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The eyes have it: influenza virus infection beyond the respiratory tract

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Abstract

Avian and human influenza A viruses alike have shown a capacity to use the eye as a portal of entry and cause ocular disease in human beings. However, whereas influenza viruses generally represent a respiratory pathogen and only occasionally cause ocular complications, the H7 virus subtype stands alone in possessing an ocular tropism. Clarifying what confers such non-respiratory tropism to a respiratory virus will permit a greater ability to identify, treat, and prevent zoonotic human infection following ocular exposure to influenza viruses; especially those within the H7 subtype, which continue to cause avian epidemics on many continents.

Introduction

There is a great diversity among influenza A viruses associated with human infection. Human influenza viruses are responsible for annual epidemics and infrequent pandemics, leading to a high burden of disease worldwide each year. Zoonotic influenza viruses have repeatedly crossed the species barrier, causing human disease that ranges from subclinical to life-threatening.[1] Although these influenza viruses generally lack the capacity for sustained human-to-human transmission, the absence of pre-existing immunity in human populations to these viruses and the ability to cause severe human illness nonetheless underscore their pandemic potential. The high infectivity of influenza viruses, and capacity for viruses to

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remain suspended in the air for sustained distance and duration,[2,3] further illustrates the constant public health threat posed by this pathogen.

Influenza viruses typically cause respiratory disease in human beings, associated with fever, chills, headache, nasal discharge, sore throat, coughing, and sneezing in uncomplicated cases.[4] However, several non-respiratory clinical features can also occur among infected individuals, including ocular (typically mild conjunctivitis) and gastrointestinal (typically diarrhoea) depending on the severity of disease and causative strain; complications including secondary bacterial pneumonia or (rarely) neurological involvement (including Guillain-Barré syndrome and encephalitis) are uncommon but documented.[4,5] Similarly, respiratory exposure is but one of several potential routes of influenza virus infection in human beings. Owing to the heterogeneity inherent in the capacity of influenza A viruses to cause illness following multiple modes of infection, there is a need for both a greater understanding of how non-respiratory exposure routes influence disease presentation and progression in mammalian hosts, and heightened investigation regarding the susceptibility of non-respiratory tissues to both human and avian influenza viruses.

The eye is susceptible to avian and human influenza virus infection

In human beings, influenza virus infections generally follow respiratory exposure and cause respiratory symptoms as the primary manifestation of disease. The distribution of influenza virus cellular receptors in the human respiratory tract (terminal sialic acids linked to galactose via α2,3 or α2,6 glycosidic bonds) is believed to govern host range and tropism, with human influenza viruses preferentially binding to α2,6 linked sialic acid, and avian influenza viruses preferentially binding to α2,3 linked sialic acid.[6] However, the ocular surface (notably the corneal and conjunctival epithelia) represents an often overlooked mucosal surface that, like the respiratory tract, bears permissive receptors for influenza virus, primarily in an α2,3 linkage.[7]

Thus, a better understanding of viruses or virus subtypes that exhibit a non-respiratory tropism will facilitate identification of the properties that confer tissue preference in human beings. With the exception of low pathogenic avian influenza (LPAI) and high pathogenic avian influenza (HPAI) A H7N9 viruses causing human respiratory infection in east Asia, roughly 80% of documented human infections with H7 subtype viruses have been associated with ocular complications (often with concurrent mild respiratory disease)[8] and an influenza-virus positive eye swab (table 1), supporting the ocular tropism of this virus subtype. This finding clearly contrasts with other avian and human influenza viruses, which have occasionally shown a capacity to cause ocular complications (typically reported as conjunctivitis) but do not exhibit a particular affinity towards ocular tissue (table 2). For example, conjunctivitis or pink eye was reported in 0·45% and 0·70% of patients admitted to hospital of all ages with laboratory-confirmed influenza during the 2014–15 to 2016–17 seasons, respectively (table 3), a low but still measurable percentage of all virus-confirmed patients in this cohort.

It should be noted that most of these reports do not confirm the presence of influenza virus by isolation from eyes (typically only tested among possible H7 virus cases), and often do

not rule out the presence of other common bacterial or viral pathogens (such as adenovirus), that are known to cause conjunctivitis. As such, these studies demonstrate an association of conjunctivitis with respiratory influenza in the absence of confirmation that the ocular symptoms are caused by influenza virus infection, and identify a need to collect and examine ocular samples (eg, eye swabs) when ocular involvement is reported during confirmed infection with a respiratory pathogen. Although these limitations make it difficult to ascertain the prevalence of ocular complications among influenza virus-infected individuals from these isolated studies, collectively these data nonetheless indicate that human beings are susceptible to ocular involvement following infection with a diverse group of influenza A viruses.

Conjunctivitis, or inflammation of the conjunctiva and eyelid, is the primary ocular complication reported in individuals with confirmed influenza virus infection, but additional ocular findings have also been documented, including (but not limited to) subconjunctival haemorrhage, uveitis, retinopathy, and optic neuritis.[32,38] Most of these reports describe previously healthy individuals; further data are needed to determine whether immunocompromised individuals are more susceptible to non-respiratory influenza virus exposure or are more likely to present with ocular complications following influenza virus infection. In the absence of antiviral treatments that specifically target ocular disease caused by RNA viruses,[7] influenza-positive patients presenting with conjunctivitis or other ocular complications are typically treated with oseltamivir (table 1).[32]

Although there are several isolated reports of ocular involvement following infection with avian and human influenza A viruses (tables 1, 2), there is a need for increased consistency in reporting the absence or presence of ocular complications in individuals with confirmed influenza virus infection, especially for individuals whose infection might be associated with occupational exposure. Studies have shown reduced viral loads in individuals exposed to live attenuated influenza vaccine wearing both ocular and respiratory protection compared with respiratory protection alone,[39] indicating a crucial role for eye protection. However, robust data regarding eye protection compliance (concurrent with use of respiratory protection) among individuals with potential occupational exposure to influenza virus is often lacking or not documented. Furthermore, potential ocular exposure (ie, by infectious aerosols, fomites, or virus-containing liquids) to influenza virus is not frequently reported in retrospective epidemiological studies among non-H7 subtype viruses, despite the capacity for many influenza viruses to use the eye to cause a respiratory infection. H7 subtype viruses in cases presenting with conjunctivitis have been confirmed in either respiratory samples or eye swabs, although eye swabs are more frequently positive than throat swabs (by either RT-PCR or virus culture), with most cases detected within the first 4–5 days after illness onset.[15,16] In support of antiviral treatment of influenza virus-associated conjunctivitis (table 1), efficacy of the neuraminidase inhibitor oseltamivir following ocular inoculation of mice or ferrets with influenza viruses has been shown to reduce viral replication and limit virus transmissibility,[40,41] but further study is needed regarding the bioavailability of oseltamivir to the eye and use of antiviral agents when conjunctivitis is the primary manifestation of PCR-confirmed influenza and co-infection with other potential pathogens has been ruled out.

Ocular tropism can be measured in the laboratory

The study of small mammalian models has greatly improved our understanding of influenza viruses to infect and cause disease by the ocular route. Ocular inoculation of ferrets using either a liquid or aerosol inoculum has identified that both human and avian influenza viruses can cause a productive, transmissible respiratory infection following this exposure route (table 4). Interestingly, these studies have revealed reduced clinical signs of infection, less efficient virus transmission, and diminished induction of innate host responses following ocular compared with respiratory inoculation.[43,44] As supported by studies in human beings,[39] replication-independent drainage of inoculum from the ocular surface to the nasal mucosa and respiratory tract via the nasolacrimal duct has been shown in the ferret model.[43] Although these ferret studies have underscored the capacity for both avian and human influenza viruses to cause respiratory disease following ocular-only exposure, this species does not reflect the apparent ocular tropism associated with H7 virus infection; further immunohistochemical or histopathological studies are warranted to more closely examine this finding. By contrast, mice inoculated by the ocular route with H7 subtype viruses possess detectable virus in ocular and respiratory tissues with increased frequency postinoculation compared with A H5N1 or seasonal influenza viruses.[45,46]

Similar to other principal respiratory viruses such as adenovirus and respiratory syncytial virus, numerous ocular cell types support productive replication of both avian and human influenza viruses in vitro.[47–51] These studies have largely examined the capacity for influenza virus replication in cultured human ocular (corneal or conjunctival) epithelial cells or human conjunctival organ cultures, and have revealed that, in agreement with the ferret studies described above, many disparate influenza viruses that exhibit a respiratory tropism in human beings are nonetheless capable of binding to and replicating in human ocular cells. Unfortunately, as these studies have largely been done with cultured monolayers or ex-vivo tissues, they are not designed to capture the involvement of ocular surface mucins or tear film in infection dynamics. As ocular secretory mucins possess sialic acids and serve an important role in host defence,[52,53] characterisation of the role ocular secretions play in preventing or facilitating influenza virus infection is necessary.

Experimental demonstration of the susceptibility of the ocular epithelial surface to influenza virus infection with both avian and human viruses has shed further light on poorly understood areas for which additional research is needed to address questions regarding ocular tropism independent of virus subtype. Although our understanding of the receptor-binding profile of H7 haemagglutinins has improved in recent years,[54] it is unlikely that ocular tropism is governed solely by this property, as binding of both human and avian influenza viruses to mammalian ocular tissue has been reported.[43] However, when considering the role cellular receptors appear to play in the ocular tropism of other respiratory pathogens,[52] a more detailed investigation regarding the distribution of glycan receptors on the human ocular surface, as conducted previously for human respiratory tissue,[55] is warranted. In situations where respiratory but not ocular protection is worn, the nasolacrimal duct plays a critical function in facilitating the drainage of virus-containing fluid from the eye to the nasopharyngeal space, but does not represent a frequently studied tissue in influenza research, nor has the ability of influenza virus to replicate specifically

within this tissue (found to possess both α2,3 and α2,6 linked sialic acid) been shown experimentally.[56] The dynamics of tear fluid exchange, from eye to nose but also from nose to eye, is similarly understudied in the context of viral infection, but nonetheless warrants investigation,[53] as intranasally administered solutions can be detected at the conjunctival mucosal surface and infectious virus has been detected in ocular samples (conjunctival washes and whole eye tissue) of ferrets inoculated intranasally.[43,57] Continued research in these areas is needed to more fully elucidate how influenza viruses reach the corneal and conjunctival epithelia and spread to the nasopharyngeal space. This is of special importance, as the eye mucosa shares several immunological features with other mucosal compartments, and as such, the use of eyedrop vaccination against influenza virus is under investigation as an alternative vaccine strategy capable of inducing protective immunity.[58,59]

H7 viruses represent a critical tool for unlocking ocular tropism

Due to their breadth of mammalian virulence, varied tropism, and establishment of lineages on multiple continents, H7 subtype viruses exhibit a wide and often underappreciated heterogeneity compared with other avian influenza virus subtypes associated with human infection, representing a challenge for their study. H7 outbreaks in poultry have been reported throughout North America, Europe, and Asia (figure); depopulation activities related to containment of these epornitics (ie, outbreaks in avian populations) can lead to occupational exposure of workers, as numerous human cases with A H7N3 and A H7N7 viruses have resulted concurrent with this work (table 1).[15,16,20] Continued surveillance of H7 viruses is needed in both wild bird and gallinaceous poultry populations to assess the generation of HPAI viruses from LPAI precursors and the associated potential exposure risk posed to human beings with these viruses.[60]

Avian influenza viruses, notably H5 and H7 subtype viruses associated with human infection, have been found to be poorly immunogenic in mammals,[61] leading to difficulties in identifying mild or asymptomatic cases. Although supportive evidence is lacking, it is possible, in conjunction with a poorly immunogenic H7 haemagglutinin that infection stemming from ocular exposure, or disease when ocular and not respiratory symptoms are the primary indicator of disease, contributes to this decreased immune activation or depressed serological responses to infection, or both.[62] Retrospective studies from H7 outbreaks have identified many individuals with evidence of seroconversion to H7 virus using modified, untraditional assay conditions (in the absence of detectable neutralising antibody titres).[63] Furthermore, individuals with positive PCR tests for influenza H7 have been identified in the absence of diagnostic seroconversion.[64] Just as increased efforts to identify immune correlates of protection are needed, continued investigation to understand differences in the magnitude of induction of host responses following ocular exposure or ocular disease is required to best identify all potentially exposed individuals. Additional studies in this area will greatly facilitate our understanding of these properties.

Research regarding the ocular tropism associated with H7 viruses has focused primarily on the contribution of surface glycoproteins, and rightfully so, as one study identified that the combination of haemagglutinin and neuraminidase genes was necessary to maintain the conjunctival tropism of a 2009 A H1N1 virus in vitro.[50] That said, the presence of an H7

haemagglutinin was found to most strongly affect the frequency of murine infection with influenza virus following ocular inoculation, suggesting that the neuraminidase with which the H7 haemagglutinin was paired or the lineage from which the neuraminidase was derived were less crucial for this property.[46] It is likely that the H7 haemagglutinin possesses unique features compared with other virus subtypes; for example, it appears that differential molecular mechanisms confer an HPAI phenotype in H5 viruses (acquisition of multiple basic aminoacids at the haemagglutinin cleavage site) versus H7 viruses (both multiple basic aminoacid acquisition and non-homologous recombination with other viral proteins or host rRNA).[20,65] Further identification of subtype-specific properties of the haemagglutinin are needed to better explain these functional differences. Beyond surface glycoproteins, there is growing evidence that internal proteins might play a role in H7 subtype-specific immune activation[66] and ocular tropism.[46] Unlike HPAI A H5N1 viruses, which frequently elicit heightened induction of proinflammatory mediators, HPAI H7 subtype viruses often elicit delayed and weakened responses in laboratory assays.[61,67] As such, identification of differential induction of host signalling pathways between influenza viruses associated with respiratory disease compared with influenza viruses associated primarily with human conjunctivitis points to potential roles in host responses governing tissue tropism.[47,66]

It is likely that, like virus transmissibility, ocular tropism is a polygenic trait. Although several properties have been observed more frequently among ocular-tropic compared with respiratory-tropic influenza viruses (such as the presence of an H7 haemagglutinin and maintenance of an avian α2,3 receptor binding preference), these features appear neither necessary nor sufficient for a virus to bind to, replicate in, or spread from the eye to susceptible respiratory tissue. In this regard, the unanswered question of what separates the respiratory tropism evident following human infection with LPAI and HPAI A H7N9 viruses and the ocular disease associated with the majority of other H7 subtype viruses in human beings offers an opportunity to examine in more detail the molecular correlates of ocular tropism. With more than 1600 confirmed cases and a greater than 30% fatality rate since their first detection in human beings in 2013, the pandemic threat posed by A H7N9 viruses is evident.[23] Research is ongoing to elucidate what features differentiate the severe respiratory disease associated with A H7N9 and A H5N1 human infection,[68] but further efforts should similarly be made to better understand the respiratory tropism associated with this ongoing outbreak. Thus, although non-H7N9 H7 subtype viruses are not as frequently studied in the laboratory as A H7N9 or A H5N1 viruses, greater inclusion of ocular-tropic H7 viruses in influenza virus research will facilitate identification of what molecular determinants govern virus tropism, in both ocular and respiratory tissues.

Conclusions

Laboratory data show that a diverse range of human and avian influenza viruses are capable of replicating in several discrete ocular cell types in vitro, and can effectively use ocular exposure to mount a productive respiratory infection in vivo. It is reasonable to assume similar occupational exposure during culling and depopulation activities necessitated by either H5 or H7 infection in poultry, yet reports of ocular complications predominate among workers exposed to H7 subtype viruses only, indicating that not all virus subtypes appear to equally exploit this entry route in human beings. Thus, there remains a need to distinguish

what is possible among all viruses (as we demonstrate in the laboratory) from what is unique to H7 subtype viruses (as is supported by epidemiological data). Only then will we understand the properties that confer an ocular tropism to select groups of influenza viruses in human beings.

Only a fraction of all human infections with influenza viruses present with ocular complications. Although routes of influenza virus transmission between human beings are varied,[69] it is assumed that exposure of respiratory tract tissue, and not ocular tissue, to aerosolised influenza virus represents a dominant mode. Protecting the ocular mucosal surface prevents influenza virus from potentially exploiting a mucosal surface with an anatomical conduit to the nasopharynx and respiratory tract. Use of eye protection is recommended in some circumstances where there is risk of influenza virus infection.[70–73] Continued investigation of the capacity for respiratory viruses to gain entry to the respiratory tract and to cause ocular complications will improve understanding of how these pathogens cause human disease, regardless of the virus subtype or exposure route.

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References

1. Horimoto T, Kawaoka Y. Influenza: lessons from past pandemics, warnings from current incidents. Nat Rev Microbiol. 2005; 3:591–600. [PubMed: 16064053]
2. Tellier R. Aerosol transmission of influenza A virus: a review of new studies. J R Soc Interface. 2009; 6(suppl 6):S783–90. [PubMed: 19773292]
3. Xie X, Li Y, Chwang AT, Ho PL, Seto WH. How far droplets can move in indoor environments–revisiting the Wells evaporation-falling curve. Indoor Air. 2007; 17:211–25. [PubMed: 17542834]
4. Hayden, FG., Ison, MG. Respiratory viral infections. In: Dale, DC., Feldman, DD., editors. ACP medicine, 2006 edn, Section 7 Chapter XXV. New York, NY: WebMD Professional Publishing; 2006.
5. Britton PN, Dale RC, Blyth CC, et al. Influenza-associated encephalitis/encephalopathy identified by the Australian Childhood Encephalitis Study 2013–2015. Pediatr Infect Dis J. 2017; 36:1021–26. [PubMed: 28654561]
6. Kumlin U, Olofsson S, Dimock K, Arnberg N. Sialic acid tissue distribution and influenza virus tropism. Influenza Other Respir Viruses. 2008; 2:147–54. [PubMed: 19453419]
7. Belser JA, Rota PA, Tumpey TM. Ocular tropism of respiratory viruses. Microbiol Mol Biol Rev. 2013; 77:144–56. [PubMed: 23471620]
8. Belser JA, Bridges CB, Katz JM, Tumpey TM. Past, present, and possible future human infection with influenza virus A subtype H7. Emerg Infect Dis. 2009; 15:859–65. [PubMed: 19523282]
9. Taylor HR, Turner AJ. A case report of fowl plague keratoconjunctivitis. Br J Ophthalmol. 1977; 61:86–88. [PubMed: 843515]
10. Webster RG, Geraci J, Petursson G, Skirnisson K. Conjunctivitis in human beings caused by influenza A virus of seals. N Engl J Med. 1981; 304:911.
11. Kurtz J, Manvell RJ, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet. 1996; 348:901–02. [PubMed: 8826845]
12. CDC. Update: influenza activity—United States, 2003–04 season. MMWR Morb Mortal Wkly Rep. 2004; 53:284–87. [PubMed: 15071427]

13. Ostrowsky B, Huang A, Terry W, et al. Low pathogenic avian influenza A (H7N2) virus infection in immunocompromised adult, New York, USA, 2003. Emerg Infect Dis. 2012; 18:1128–31. [PubMed: 22710273]
14. Puzelli S, Di Trani L, Fabiani C, et al. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. J Infect Dis. 2005; 192:1318–22. [PubMed: 16170747]
15. Koopmans M, Wilbrink B, Conyn M, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet. 2004; 363:587–93. [PubMed: 14987882]
16. Tweed SA, Skowronski DM, David ST, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis. 2004; 10:2196–99. [PubMed: 15663860]
17. Nguyen-Van-Tam JS, Nair P, Acheson P, et al. Outbreak of low pathogenicity H7N3 avian influenza in UK, including associated case of human conjunctivitis. Euro Surveill. 2006; 11:E060504.2.
18. Anon. Avian influenza A/(H7N2) outbreak in the United Kingdom. Euro Surveill. 2007; 12:E070531.2.
19. Dudley JP. Public health and epidemiological considerations for avian influenza risk mapping and risk assessment. Ecol Soc. 2008; 13:21.
20. Lopez-Martinez I, Balish A, Barrera-Badillo G, et al. Highly pathogenic avian influenza A(H7N3) virus in poultry workers, Mexico, 2012. Emerg Infect Dis. 2013; 19:1531–34. [PubMed: 23965808]
21. Puzelli S, Rossini G, Facchini M, et al. Human infection with highly pathogenic A(H7N7) avian influenza virus, Italy, 2013. Emerg Infect Dis. 2014; 20:1745–49. [PubMed: 25271444]
22. Puzelli S, Rizzo C, Fabiani C, et al. Influenza A(H7N7) virus among poultry workers, Italy, 2013. Emerg Infect Dis. 2016; 22:1512–13. [PubMed: 27434025]
23. FAO. H7N9 situation update. 2018. http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html (accessed Feb 7, 2018).
24. Jhung MA, Epperson S, Biggerstaff M, et al. Outbreak of variant influenza A(H3N2) virus in the United States. Clin Infect Dis. 2013; 57:1703–12. [PubMed: 24065322]
25. CDC. Avian influenza A (H7N2) in cats in animal shelters in NY; one human infection. Atlanta, GA: Centers for Disease Control and Prevention; 2016. https://www.cdc.gov/flu/spotlights/avian-influenza-cats.htm (accessed Feb 21, 2017).
26. McLean E, Pebody RG, Campbell C, et al. Pandemic (H1N1) 2009 influenza in the UK: clinical and epidemiological findings from the first few hundred (FF100) cases. Epidemiol Infect. 2010; 138:1531–41. [PubMed: 20594381]
27. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009; 374:451–58. [PubMed: 19643469]
28. Skarbinski J, Jain S, Bramley A, et al. Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States—September–October 2009. Clin Infect Dis. 2011; 52(suppl 1):S50–59. [PubMed: 21342900]
29. Ko JH, Kim JH, Kang JH, et al. Characteristics of hospitalized children with 2009 pandemic influenza A (H1N1): a multicenter study in Korea. J Korean Med Sci. 2012; 27:408–15. [PubMed: 22468105]
30. Koliou M, Soteriades ES, Toumasi MM, Demosthenous A, Hadjidemetriou A. Epidemiological and clinical characteristics of influenza A(H1N1)v infection in children: the first 45 cases in Cyprus, June–August 2009. Euro Surveill. 2009; 14:19312. [PubMed: 19712641]
31. Witkop CT, Duffy MR, Macias EA, et al. Novel influenza A (H1N1) outbreak at the US Air Force Academy: epidemiology and viral shedding duration. Am J Prev Med. 2010; 38:121–26. [PubMed: 19850440]
32. Mansour DE, El-Shazly AA, Elawamry AI, Ismail AT. Comparison of ocular findings in patients with H1N1 influenza infection versus patients receiving influenza vaccine during a pandemic. Ophthalmic Res. 2012; 48:134–38. [PubMed: 22572924]

33. Lee VJ, Yap J, Cook AR, et al. A clinical diagnostic model for predicting influenza among young adult military personnel with febrile respiratory illness in Singapore. PLoS One. 2011; 6:e17468. [PubMed: 21399686]
34. Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, et al. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med. 2008; 358:261–73. [PubMed: 18199865]
35. Oner AF, Bay A, Arslan S, et al. Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med. 2006; 355:2179–85. [PubMed: 17124015]
36. Arzey GG, Kirkland PD, Arzey KE, et al. Influenza virus A (H10N7) in chickens and poultry abattoir workers, Australia. Emerg Infect Dis. 2012; 18:814–16. [PubMed: 22516302]
37. Chaves SS, Lynfield R, Lindegren ML, Bresee J, Finelli L. The US Influenza Hospitalization Surveillance Network. Emerg Infect Dis. 2015; 21:1543–50. [PubMed: 26291121]
38. Ranjan R, Ranjan S. Ocular pathology: role of emerging viruses in the Asia-Pacific region—a review. Asia Pac J Ophthalmol (Phila). 2014; 3:299–307. [PubMed: 26107917]
39. Bischoff WE, Reid T, Russell GB, Peters TR. Transocular entry of seasonal influenza-attenuated virus aerosols and the efficacy of n95 respirators, surgical masks, and eye protection in humans. J Infect Dis. 2011; 204:193–99. [PubMed: 21673029]
40. Belser JA, Maines TR, Creager HM, Katz JM, Tumpey TM. Oseltamivir inhibits influenza virus replication and transmission following ocular-only aerosol inoculation of ferrets. Virology. 2015; 484:305–12. [PubMed: 26142497]
41. Belser JA, Sleeman K, Pearce MB, Katz JM, Gubareva LV, Tumpey TM. Oseltamivir inhibits H7 influenza virus replication in mice inoculated by the ocular route. Antimicrob Agents Chemother. 2012; 56:1616–18. [PubMed: 22155827]
42. Belser JA, Gustin KM, Katz JM, Maines TR, Tumpey TM. Influenza virus infectivity and virulence following ocular-only aerosol inoculation of ferrets. J Virol. 2014; 88:9647–54. [PubMed: 24920819]
43. Belser JA, Gustin KM, Maines TR, Pantin-Jackwood MJ, Katz JM, Tumpey TM. Influenza virus respiratory infection and transmission following ocular inoculation in ferrets. PLoS Pathog. 2012; 8:e1002569. [PubMed: 22396651]
44. Belser JA, Maines TR, Gustin KM, Katz JM, Tumpey TM. Kinetics of viral replication and induction of host responses in ferrets differs between ocular and intranasal routes of inoculation. Virology. 2013; 438:56–60. [PubMed: 23415392]
45. Belser JA, Wadford DA, Xu J, Katz JM, Tumpey TM. Ocular infection of mice with influenza A (H7) viruses: a site of primary replication and spread to the respiratory tract. J Virol. 2009; 83:7075–84. [PubMed: 19458003]
46. Belser JA, Sun X, Creager HM, et al. Role of H7 hemagglutinin in murine infectivity of influenza viruses following ocular inoculation. Virology. 2017; 502:13–19. [PubMed: 27960109]
47. Belser JA, Zeng H, Katz JM, Tumpey TM. Ocular tropism of influenza A viruses: identification of H7 subtype-specific host responses in human respiratory and ocular cells. J Virol. 2011; 85:10117–25. [PubMed: 21775456]
48. Lenny BJ, Shanmuganatham K, Sonnberg S, et al. Replication capacity of avian influenza A(H9N2) virus in pet birds and mammals, Bangladesh. Emerg Infect Dis. 2015; 21:2174–77. [PubMed: 26583371]
49. Michaelis M, Geiler J, Klassert D, Doerr HW, Cinatl J Jr. Infection of human retinal pigment epithelial cells with influenza A viruses. Invest Ophthalmol Vis Sci. 2009; 50:5419–25. [PubMed: 19553611]
50. Chan RW, Kang SS, Yen HL, et al. Tissue tropism of swine influenza viruses and reassortants in ex vivo cultures of the human respiratory tract and conjunctiva. J Virol. 2011; 85:11581–87. [PubMed: 21880750]
51. Chan MC, Chan RW, Yu WC, et al. Tropism and innate host responses of the 2009 pandemic H1N1 influenza virus in ex vivo and in vitro cultures of human conjunctiva and respiratory tract. Am J Pathol. 2010; 176:1828–40. [PubMed: 20110407]
52. Olofsson S, Kumlin U, Dimock K, Arnberg N. Avian influenza and sialic acid receptors: more than meets the eye? Lancet Infect Dis. 2005; 5:184–88. [PubMed: 15766653]

53. Creager HM, Kumar A, Zeng H, et al. Infection and replication of influenza virus at the ocular surface. J Virol. 2018; doi: 10.1128/JVI.02192-17
54. Yang H, Carney PJ, Donis RO, Stevens J. Structure and receptor complexes of the hemagglutinin from a highly pathogenic H7N7 influenza virus. J Virol. 2012; 86:8645–52. [PubMed: 22674977]
55. Chandrasekaran A, Srinivasan A, Raman R, et al. Glycan topology determines human adaptation of avian H5N1 virus hemagglutinin. Nat Biotechnol. 2008; 26:107–13. [PubMed: 18176555]
56. Paulsen F, Thale A, Kohla G, et al. Functional anatomy of human lacrimal duct epithelium. Anat Embryol (Berl). 1998; 198:1–12. [PubMed: 9683063]
57. Chentoufi AA, Dasgupta G, Nesburn AB, et al. Nasolacrimal duct closure modulates ocular mucosal and systemic CD4(+) T-cell responses induced following topical ocular or intranasal immunization. Clin Vaccine Immunol. 2010; 17:342–53. [PubMed: 20089796]
58. Yoon S, Kim ED, Song MS, et al. Eyedrop vaccination induced systemic and mucosal immunity against influenza virus in ferrets. PLoS One. 2016; 11:e0157634. [PubMed: 27333331]
59. Seo KY, Han SJ, Cha HR, et al. Eye mucosa: an efficient vaccine delivery route for inducing protective immunity. J Immunol. 2010; 185:3610–19. [PubMed: 20709955]
60. Krauss S, Stucker KM, Schobel SA, et al. Long-term surveillance of H7 influenza viruses in American wild aquatic birds: are the H7N3 influenza viruses in wild birds the precursors of highly pathogenic strains in domestic poultry? Emerg Microbes Infect. 2015; 4:e35. [PubMed: 26954883]
61. Blanchfield K, Kamal RP, Tzeng WP, et al. Recombinant influenza H7 hemagglutinins induce lower neutralizing antibody titers in mice than do seasonal hemagglutinins. Influenza Other Respir Viruses. 2014; 8:628–35. [PubMed: 25213778]
62. Skowronski DM, Li Y, Tweed SA, et al. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. CMAJ. 2007; 176:47–53. [PubMed: 17200390]
63. Meijer A, Bosman A, van de Kamp EE, Wilbrink B, Du Ry van Beest Holle M, Koopmans M. Measurement of antibodies to avian influenza virus A(H7N7) in humans by hemagglutination inhibition test. J Virol Methods. 2006; 132:113–20. [PubMed: 16271401]
64. Eames KT, Webb C, Thomas K, Smith J, Salmon R, Temple JM. Assessing the role of contact tracing in a suspected H7N2 influenza A outbreak in humans in Wales. BMC Infect Dis. 2010; 10:141. [PubMed: 20509927]
65. Pasick J, Handel K, Robinson J, et al. Intersegmental recombination between the haemagglutinin and matrix genes was responsible for the emergence of a highly pathogenic H7N3 avian influenza virus in British Columbia. J Gen Virol. 2005; 86:727–31. [PubMed: 15722533]
66. Lam WY, Yeung AC, Chan PK. Apoptosis, cytokine and chemokine induction by non-structural 1 (NS1) proteins encoded by different influenza subtypes. Virol J. 2011; 8:554. [PubMed: 22185562]
67. Belser JA, Zeng H, Katz JM, Tumpey TM. Infection with highly pathogenic H7 influenza viruses results in an attenuated proinflammatory cytokine and chemokine response early after infection. J Infect Dis. 2011; 203:40–48. [PubMed: 21148495]
68. Josset L, Zeng H, Kelly SM, Tumpey TM, Katze MG. Transcriptomic characterization of the novel avian-origin influenza A (H7N9) virus: specific host response and responses intermediate between avian (H5N1 and H7N7) and human (H3N2) viruses and implications for treatment options. mBio. 2014; 5:e01102–13. [PubMed: 24496798]
69. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. Lancet Infect Dis. 2007; 7:257–65. [PubMed: 17376383]
70. CDC. Interim guidance for protection of persons involved in US avian influenza outbreak disease control and eradication activities. Atlanta, GA: Centers for Disease Control and Prevention; 2004. http://www.yolocounty.org/home/showdocument?id=288 (accessed Feb 7, 2018).
71. IOM. Preventing transmission of pandemic influenza and other viral respiratory diseases. Washington, DC: National Academy of Sciences; 2011.
72. CDC. Prevention treatment of avian influenza A viruses in people. Atlanta, GA: Centers for Disease Control and Prevention; 2017. https://www.cdc.gov/flu/avianflu/prevention.htm (accessed Feb 7, 2018).

73. CDC. Interim guidance for infection control within healthcare settings when caring for confirmed cases, probable cases, and cases under investigation for infection with novel influenza A viruses associated with severe disease. Atlanta, GA: Centers for Disease Control and Prevention; 2016. https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm (accessed Feb 7, 2018).

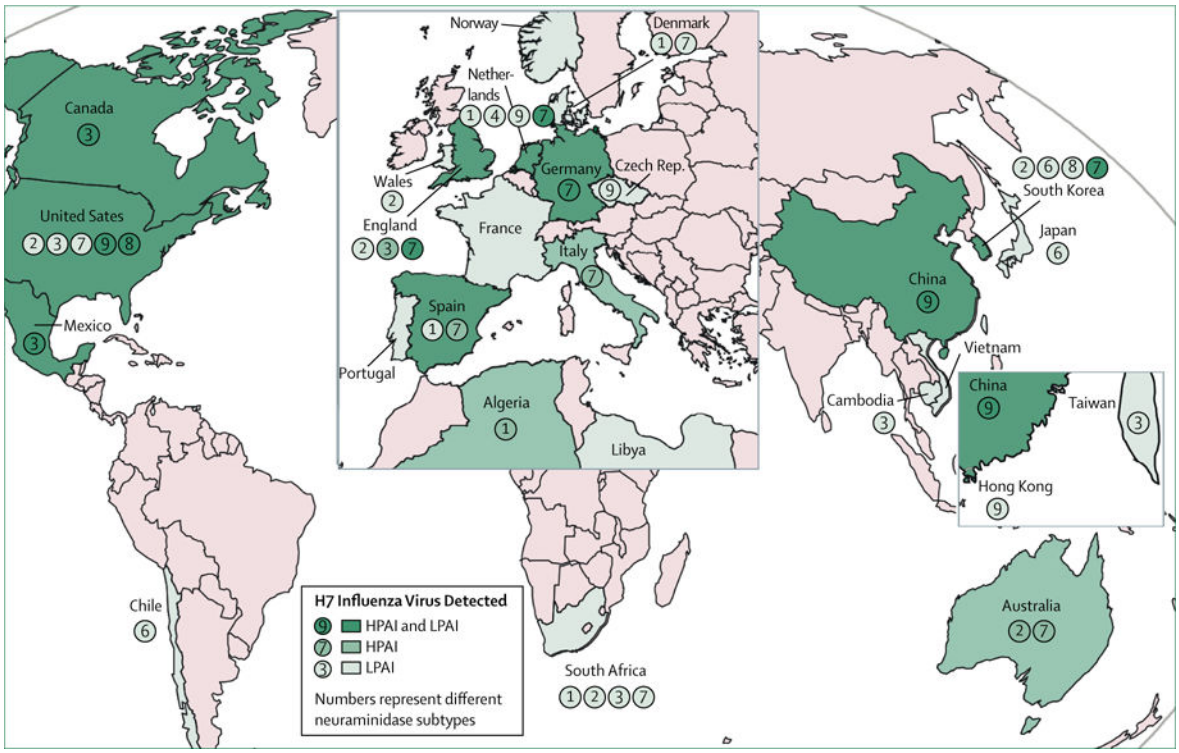

Figure. Detection of H7 subtype influenza viruses in avian species

Outbreaks of H7 subtype highly pathogenic avian influenza (HPAI) and low pathogenic avian influenza (LPAI) in avian species reported to the World Animal Health Information Database and the World Organization for Animal Health since 2005 and 2006, respectively; detailed outbreak reports can be located from these sources. Neuraminidase subtype paired with H7 haemagglutinin is shown. Norway, Portugal, Vietnam, and France reported presumed or confirmed H7 subtype outbreaks of low avian pathogenicity in the absence of neuraminidase determination.

Table 1

Documented human infection with H7 influenza virus by year

	IVPI	Subtype*	Country	Number of cases†	Ocular disease‡	Positive eye swab§	Ocular exposure‡	Treatment¶
1976[9]	HPAI	FPV	Australia	1	Yes	Yes	Yes	Phenylephrine/zinc sulphate eye drops
1980[10]	LPAI	H7N7	USA	5	Yes	No	Yes	No
1996[11]	LPAI	H7N7	UK	1	Yes	Yes	Yes	No
2002[12]	LPAI	H7N2	USA	1 (sero)	No	No	No	Not reported
2003[13]	LPAI	H7N2	USA	1	possible	No	Yes	No
2002–03[14]	LPAI	H7N3	Italy	7 (sero)	Yes	No	No	No
2003[15]	HPAI	H7N7	The Netherlands	89	Yes	Yes	Yes	Oseltamivir
2004[16]	LPAI/HPAI	H7N3	Canada	2	Yes	Yes	Yes	Oseltamivir
2006[17]	LPAI	H7N3	UK	1	Yes	Yes	No	Oseltamivir
2007[18,19]	LPAI	H7N2	UK	4	Yes	No	No	Oseltamivir
2012[20]	HPAI	H7N3	Mexico	2	Yes	Yes	No	No
2013[21,22]	HPAI	H7N7	Italy	5 (2 sero)	Yes	Yes	No	No
2013–present[23,24]	LPAI	H7N9	East Asia	>1600	No	No	No	Oseltamivir
2016[25]	LPAI	H7N2	USA	1	No	No	No	No

IVPI=intravenous pathogenicity index. HPAI=highly pathogenic avian influenza. FPV=fowl plague virus. LPAI=low pathogenic avian influenza.

*Virus subtype associated with human infection.

†Number of human cases by virological or serological diagnostics (sero indicates that human cases were identified by serological evidence only in the absence of virological confirmation).

‡Ocular disease (typically reported as conjunctivitis) or ocular exposure reported among confirmed cases.

§Yes, detection of influenza virus from an eye/conjunctival swab. No, no solo eye swabs were reported, collected, or tested, as indicated in the reference.

¶When reported, use of pre-exposure or post-exposure pharmacological treatment among individuals with potential or confirmed exposure to virus.

Table 2

Documented ocular complications concurrent with non-H7 influenza virus infection in human beings by subtype

	Population	Clinical presentation	Demographic	Proportion*
A H1N1 pdm09[26]	Laboratory-confirmed cases in the UK	Conjunctivitis	Children Adults	25/149 (16·8%) 12/155 (7·7%)
A H1N1 pdm09[27]	Laboratory-confirmed cases in the USA	Conjunctivitis	Pregnant women Non-pregnant people	3/34 (9%) 81/730 (11%)
A H1N1 pdm09[28]	Hospitalised cases in the USA	Conjunctivitis	Children Adults	1/86 (1%) 4/169 (2%)
A H1N1 pdm09[29]	Hospitalised children, South Korea	Conjunctivitis	Children	6/777 (0·8%)
A H1N1 pdm09[30]	Laboratory-confirmed cases, Cyprus	Conjunctivitis	Children	3/45 (7%)
A H1N1 pdm09[31]	Military cadets with confirmed infection	Conjunctivitis	Young adults (17–24 years)	6/86 (7%)
A H1N1 pdm09[32]	Laboratory-confirmed cases, Egypt	Conjunctivitis	Not specified	58/89 (65%): 81% of which were bilateral
seasonal A H1N1, A H3N2, B[33]	Military personnel with febrile respiratory illness, Singapore	Sore eyes/eye pain	Adults	>30% among 821
A H3N2 variant[24]	Laboratory-confirmed cases in the USA, 2012	Eye irritation/redness	Not specified	57/243 (23%)
A H5N1[34]	Hospitalised cases in Egypt, 2006–07	Conjunctivitis	Not specified	14/38 (37%)
A H5N1[35]	Hospitalised cases in Turkey, 2006	Conjunctivitis	Children (5–15 years)	1/8 (12·5%)
A H10N7[36]	Poultry abattoir workers in Australia, 2010	Conjunctivitis	Adults	2/2 (100%)†

*Number of cases presenting with ocular complications as described among all individuals with confirmed influenza virus infection.

†Nine additional abattoir workers and farm staff members showed signs of conjunctivitis but influenza virus infection was not confirmed by RT-PCR.

Table 3

Frequency of reported ocular complications (conjunctivitis or pink eye) reported within 2 weeks of hospital admittance with a positive influenza test, Influenza Hospitalization Surveillance Network (FluSurv-NET[*]), 2014–15 to 2015–17

	2014–15	2015–16	2016–17
Patients with conjunctivitis[†]	80 (0·45%)[†]	57 (0·65%)[†]	118 (0·70%)[†]
Age group, years			
0–4	22 (27·5%)	30 (52·63%)	13 (11·02%)
5–17	11 (13·75%)	13 (22·81%)	11 (9·32%)
18–49	8 (10%)	3 (5·26%)	16 (13·56%)
50–64	7 (8·75%)	7 (12·28%)	22 (18·64%)
65+	32 (40%)	4 (7·02%)	56 (47·46%)
Influenza type			
A	64 (80%)	44 (77·19%)	91 (77·12%)
B	15 (18·75%)	12 (21·05%)	25 (21·19%)
A/B	1 (1·25%)	1 (1·75%)	2 (1·69%)
A subtype[‡]			
H3N2	28 (43·75%)	3 (6·82%)	58 (63·04%)
H1N1 pdm09	0	19 (43·18%)	1 (1·09%)
Unknown	36 (56·25%)	22 (50·00%)	33 (35·87%)

Data are n (%).

[*] FluSurv-NET previously described.[37]

[†] Percentage of patients with conjunctivitis out of all respondents, n=17 623 (2014–15), n=8780 (2015–16), and n=16 885 (2016–17). Samples represent any influenza virus-positive clinical isolate; ocular samples were not uniformly tested.

[‡] In 2016–17, one case with influenza type “A/B” was subtyped and is thus counted twice in the table.

Table 4

Permissiveness of influenza A virus infection following ocular exposure in ferrets, by subtype

	Liquid ocular inoculation*		Aerosol ocular-only inoculation†	
	Virus	Inf‡	Virus	Inf‡
HPAI A H7N7	A/Netherlands/219/03	3/3	A/Netherlands/219/03	3/3
HPAI A H7N3	A/Canada/504/04	2/3	A/Mexico/7218/12	3/3
LPAI A H7	A/NY/107/03 (H7N2)	3/3	A/Shanghai/1/13 (H7N9)	3/3
HPAI A H5N1	A/Thailand/16/04	3/3	A/Thailand/16/04	3/3
A H1N1	A/Brisbane/59/07	3/3	A/Brisbane/59/07	3/3
A H1N1 pdm09	A/Mexico/4108/09	3/3	A/Mexico/4482/09	3/3
A H3N2	A/Panama/2007/99 (seasonal)	3/3	A/Indiana/8/11 (variant)	3/3

*100 μL of diluted virus deposited onto the surface of the right eye of a sedated ferret. Experimental data previously published.[42]

†Passage of aerosolised virus through close-fitting goggles worn by a sedated ferret in the absence of respiratory exposure. Experimental data previously published.[40,42]

‡Number of infected ferrets/total number of inoculated ferrets, as determined by the presence of infectious virus in nasal wash specimens collected days 1–7 post inoculation.