

# Canine Infectious Respiratory Disease: The Flu or Not The Flu?

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## Introduction

Canine infectious respiratory tract disease (CIRD) remains a major problem in shelter and boarding kennel environments, despite widespread vaccination against the disease. As a result of improvements in diagnostic testing, there is increasing awareness of the multiplicity of infections that occur in affected animals. In environments such as shelters, co-infections may be more common than infections with a single pathogen. In addition, several pathogens have emerged in recent years as important contributors to CIRD in kennel and shelter situations. The purpose of this talk is to discuss emerging causes of infectious respiratory disease in dogs, including the perils and pitfalls of diagnosis of these infections.

Ironically, pathogens causing CIRD can actually HELP each other infect the host. For example, canine distemper virus is a highly lymphocytolytic virus – it causes profound immunosuppression, which predisposes dogs to infection with other respiratory viruses and bacteria. *Bordetella bronchiseptica* causes ciliostasis and impairs phagocytosis, so it can also predispose to other bacterial infections and respiratory viral infections. Pathogens may act synergistically to cause disease, and severe disease is more likely to be associated with co-infections. Single infections may be present in some asymptomatic animals. Similar findings have been reported in children with community acquired pneumonia.

## Differential Diagnosis

Understanding the differential diagnosis for CIRD is important because it helps you to select appropriate diagnostic tests, understand rational therapy, and institute proper preventative measures for CIRD. There are now at least 9 organisms known to play a role in canine infectious respiratory disease.

Bacterial causes of canine infectious respiratory disease include:

*Bordetella bronchiseptica*  
*Streptococcus equi* subspecies *zooepidemicus*  
*Mycoplasma* spp.

Viral causes of canine infectious respiratory disease include:

Canine influenza virus  
Canine distemper virus  
Canine respiratory coronavirus  
Canine parainfluenza virus  
Canine adenovirus, especially canine adenovirus-2  
Canine herpesvirus

Establishment of a diagnosis may not be necessary in dogs that are otherwise healthy but just have the characteristic honking cough of the kennel cough syndrome. The vast majority of these dogs will have self-limiting infections, with clinical signs generally resolving within 5-7 days without antimicrobial therapy. Some dogs may need a short course of antimicrobial therapy.

Diagnostic testing is indicated if

- An outbreak has occurred.
- Affected dogs are systemically unwell.
- The cough is persisting despite treatment.

Establishment of a diagnosis can help with proper control and prevention in kennel situations, and appropriate antimicrobial therapy for dogs with bacterial infections, eg. *Bordetella bronchiseptica* infections. Some *B. bronchiseptica* infections can be refractory to therapy. Therapy with nebulized gentamicin may be indicated following documentation of persistent bordetellosis.

### **Making a Diagnosis**

None of the infections listed can be diagnosed based on clinical signs because the signs are overlapping and non-specific. Diagnostic tests available for diagnosis of canine infectious respiratory disease include culture for bacteria and mycoplasmas, serologic tests for antibody against canine influenza virus and canine distemper virus, and polymerase chain reaction (PCR) testing for the presence of DNA and RNA of respiratory viruses and bacteria. Virus isolation is cumbersome and is mostly done on a research basis now. Sometimes a diagnosis is best obtained by combining multiple different diagnostic modalities.

Culture remains a useful test for bacteria such as *Bordetella bronchiseptica* and mycoplasmas, although the growth of mycoplasmas can be slow. It is essential for *Streptococcus equi* subspecies *zooepidemicus* infections as PCR assays are not generally available for that pathogen. It also allows sensitivity testing of *B. bronchiseptica*, as some strains may demonstrate antimicrobial resistance.

Serologic tests are plagued by confounding as a result of prior vaccination, which can help to reduce the severity of disease but does not prevent infection, so just because a dog has been previously vaccinated, it does not rule out the presence of infection. Currently serology is useful for diagnosis of canine influenza virus infection in populations of dogs residing in non-endemic areas.

The commercial availability of PCR assays for veterinary use is becoming more widespread, along with increased quality assurance. Laboratories usually offer 1 of 2 basic types of PCR assays: either conventional PCR assays or real-time PCR assays. Real-time PCR assays are preferable for diagnostic purposes because they have reduced false positives associated with laboratory contamination, although it is still important that laboratories include appropriate positive and negative controls with each run. Many respiratory viruses are RNA viruses (eg. canine distemper virus, canine influenza virus, canine parainfluenza virus, canine respiratory coronavirus). Thus, PCR assays for these organisms must detect RNA rather than DNA, using a

process known as RT (reverse transcriptase) PCR. RNA is much more labile than DNA, and so can be easily degraded during sample transport and storage. This can lead to false negative results using PCR. It is important to check with the laboratory regarding the best method for sample collection and transport to optimize the detection of canine infectious respiratory pathogens, depending on the organisms of interest. Many laboratories now offer canine respiratory disease *panels*. This has led to increased detection of canine infectious respiratory pathogens and an increasing awareness of co-infections.

The results of a typical respiratory PCR panel might be reported as follows:

<u>'Polly Waffle' 7 year old FS Labrador Retriever</u>	
<i>Bordetella</i>	POSITIVE
Canine adenovirus type 2	NEGATIVE
Canine distemper virus	POSITIVE
Canine herpesvirus	NEGATIVE
Canine parainfluenza virus	POSITIVE
Canine influenza virus	NEGATIVE
Canine respiratory coronavirus	POSITIVE

### **Emerging and Re-emerging Respiratory Pathogens of Dogs**

#### *Bordetella bronchiseptica*

*Bordetella bronchiseptica* is an aerobic, Gram negative coccobacillus. It is the most common bacterial agent causing CIRDC, and tends to cause moderate signs of CIRDC. Infection is best diagnosed via transtracheal washing or bronchoalveolar lavage, but occasionally throat swabs or nasal washings/swabs will be positive. Both culture and PCR assays are available for detection of *Bordetella bronchiseptica*. Parenteral and intranasal vaccines can help to prevent bordetellosis.

#### *Streptococcus equi* subspecies *zooepidemicus*

*Streptococcus equi* subspecies *zooepidemicus* is a beta-hemolytic streptococcus that has caused outbreaks of acute suppurative or necrotizing hemorrhagic pneumonia in shelter situations. It is the most common beta-hemolytic streptococcus found in kennel dogs, the other one being *Streptococcus canis*. *S. canis* can be found in the lungs of both healthy dogs and dogs with kennel cough, whereas *S. equi* is rarely found in healthy dogs. The chance of isolating the organism in one study increased with increasing severity of disease, from 10% through to 87%. Whether it acts as a primary pathogen or secondary invader is not clear, but in a recent outbreak from California, the consistent presence of co-infection was not documented. It is rarely isolated from household pets.

#### *Mycoplasma* spp.

Mycoplasmas are considered normal flora in the respiratory tract of dogs, but are occasionally isolated from the lower respiratory tract of dogs without evidence of coinfection. The primary mycoplasma associated with lower respiratory disease in dogs may be *Mycoplasma cynos*. In the UK, *M. cynos* has been associated with significant bronchopneumonia in puppies, and *M. cynos* has been used to experimentally recreate lower respiratory disease in dogs. *M.*

*cynos* has been associated with moderate respiratory disease in kennel dogs in the United Kingdom. Other mycoplasmas that have been isolated from the respiratory tract of dogs include *M bovis genitalium*, *M canis*, *M edwardii*, *M feliminutum*, *M gateae* and *M spumans*, but these have not been definitively associated with lower respiratory disease. Detection of mycoplasmas can be performed using culture, although growth requires special media and sometimes incubation for longer than a week. Molecular techniques have improved our ability to detect mycoplasmas, but we still have the problem of knowing whether a positive result is associated with disease.

### Canine influenza virus

Canine influenza virus emerged in the United States from Florida as a result of a mutation of equine influenza virus H3N8, and has spread to dog populations across the United States. The infection has also been identified in England and Australia, although dog-to-dog transmission in those countries has not been demonstrated. Dogs of any age and health status are susceptible, and there is no seasonal pattern of occurrence. Major outbreaks have occurred in Florida, Denver, and the northeastern States, including New York, Pennsylvania and New Jersey. The virus causes fever, coughing, and a hemorrhagic pneumonia after an incubation period of 2 to 4 days, but has a low mortality rate. Secondary bacterial infections are common. Shedding of canine influenza virus in nasal swabs occurs early in the course of infection (days 1-7 post challenge, occasionally up to day 10), whereas clinical signs (sneezing, coughing and depression) tend to occur later (days 3 to 12). Some dogs may shed subclinically. In nonendemic areas, diagnosis in the clinical setting may be achieved via PCR on BAL samples or nasal or throat swabs, combined with the use of acute and convalescent phase serology, provided the animal does not have a history of previous vaccination. Point of care ELISA tests for human influenza virus can also be used to detect canine influenza virus in dogs having clinical signs for < 4 days, although the sensitivity is lower than for human influenza virus. A killed vaccine is now available under one-year conditional licensure for this infection (Intervet Schering Plough Animal Health), and may be useful to help prevent disease and shedding in dogs at risk of infection.

### Canine respiratory coronavirus.

Canine respiratory coronavirus is an RNA virus that represents another emerging cause of respiratory disease in dogs worldwide. It has similarity to bovine coronavirus but is distinct from canine enteric coronavirus. Its presence tends to correlate with mild disease, but it has been detected in outbreaks of severe respiratory tract disease. Infection with canine respiratory coronavirus may predispose to other bacterial and viral infections, but may also potentially be a primary pathogen. It can be detected using RT-PCR on transtracheal or bronchoalveolar lavage specimens, or throat swabs.

### Canine distemper virus

Canine distemper virus is another important cause of kennel cough. Many dogs with distemper lack neurologic or gastrointestinal signs. It is probably vastly undiagnosed as a cause of kennel cough in dogs. Canine distemper virus is an RNA virus that can be detected using RT-PCR on respiratory specimens. It can also be detected using PCR on whole blood or conjunctival scrapings. Fluorescent antibody can be applied to conjunctival scrapings, both false positives and false negatives may occur using this method.

### Other pathogens

Canine parainfluenza virus remains the number 1 viral cause of CIRDC in dogs, and intranasal and parenteral non-core vaccines are available and in widespread use for prevention of infection. Other viral pathogens include canine adenovirus (for which vaccination is available and used as a core vaccine for prevention of infectious canine hepatitis), and canine herpesvirus. The significance of canine herpesvirus as a cause of CIRDC is not well understood, but it has recently been documented as a potential cause of ocular disease in dogs.

### **Summary**

In conclusion, an increasing number of pathogens have been recognized as causes of CIRDC in dogs, and co-infections with multiple pathogens are commonly present. Diagnostic testing is indicated in outbreak situations, in dogs with severe illness, or when clinical signs are persistent or fail to respond to initial medical therapy. It is important not to overlook the possibility of coinfections, which may contribute to severe disease or result in a failure to respond as expected to therapy. Prevention is assisted by proper attention to hygiene and quarantine, minimizing overcrowding within kennels and shelters, and use of vaccines for CIRDC based on risk of exposure to each disease.