N6 clade 2.3.4.4b [A/Sichuan/06681/2021]	Oct-21	5.3	6.3	Moderate
H5N8 clade 2,3,4,4b [A/Astrakhan/3212/2020]	Mar-21	4.6	5.2	Moderate
H1N1 [A/swine/Shandong/1207/201 6]	Jul-20	7.5	6.9	Moderate
H1N2 variant [A/California/62/2018]	Jul-19	5.8	5.7	Moderate
H3N2 variant [A/Ohio/13/2017]	Jul-19	6.6	5.8	Moderate
H9N2 Y280 lineage [A/Anhui- Lujiang/13/2018]	Jul-19	6.2	5.9	Moderate
H7N9 [A/chicken/Tennessee/17- 007431-3/2017]	Oct-17	3.1	3.5	Low
H7N9 [A/ chicken/Tennessee /17- 007147-2/2017]	Oct-17	2.8	3.5	Low
H7N8 [A/turkey/Indiana/1573- 2/2016]	Jul-17	3.4	3.9	Low
H7N9 [A/Hong Kong/125/2017]	May-17	6.5	7.5	Moderate-High
H3N2 [A/canine/Illinois/12191/2015]	Jun-16	3.7	3.7	Low
H5N6 [A/Yunnan/14564/2015] - like	Apr-16	5	6.6	Moderate
H7N9 [A/Shanghai/02/2013]	Apr-16	6.4	7.2	Moderate-High

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Navigation

- There are over 350 references
- References are hyperlinked to articles
- DOI links can be pasted into a browser or clicked on to retrieve the original article
- Where possible, public access research articles were used
- Several books, interviews, and websites were used as references

