INFLUENZA VIRUS BACKGROUND

Canine influenza is caused by influenza type A viruses, which are members of the Orthomyxoviridae family. Two of the 11 proteins encoded by these viruses’ single-stranded RNA genome—hemagglutinin (H) and neuraminidase (N)—are commonly used to identify viral subtypes (e.g., H3N2). The hemagglutinin unit is essential for invasion of the host and is host-specific. The neuraminidase unit allows the virus to propagate and release viral progeny. Influenza continues to be a relevant infection because both the H and N units can adapt and mutate through antigenic shift and antigenic drift.

Antigenic shift is recombination of entire H and N genes. This occurs in permissive hosts, such as swine or fowl, that are infected by two strains of influenza simultaneously. The recombination of entire subunits can ultimately lead to the creation of new influenza strains that are then shed by the permissive hosts and may infect new hosts or new species.

Antigenic drift is the result of small mutations within the H or N genes that alter the structure of viral surface proteins. Antigenic drift increases diversity within circulating virus strains, leading to varying levels of pathogenicity. Occasionally, small mutations can lead to a significant alteration in pathogenicity for an influenza strain.

CANINE INFLUENZA STRAINS

An influenza virus that has adapted to allow transmission among dogs is considered a canine influenza virus (CIV). Both H3N8 and H3N2 CIVs are currently active in the United States. A number of other influenza type A viruses have occasionally been found to infect dogs but are not capable of dog-to-dog transmission.

H3N8

In North America, there is evidence that H3N8 jumped from horses to dogs around 1999 (FIGURE 1). Before this time, equine H3N8 had occasionally been found in dogs with direct...
exposure to horses, but a strain of influenza type A capable of dog-to-dog transmission had never been isolated. This jump was possible due to antigenic drift within the H gene. Multiple host-specific factors and defenses make the development of an entirely new strain of influenza that is capable of sustaining infection within a new host species incredibly unusual.

In 2004, the first outbreak of canine influenza A (H3N8) was documented in racing greyhounds in Florida. Samples of respiratory tissue from these dogs used for virus culture confirmed the presence of a type A influenza. Further genetic analysis revealed that the strain isolated from the dogs shared many similarities to the H3N8 equine influenza virus, leading to the

---

**FIGURE 1.** Important events in the natural history of CIV in the United States.

Prior to 1999
No documented canine-adapted influenza virus

2004
First H3N8 outbreak in racing greyhounds documented in Florida

2004–2006
Multiple outbreaks at greyhound racing tracks

2006
H3N8 documented in the pet population

2009
Monovalent H3N8 vaccine becomes available
Single case of H1N1 documented in New York, NY

2015
Outbreak of H3N2 in Chicago, IL, and then Atlanta, GA

2015
Monovalent H3N2 vaccine becomes available

2016
Bivalent H3N2/ H3N8 vaccine becomes available

2018
H3N2 found in 34 states and H3N8 found in 43 states

---

**FIGURE 2.** Genetic analysis of influenza viral RNA isolated from infected dogs during the initial influenza outbreak showed that the virus shared >96% of genes with equine-adapted H3N8. Before this time, dogs with direct contact with horses could become infected with H3N8, but there was no sustained transmission from dog to dog. Through antigenic drift, the H3N8 influenza virus gained the ability to not only infect dogs but also spread from dog to dog.
conclusion that the virus had jumped from horses to dogs as depicted in FIGURE 2.

From 2004 to 2006, there were additional disease outbreaks at 14 racetracks in 6 states across the United States. The H3N8 virus was subsequently reported in shelter dogs, proving that it was able to infect non-greyhound dogs. H3N8 spread slowly through the canine population and has now been documented in more than 40 states (FIGURE 3).

H3N2
In 2007, H3N2 was isolated from a dog in South Korea with respiratory signs and was determined to be of avian origin. This H3N2 strain was experimentally shown to infect research dogs. Several cases of H3N2 were then reported throughout China and shown to be closely related to the avian influenza viruses isolated from dogs in South Korea.

In 2015, the first outbreak of H3N2 in dogs in the United States was reported in Chicago, Illinois. Shortly thereafter, another outbreak was reported in Atlanta, Georgia. A serologic study performed in the summer of 2015 looked at 452 dogs from 13 states and found seroconversion for H3N2 to be low (2.21%), with all positive dogs coming from Indiana and Illinois. This finding suggests that in 2015, H3N2 exposure was low in certain geographic locations, and a large portion of the U.S. canine population would likely be highly susceptible to infection.

Since 2015, H3N2 has been reported sporadically from more than 30 states. Genetic analysis of material isolated from infected dogs indicates that subsequent reintroductions of H3N2 from Asia have contributed to additional U.S. outbreaks. Most U.S. CIV outbreaks in recent years have been due to H3N2.

H5N2
In 2009, H5N2 was isolated from a dog with respiratory signs in China. This strain was proven to spread among dogs housed together and through experimental inoculation of healthy dogs. The clinical signs of illness were mild, and no fatalities were associated with the infection. To date, this strain of influenza has not been reported in the United States.

OTHER INFLUENZA TYPE A VIRUSES
Several other influenza viruses may infect dogs and cause clinical signs, but they have not been demonstrated to spread among dogs. Awareness of these agents is important to understand the multispecies nature, and adaptive potential, of influenza A viruses.

H1N1, colloquially known as “the swine flu,” caused a pandemic in humans from 2009 to 2010. In 2009, H1N1 was detected in a dog with respiratory signs in New York; this dog had apparently contracted the disease from its owner. A recent serologic study in Ohio showed that 4% of dogs in a convenience sample of 1082 dogs showed seroconversion to H1N1, presumed to be due to exposure to humans with this infection.

H5N1 is a highly pathogenic avian influenza strain that has been shown to infect dogs exposed to infected poultry in high-density housing conditions. Equine H3N8 (not the dog-adapted version) has also been known to sporadically infect dogs.

CANINE INFLUENZA
Currently, the term CIV is used for dog-adapted strains of H3N8 and H3N2. Although CIV has continued to spread throughout the United States since 2004, canine influenza is still a relatively novel infectious disease in the canine population (BOX 1). Species with high exposure to endemic influenza viruses (humans, birds, and pigs) have a certain level of background immunity that provides a degree of protection against similar strains encountered in the future; however, most dogs
BOX 1 Canine Influenza Outbreaks

CIV was expected to spread rapidly across the United States as a pandemic. In the 15 years since its emergence, there have been regional outbreaks of the disease, but overall its spread has been more sporadic than initially anticipated. Some investigators use the term “popcorn outbreaks” because the disease appears suddenly and spreads rapidly throughout a focal community or region. The rate of diagnosis of new cases declines in a matter of months, presumably as the community is exposed to CIV and develops resistance. The infection then emerges suddenly—resumably as the community is exposed to CIV and through a focal community or region. The rate of diagnosis of new cases declines in a matter of months, presumably as the community is exposed to CIV and develops resistance. The infection then emerges suddenly, presumably as the community is exposed to CIV and develops resistance. The infection then emerges suddenly, presumably as the community is exposed to CIV and develops resistance.

In the United States, the CIV morbidity—that is, the number of dogs that become infected and show clinical signs—has been reported as high as 80% in naive canine populations. In initial outbreaks of H3N8, mortality within the greyhound population reached 36%. Fortunately, CIV has proven to be less lethal, and mortality in the general population of dogs is generally estimated to be 1% to 5%. Based on these values, most dogs will become infected when exposed to the virus but only a very small percentage will die of the disease. There was no difference in the clinical signs or case fatality rate (3%) of dogs infected in the 2015 Atlanta H3N2 outbreak compared with previous H3N8 outbreaks.13

Transmission

Like other influenza A viruses, CIV is spread through respiratory secretions, respiratory aerosols, and fomites. A 2- to 3-day incubation period follows infection, during which virus replication and viral shedding are high. At the end of the incubation period, most exposed dogs develop clinical signs and viral shedding begins to rapidly decline.

Dogs infected with H3N8 CIV continue to shed the virus for approximately 7 to 10 days after infection. Viral shedding of H3N2 CIV in nasal secretions was documented in a group of infected shelter dogs in Chicago for more than 21 days after infection.14 It is important to note that dogs infected with CIV shed virus before developing clinical signs and can continue to shed virus after clinical signs have resolved, which can continue for more than 3 weeks for H3N2.

Clinical Signs

Dogs clinically affected with CIV have signs of an upper respiratory infection, such as sneezing, serous to mucopurulent nasal discharge, and cough. They may also have evidence of systemic illness, such as fever, lethargy, and decreased appetite. Clinical signs of CIV infection are essentially indistinguishable from those of other pathogens that cause canine infectious respiratory disease (CIRD), and therefore diagnosis based on history and clinical signs alone is not possible. Due to the lack of natural immunity, CIV typically spreads more rapidly than other CIRD pathogens in a population of naive dogs. Dogs with CIV or any other cause of CIRD also commonly have a suspicious exposure history, such as being at a boarding facility, kennel, dog show, or shelter. In severe cases, an initial infection with CIV can lead to the development of pneumonia, likely secondary to compromised airway defenses allowing bacterial colonization.

A severe, peracute form of illness was reported in the initial CIV outbreak affecting racing greyhounds; this form may have been due to co-infection or some risk factor within the greyhound population resulting in more severe disease. It resulted in severe pulmonary, pleural, and mediastinal hemorrhage and death.2 This disease manifestation is not common in the pet population.

Diagnosis

Multiple diagnostic laboratories offer either serology or polymerase chain reaction (PCR) testing for canine influenza. The preferred clinical diagnostic test for acute disease is influenza PCR, using an assay that has demonstrated detection of both H3N8 and H3N2 subtypes. Testing should be done as soon as possible in the course of disease, when viral shedding is at its peak. Because of the delay from infection to clinical signs, it is recommended to perform PCR within the first 4 to 5 days of clinical illness, since by this time the animal has likely been infected anywhere from 6 to 8 days, particularly for H3N8 CIV. If samples are collected later in the course of disease when viral shedding is declining, the risk of a false-negative result increases.
PCR may be of use in detecting H3N2 later in the course of disease due to its prolonged shedding period.

Ideal specimens for PCR are obtained from deep nasal or pharyngeal swabs. To increase diagnostic sensitivity, specimens from multiple sites, including both nostrils and the oropharynx, should be collected and pooled. Use of a sterile sampling swab with a plastic handle is recommended for specimen collection. The specimen should then be placed into a sterile tube, refrigerated, and shipped overnight on ice to the diagnostic laboratory according to the laboratory’s specific collection and handling instructions. Some labs request dry samples and others request samples sent with sterile saline. Improperly storing or shipping the specimen will significantly decrease diagnostic yield.

Serology can be performed in combination with PCR if the patient has been ill longer than 5 days and/or a false-negative PCR result is suspected. Both acute and convalescent CIV titers are needed to confirm diagnosis of canine influenza. When CIV was first described, any positive serology result was consistent with infection. Now that CIV is present in most states and some dogs have been vaccinated, a single positive serology result is no longer sufficient for diagnosis. If infection is suspected, serology samples should be collected at initial examination and convalescent CIV titers measured 2 to 3 weeks later. Infection is confirmed by a fourfold increase in convalescent influenza titers. For example, a dog that has been vaccinated for CIV and is infected with a different CIRD pathogen should have a positive acute CIV titer but should exhibit a minimal or zero increase in CIV titer at the 2- to 3-week recheck. It should also be noted that serologic detection of antibodies against H3N8 does not distinguish between the equine and canine-adapted influenza subtypes.

**Treatment**

There is no definitive or specific treatment for canine influenza. As with all CIRD infections, most CIV infections are self-limiting and resolve over several weeks (“uncomplicated” CIRD). Treatment revolves around supportive care. Dogs with any respiratory illness should be rested, provided optimal nutrition, and kept well hydrated, clean, dry, and warm.

A subset of patients will develop clinical signs or radiographic evidence of pneumonia (“complicated” CIRD). These patients may require more aggressive therapy, including antibiotic therapy, intravenous fluids, supplemental oxygen or nebulization, and decoupage. Ideally, tracheal wash or bronchoalveolar lavage should be performed for aerobic and anaerobic culture to guide appropriate antibiotic choice. If this is not possible, empirical broad-spectrum antibiotic therapy is recommended for these patients. Cough suppressants should not be used in patients with a productive cough or evidence of pneumonia.

To decrease the risk of creating antimicrobial resistance, current guidelines encourage clinicians to be conscientious when prescribing antibiotics when a bacterial infection is not confirmed.

To decrease the risk of creating antimicrobial resistance, current guidelines encourage clinicians to be conscientious when prescribing antibiotics when a bacterial infection is not confirmed. A recent review recommended that antibiotics be considered for suspected cases of CIRD only when evidence of a bacterial component is present, such as a patient presenting with lethargy, inappetence, and fever in combination with mucopurulent discharge or evidence of bronchopneumonia. In the absence of bacterial pneumonia, prophylactic antibiotics may be unnecessary, even for geriatric, young, or immunocompromised patients.

There is often a question as to whether antiviral therapy is beneficial in the treatment of canine influenza. Antiviral medications used in human medicine, such as oseltamivir, block the release of viral progeny from infected cells. Thus, they would theoretically be most effective early in the course of CIV infection, when a reduction in viral burden still be possible. This window has often passed by the time dogs present to a veterinarian and infection is confirmed. Additionally, in most patients, canine influenza is self-limiting and there is no evidence that antiviral therapy is effective or improves outcome.
Further, antivirals, like antibiotics, can induce resistance in viral strains. Appropriate antiviral stewardship is needed to prevent the emergence of resistant influenza strains.

Dogs that are frequently boarded, compete in sporting events, frequent dog parks or dog shows, or are in a shelter/kennel environment have higher risk of coming into contact with dogs infected with CIV and should be vaccinated.

Prevention
In 2009, a killed, adjuvant, monovalent vaccine for H3N8 CIV was approved for use in dogs. A vaccine for H3N2 CIV became available in 2015. In 2016, a bivalent vaccine was produced containing both H3N2 and H3N8 CIV. Multiple formulations now exist on the market.

The CIV vaccine is considered a non-core vaccination according to the 2017 AAHA canine vaccination guidelines. Vaccination against CIV is recommended for patients with lifestyles that may increase their risk of exposure or factors that may increase their risk of a more severe illness if infected. Dogs that are frequently boarded, compete in sporting events, frequent dog parks or dog shows, or are in a shelter/kennel environment have higher risk of coming into contact with dogs infected with CIV and should be vaccinated. Dogs with risk factors that justify the use of non-core Bordetella bronchiseptica or parainfluenza vaccine should also be vaccinated against CIV. Due to the prevalence of both strains in the United States and the unpredictable nature of CIV outbreaks, the authors believe that dogs at risk of exposure should be vaccinated against both H3N2 and H3N8.

Information about the field efficacy of CIV vaccines is limited. Based on experimental studies, vaccination against H3N8 did not prevent disease in all vaccinated dogs but did significantly decrease the severity of infection, viral load, and viral shedding. The H3N8 vaccine has been shown to provide protection against multiple H3N8 isolates. Vaccinated dogs that were exposed to H3N8 and co-infected with Streptococcus zooepidemicus, a member of the CIRD complex, exhibited milder clinical signs for a shorter duration than dogs that were unvaccinated. While additional research is needed to fully understand the field efficacy of CIV vaccines, it is recommended to vaccinate dogs at risk of exposure or dogs at risk of severe complications if infected.

Infection Control
Quick detection of potential cases of canine influenza is imperative in preventing an outbreak within a facility. Patients that present with clinical signs consistent with canine influenza and a compatible exposure history should be treated as though they could be highly infectious. It is important to minimize exposure of other animals by keeping possible cases of canine influenza isolated. Given that CIV is a respiratory pathogen and is spread through respiratory secretions, aerosols, and fomites, suspected cases should be physically separated from other animals in an enclosed room.

All dogs with suspected CIV infection should be tested. If a patient tests positive, it is important that appropriate precautions are taken within the clinic or shelter to help prevent spread of infection. Positive test results also need to be communicated to owners, who should be urged to isolate their pets until clinical signs are fully resolved and the shedding period has passed. Patients exposed to infection should also remain quarantined until the incubation period has passed, or until they develop and recover from clinical signs and the shedding period has passed.

Proper cleaning and decontamination are necessary to prevent spread of the virus. The influenza virus is easily killed with quaternary ammonium compounds, accelerated hydrogen peroxide compounds, and bleach. Contaminated areas should be thoroughly cleaned and disinfected before healthy animals are reintroduced. Veterinarians, veterinary nurses, and owners who are in contact with an infected animal need to be careful to ensure that they do not act as fomites by spreading the virus to other animals on their hands, gloves, or clothing.
PUBLIC HEALTH

At this time, there are no reports of transmission of canine H3N2 or H3N8 from dogs to humans. A study from China recently reported that co-infection with H1N1 and H3N2 resulted in recombination of the viruses in dogs, leading to the creation of new recombinant strains. This finding sparked concern that dogs carrying these new strains of influenza could pose a zoonotic risk to humans. These concerns have not yet become reality.

The influenza virus is constantly changing and adapting, and it will continue to be important to identify new and emerging strains. As CIV continues to spread within the canine population, increased awareness, vaccination, public health considerations, and surveillance are necessary to keep clients and pets safe. TVP

References


Amber Graham

Dr. Graham received her DVM from the University of Missouri in 2017. She then completed an internal medicine focused small animal rotating internship at North Carolina State University. She is currently pursuing a residency in small animal internal medicine at Texas A&M University. Her research interests include small animal respiratory disease, endocrinology, and hepatobiliary disease.

Kate E. Creevy

Dr. Crevey received her DVM from the University of Tennessee and completed a small animal rotating internship at the University of Minnesota. She spent several years in emergency practice before completing her small animal internal medicine residency and master’s degree in infectious disease at the University of Georgia. After 10 years on UGA’s faculty, in 2016 she joined Texas A&M University’s College of Veterinary Medicine as an associate professor in small animal internal medicine. Dr. Crevey’s research interests include healthy aging in companion dogs, infectious disease, and a pedagogical interest in the development of lifelong learning skills among veterinary students.

PEER REVIEWED • CONTINUING EDUCATION
Canine Influenza: New Strains and Treatment

LEARNING OBJECTIVES
After completing this article, readers should be able to recognize the clinical signs of canine influenza virus infection, select appropriate diagnostic tests, and confidently develop a therapeutic plan. They should also understand when to recommend vaccination for canine influenza and be ready to deploy strategies to prevent spread of disease if a suspected case presents to their practice.

TOPIC OVERVIEW
This article details the natural history of canine influenza in the United States and describes the clinical signs, diagnosis, treatment, and prevention of canine influenza infection.

1. Which most accurately describes the current prevalence of CIV in the United States?
   a. Widespread reports of H3N8
   b. Scattered reports of H3N2
   c. Regionally scattered reports of H3N8 and H3N2
   d. Widespread H3N2 and H3N8 as well as emerging H1N1 and H5N2

2. Canine influenza clinically resembles other forms of canine infectious respiratory disease (CIRD). Which of the following findings most strongly suggests CIV as the cause of an outbreak of CIRD?
   a. Clinical signs in most exposed healthy adult dogs
   b. Tendency to preferentially infect puppies
   c. Marked tracheal sensitivity on physical examination
   d. Simultaneous disease in people in the household

3. Regarding the course of canine influenza, which of the following is true?
   a. While the disease is highly contagious, most healthy adult dogs recover with supportive care alone.
   b. Because the disease is highly contagious, most healthy adult dogs that are exposed will become critically ill.
   c. Healthy puppies frequently exhibit a self-limiting course of disease, while adult dogs are slower to “bounce back” from illness.
   d. Most dogs develop hemorrhagic pneumonia, which can be fatal.

4. Which of the following statements is true regarding viral shedding in dogs infected with CIV?
   a. Dogs are only shedding virus and therefore infectious while they are showing clinical signs.
   b. Viral shedding is highest early in disease and ends before clinical signs are present.
   c. Dogs infected with H3N2 have been shown to shed virus for over 3 weeks following infection.
   d. CIV infection can become latent, and dogs may continue to spread virus in the future during times of stress.

5. Diagnosis of canine influenza virus infection is almost always accomplished by_____
   a. identification of the agent on culture and sensitivity panel.
   b. identification of pathognomonic history and clinical signs.
   c. identification of one of the causative viruses by PCR.
   d. identification of rising serologic titers to one of the causative agents over the 3- to 4-week period of clinical disease and recovery.

6. Which of the following samples is suitable for CIV PCR submission?
   a. Deep nasal pharyngeal swab placed into bacterial transport medium
   b. Collection of nasal secretions placed into a sterile tube and overnighted on ice
   c. Deep nasal and pharyngeal swabs placed into a sterile tube and overnighted to the laboratory on ice
   d. Deep nasal and pharyngeal swabs collected and mailed to the laboratory without refrigeration.
7. Which of the following correctly describes available CIV vaccines?
   a. Commercially available intranasal CIV vaccines are more likely to be effective in the face of an outbreak than subcutaneous CIV vaccines.
   b. Choices include monovalent vaccines (containing either H3N8 or H3N2) and bivalent vaccines (containing both).
   c. There is a modified live intranasal and a killed injectable preparation, and either form may contain more than one agent.
   d. H3N2 vaccine is given intranasally while H3N8 vaccine is given subcutaneously.

8. Which of the following is true regarding spread of CIV to humans?
   a. Influenza viruses are frequently passed from owners to pets and vice versa.
   b. There have been scattered reports of H3N2 infecting young children who have come into contact with infected dogs.
   c. It is impossible for an influenza virus to infect more than one species.
   d. There have been no documented cases of spread of canine influenza from a dog to a human.

9. CIV is an enveloped RNA virus that is easily disinfected with bleach or quaternary ammonia compounds.
   True or False

10. What is the first and most important step in preventing an outbreak of CIV in a practice, boarding facility, or shelter?
    a. Widespread vaccination
    b. Disease recognition and isolation of suspected infected patients
    c. Testing all patients with respiratory illness for CIV
    d. Regular cleaning of common areas