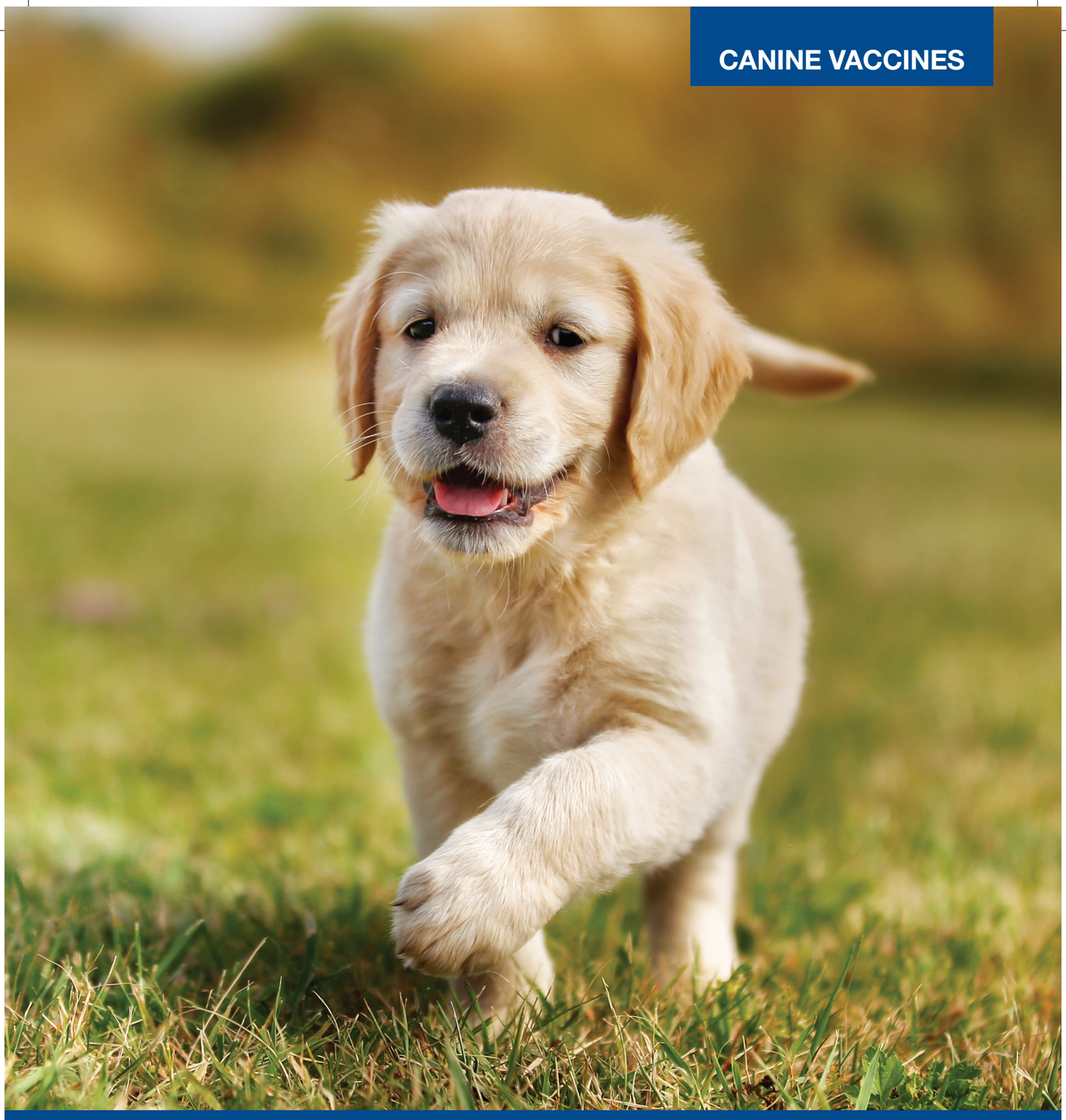
CANINE VACCINES



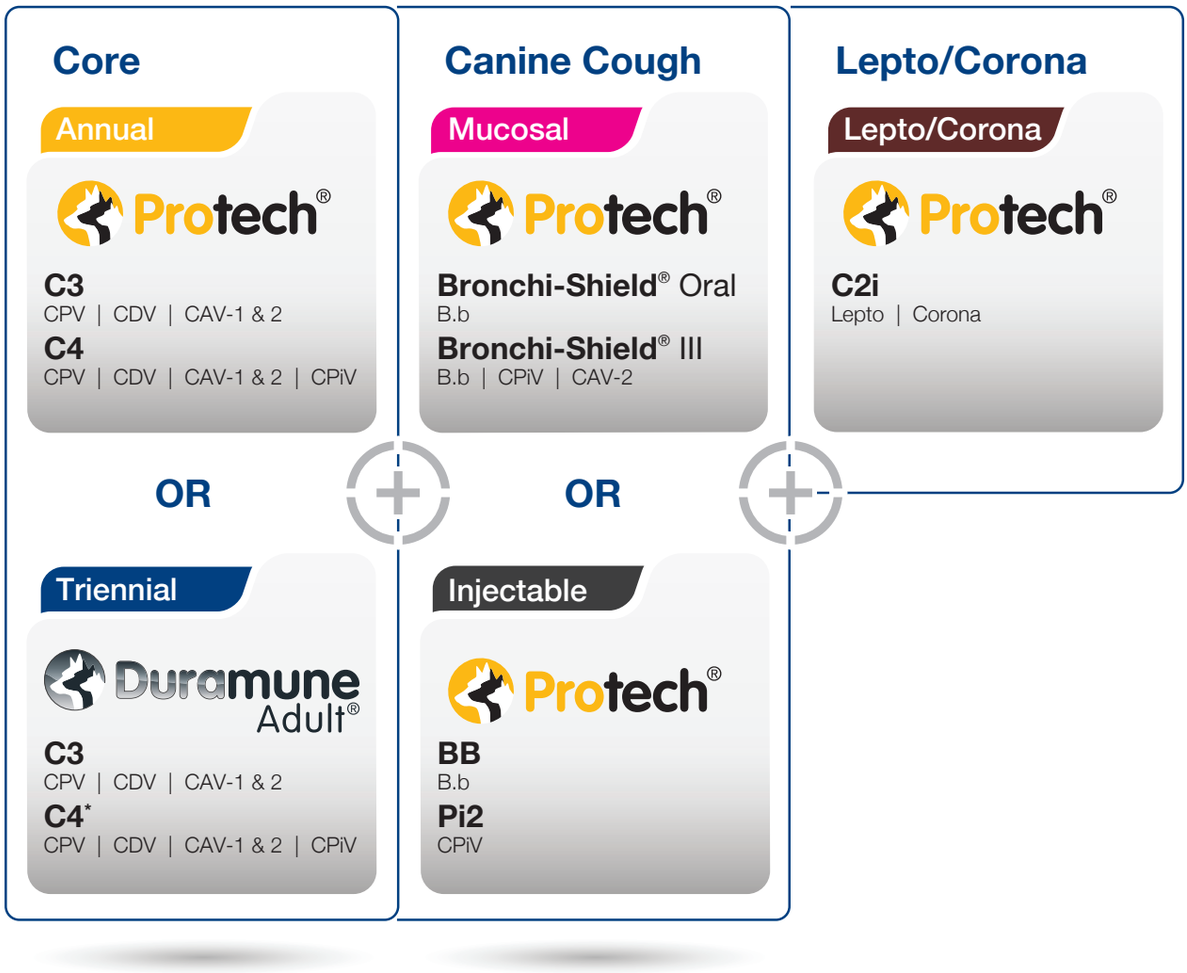
Australia's most comprehensive canine vaccine range

A detailed look

Boehringer Ingelheim

Canine Vaccination

Boehringer Ingelheim Animal Health offers Australia's most comprehensive canine vaccine range, allowing you to tailor protocols to the individual needs of your patients.



CPV = canine parvovirus

CDV = canine distemper virus

CAV-1 = canine adenovirus type 1 (infectious canine hepatitis)

CAV-2 = canine adenovirus type 2

CPiV = canine parainfluenza virus

B.b = *Bordetella bronchiseptica*

Lepto = *Leptospira interrogans* serovar Copenhageni

Corona = canine enteric coronavirus

*Three years of protection demonstrated for canine distemper virus, canine parvovirus and canine adenovirus (types 1 and 2). For protection against canine parainfluenza virus, annual revaccination is recommended (e.g. with Protech® Pi2)

Vaccination is a vital part of infectious disease management in companion animals.

In Australia, vaccination against the three core canine pathogens (canine parvovirus, canine distemper virus and canine adenovirus type 1) is indicated for all dogs, regardless of their lifestyle or location.[1] For other "lifestyle" pathogens (*Bordetella bronchiseptica*, canine parainfluenza virus, *Leptospira interrogans* and canine enteric coronavirus), a risk:benefit assessment should be performed when deciding if vaccination is indicated.

There are three basic factors to consider:

1. How important is the pathogen?
2. How effective is the vaccine?
3. How safe is the vaccine?

Contents

The importance of each pathogen and the efficacy of the relevant vaccine is discussed in more detail on pages 4-11, while the safety of canine vaccination is discussed on page 14.

Canine parvovirus

How important is the pathogen?

Risk

Canine parvovirus (CPV) is recognised globally as one of the most important pathogens in domestic dogs. In evolutionary terms, CPV is a relatively new viral infection, emerging and rapidly spreading in the global dog population from the late 1970s. This new virus was named CPV-2, but by the early 1980s, genetic mutations resulted in the appearance of two antigenic variants, CPV-2a (in 1980) and CPV-2b (in 1984).[2] These new variants quickly replaced the original CPV-2 subtype. A third variant, CPV-2c, was first identified in Italy in 2000.[3] CPV-2a was reported as the dominant subtype in Australia until around 2010-2012, with CPV-2b now the most common subtype identified in clinical cases of CPV (as shown in Figure 1).[4,5] CPV-2c was identified for the first time in Australia in 2015, but only a small number of confirmed cases have been reported.[6] It is estimated that approximately 20,000 cases of CPV are diagnosed by veterinarians annually in Australia.[7]

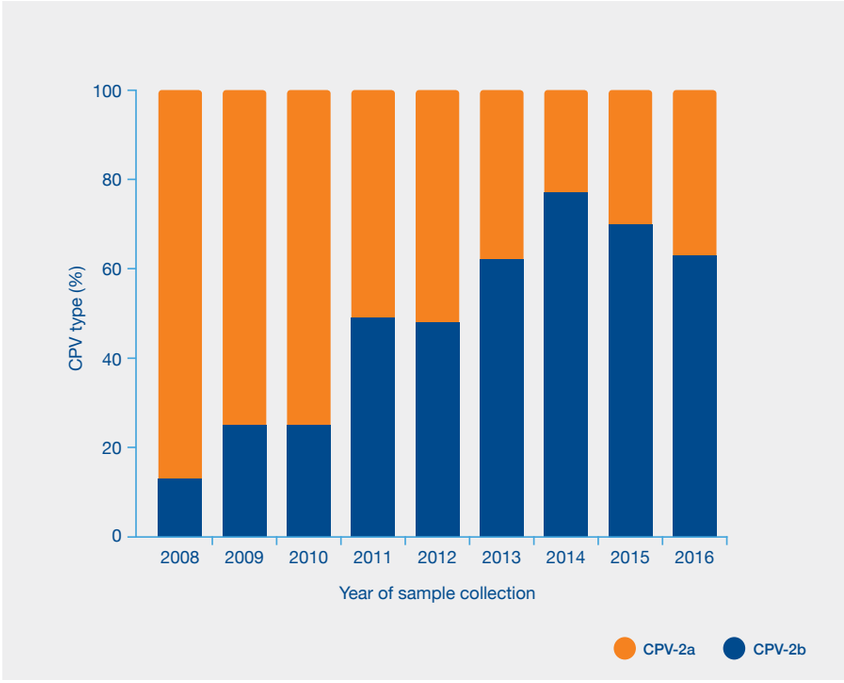


Figure 1. Results of genetic typing from clinical CPV cases in Australia 2008-2016. Adapted from Clark et al 2018.[5]

Consequence

Unlike the original CPV-2 subtype, the three later antigenic variants have the ability to infect and cause disease in cats, although a recent study failed to find any evidence of faecal CPV shedding in Australian shelter cats.[8] Whilst CPV-2a, -2b, and -2c have a shorter incubation period and may be associated with a more rapid disease progression than the original CPV-2, there is no strong evidence of variations in virulence between the three more recent types.[2] There is a marked variation in the severity of signs associated with CPV infection, which can range from subclinical infections, to mild signs of gastroenteritis, to acute, fatal disease.[2] The difference in the clinical picture seen in infected dogs is likely attributable to factors such as the host's immune response or concurrent infections rather than a difference in the virulence of the infecting virus. Survival rates of over 90% have been reported in dogs receiving intensive treatment, but many dogs are euthanised because their owners are unable to afford appropriate treatment.[9]

Figure 2. A puppy infected with canine parvovirus. (Courtesy of Professor Nicola Decaro, University of Bari.)

CPV Diagnostics

There is no significant difference in the ability of point-of-care faecal antigen tests (ELISA) to detect the three CPV variants.[2] These tests have high specificity but relatively low sensitivity, meaning that false negatives are common. This is due to the limited period in which high levels of faecal antigen are shed, the intermittent nature of shedding, and through interference by faecal antibodies which can bind to viral antigen making it unavailable to interact with the capture antibodies of the test.[2] Several studies have investigated the likelihood of false positives arising in dogs recently administered a modified live CPV vaccine.[10,11] They demonstrated that although vaccine virus could be detected by more sensitive PCR testing, there was no diagnostic interference with point-of-care faecal antigen testing. It is therefore reasonable to conclude that a positive antigen test in a dog showing signs compatible with CPV infection is a true positive regardless of a recent vaccination history.

How effective is the vaccine?

CPV vaccines are among the most effective of the veterinary vaccines. Current vaccines, both in Australia and overseas, use either the original CPV-2 or newer CPV-2b antigenic types. Challenge studies have been reported with both types and have demonstrated cross protection against all existing CPV antigenic variants (2a, 2b, and 2c).[1]

Although adequate clinical protection from disease is expected with both CPV-2 and CPV-2b vaccines, there is evidence to suggest that immunity against virulent CPV-2b viruses (the predominant variant causing disease in Australia) is optimal if a CPV-2b vaccine is used.[5,12,13] Protech® and Duramune® are the only CPV vaccines in Australia to contain the more recent CPV-2b subtype.

Immunity to CPV may develop as soon as 3 days after vaccination and is usually present within 5 days.[1] Regardless of the vaccine used, it is estimated that 1 in every 1,000 dogs may be a genetic non-responder to CPV vaccination, and although unproven, some breeds (e.g. Rottweilers and Dobermans) have been suspected to be at greater risk.[1] If there is a concern that a particular breed line may be associated with a poor response to vaccination, antibody titres can be measured to determine whether a particular animal has responded appropriately. It is suggested to wait until at least 20 weeks of age to perform this testing to ensure that the measured titre reflects an active immune response to vaccination and not passively derived maternal antibodies.[1]

Protech® and Duramune® CPV vaccines are registered to provide cross-protection against CPV-2a, CPV-2b and CPV-2c, and to prevent viral shedding caused by CPV infection. Preventing CPV shedding in vaccinated dogs reduces contamination of the environment, thereby decreasing the risk of infection for pups which haven't yet completed their vaccination course.

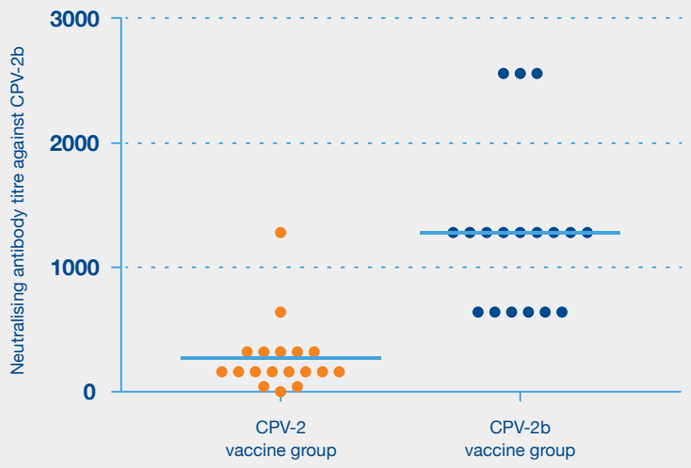


Figure 3. Comparison of neutralising antibody titres against CPV-2b following vaccination with a CPV-2 or CPV-2b vaccine. Adapted from Pratelli et al 2001.[12]

Thirty-six pups were randomly assigned to two groups. One group received a vaccine containing the older CPV-2 subtype and the other group received an experimental vaccine containing the newer CPV-2b subtype. The neutralising antibody titre against a CPV-2b virus was determined for each pup. Pups vaccinated with the CPV-2b vaccine had significantly higher neutralising antibody titres against CPV-2b than pups vaccinated with the CPV-2 vaccine, with mean neutralising titres of 1,138 and 162 respectively. This supports that optimal immunity is expected against CPV-2b if a CPV-2b vaccine is used.

Protech® and Duramune® C3/C4

- The only Australian vaccines to contain the more recent CPV-2b subtype
- Registered to provide cross protection against CPV-2a, CPV-2b and CPV-2c
- Prevent viral shedding caused by CPV infection
- High titre low passage vaccines to overcome high levels of maternally derived antibodies
- Can be used in early (from 10 weeks of age) or later finishing puppy protocols

The risk of CPV is an important consideration when designing a puppy vaccination protocol. For more information on puppy vaccination protocols please see pages 12-13.

Canine distemper virus

How important is the pathogen?

Risk

Canine distemper virus (CDV) is an enveloped RNA virus in the family *Paramyxoviridae*. **It is known to occur in many species of carnivore including domestic dogs, dingos, foxes, ferrets and big cats, however domestic cats are not affected (feline distemper is a term sometimes used to refer to feline panleukopenia virus).**[14,15] Despite the wide host range, dogs are the principal reservoir host for CDV.[16] CDV is rarely seen in Australia's owned dog population due to widespread vaccination.[15]

An Australian study reported that there were 9 confirmed cases of CDV in dogs and 20 in ferrets between 2006 and 2014.[17] A further 19 suspected cases were reported during that time period. As an enveloped virus, CDV is extremely susceptible to heat and drying, and survives for less than one day at room temperature.[14] It is highly contagious and dogs are usually exposed through contact with infected oronasal secretions.[14]

Consequence

Infection can result in multisystemic disease that commonly affects the respiratory, gastrointestinal, or central nervous systems (CNS).[15] The type and severity of clinical signs associated with infection varies depending on factors such as the virulence of the virus strain, environmental conditions, and the age and immune status of the host.[16] **Many infected dogs experience subclinical infections, while others experience a rapidly progressive infection and death.**[14] CDV is a potential cause of canine infectious respiratory disease complex (CIRDC) and if respiratory signs develop, they may be indistinguishable from those caused by other viral or bacterial pathogens. Up to 30% of infected dogs develop CNS signs which usually occur 1 to 6 weeks after the onset of acute illness.[14] Dogs with chronic disease may show hyperkeratosis of the nasal planum and footpads.[14]

Figure 4. Hyperkeratosis of the footpads associated with CDV. (Courtesy of Professor Nicola Decaro, University of Bari.)

How effective is the vaccine?

Currently available modified live CDV vaccines, such as Protech® and Duramune® core vaccines, are very effective, with complete protection from disease expected. All current CDV vaccines provide protection from all known isolates of CDV.[1] In the absence of maternally derived antibody interference, modified live CDV vaccines provide immunity rapidly after vaccination.[1] It is estimated that approximately 1 in 5,000 dogs may be a genetic non-responder to CDV vaccination, regardless of the vaccine used.[1]

CDV is one of the core canine pathogens, and vaccination is indicated for all dogs regardless of their lifestyle. Although cases of CDV are rare in Australia, there is a need for continued vaccination due to the severe consequences of infection in immunologically naïve dogs.[15]

Canine adenovirus type 1 (infectious canine hepatitis)

How important is the pathogen?

Risk

Infectious canine hepatitis (ICH) caused by canine adenovirus type 1 (CAV-1) affects dogs, foxes, other Canidae and Ursidae (bears), although ferrets are not susceptible.[18,19] The disease is rare in countries where vaccination is widely performed, such as Australia and the USA. CAV-1 is shed in saliva, faeces and urine and transmitted by direct contact with an infected dog or by contact with contaminated fomites.[1,18] In chronically infected dogs, shedding of CAV-1 in the urine can persist for at least 6 to 9 months after the initial infection.[19] As with other adenoviruses, CAV-1 is stable in the environment and can survive for months at room temperature.[18] Disease is more likely in dogs less than 1 year of age, although unvaccinated dogs of all ages may be affected.[19]

Consequence

The clinical presentation of ICH is variable. Viral infection of hepatocytes and endothelial cells within a range of tissues can result in haemorrhage, inflammation and necrosis.

Some dogs develop peracute disease, with death occurring rapidly within 24-48 hours.[18] Acute disease is the most common presentation, resulting in recovery or death within 2 weeks.[18]

Dogs with acute disease may present with signs such as fever, inappetance, vomiting and diarrhoea. Abdominal palpation may reveal hepatomegaly or abdominal pain. Corneal oedema and uveitis ("blue eye"), and interstitial nephritis, may occur as a consequence of the deposition of circulating immune complexes.[20] Typical serum biochemical changes include increased ALT and ALP, hyperbilirubinaemia, hypoglycaemia and hypoalbuminaemia.[18] In dogs which die from acute ICH the liver is enlarged, dark, and mottled in appearance.[19]

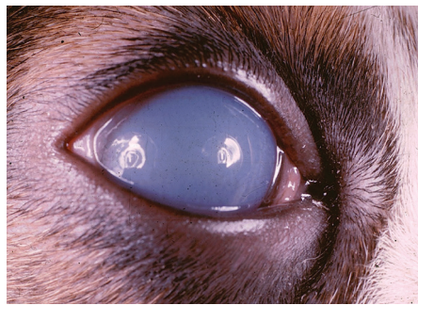


Figure 5. Corneal oedema secondary to CAV-1 infection. (Courtesy of Professor Nicola Decaro, University of Bari.)

How effective is the vaccine?

Vaccines containing CAV-1 are no longer used, as they were associated with significant side effects in some dogs, such as corneal oedema and glomerulonephritis. Currently available vaccines against ICH, such as the Protech® and Duramune® core vaccines, are modified live vaccines containing canine adenovirus type 2 (CAV-2), which is a potential cause of canine infectious respiratory disease complex. Injectable CAV-2 vaccines provide cross-protection against CAV-1 but without the side effects associated with earlier CAV-1 vaccines. In the absence of maternally derived antibody interference, immunity develops as early as 5 days after vaccination.[1]

Infectious canine hepatitis has been practically eliminated in domestic dogs by widespread vaccination. Given the grave consequences of infection, and the risk of re-emergence if vaccination rates fall, CAV-1 remains one of the core canine pathogens and vaccination is indicated for all dogs regardless of their lifestyle.

Canine infectious respiratory disease complex (canine cough)

How important is the pathogen?

Risk

Canine infectious respiratory disease complex (CIRDC) is recognised as one of the most prevalent infectious diseases of dogs.[21] It poses a global issue for animal shelters, boarding kennels, pet owners and veterinarians. The bacterium *Bordetella bronchiseptica* has been considered a primary cause of CIRDC for many years.[22] **However, there is a growing list of emerging or newly recognised pathogens that are thought to contribute to CIRDC, either as a primary pathogen or by acting synergistically or sequentially to cause disease.**

Transmission of the pathogens involved in CIRDC is usually by direct oronasal contact with infected dogs or with aerosolised microdroplets of respiratory secretions, however contaminated fomites such as bedding, dishware and clothing can also be involved in transmission. *B. bronchiseptica* can survive for several weeks in environmental water, which highlights a risk of infection even in the absence of direct dog-to-dog contact.[23]

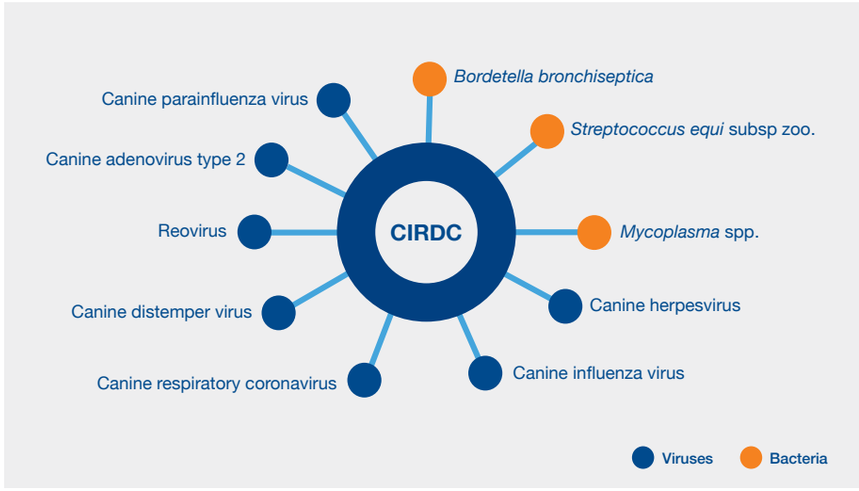


Figure 6. Pathogens associated with CIRDC.

Consequence

CIRDC can be expected to have a high morbidity but low mortality. In uncomplicated cases, dogs are generally bright and alert with no signs of systemic illness. Puppies and immunocompromised dogs are at a greater risk of developing bronchopneumonia and in these cases systemic signs such as lethargy, tachypnoea and pyrexia may be seen. **Outbreaks can occur when groups of dogs are mixed or housed together, such as in shelters, boarding facilities and dog shows.**

How effective is the vaccine?

Vaccines are not available against every pathogen implicated in CIRDC and so vaccination cannot completely prevent disease. However, vaccinating against primary pathogens such as *B. bronchiseptica*, canine adenovirus type 2, and canine parainfluenza virus will offer protection against these specific organisms, and will also reduce or remove their impact in coinfections with other respiratory pathogens.

Mucosal vs injectable

The pathogens which cause CIRDC infect dogs through the mucosal lining of the respiratory tract and therefore the host's defense relies heavily on local mucosal immunity.[24] **There are key differences between the nature and degree of protection offered by the available vaccines because the adaptive immune response differentiates between the more natural mucosal entry of antigens (intranasal or oral administration) and systemic entry (subcutaneous injection).** The mucosal immune response involves the production of pathogen-specific mucosal IgA which is secreted into the mucus where it can bind to pathogens. This provides protection against pathogen adherence and colonisation, a process known as immune exclusion (as shown in Figure 7).[24] Due to their route of administration injectable vaccines are considered to be relatively poor at inducing mucosal immunity and instead produce primarily a systemic IgG response.[24,25] **The only way a significant mucosal IgA response can be triggered is to use live mucosal vaccines where vaccine organisms can temporarily invade mucous membranes.**[26] Mucosal vaccines stimulate both a mucosal and systemic response, which also occurs following a natural infection.[24]

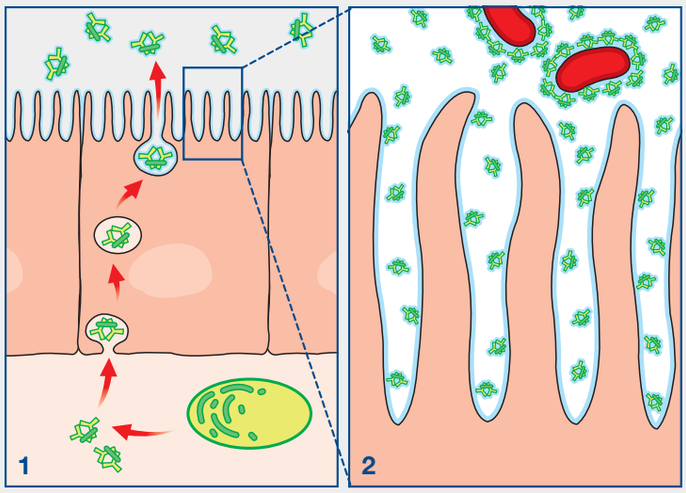


Figure 7. Mucosal vaccination - local immunity in the upper respiratory tract.

1 Mucosal vaccines stimulate the production of pathogen-specific mucosal IgA (e.g. for *B. bronchiseptica*) which is secreted into the mucus of the upper respiratory tract.
2 Mucosal IgA can bind virulent *B. bronchiseptica*, protecting against adherence and colonisation.[24] This process is known as immune exclusion.

A study involving vaccines available in the USA demonstrated that dogs receiving an intranasal vaccine were significantly better protected against a challenge with virulent *B. bronchiseptica* compared to an injectable cell antigen extract *B. bronchiseptica* vaccine.[25] This study also demonstrated that the intranasally vaccinated dogs shed significantly fewer virulent organisms post challenge. The efficacy of oral *B. bronchiseptica* vaccination has been demonstrated in several peer-reviewed, published challenge studies.[27,28,29] Protech® Bronchi-Shield® Oral has been shown to offer protection against *B. bronchiseptica* equivalent to intranasal Protech® Bronchi-Shield® III.[28] Only a single dose of Bronchi-Shield® Oral or intranasal Bronchi-Shield® III from 8 weeks of age is required in the initial course.

Injectable vaccines trigger primarily a systemic immune response, mediated by IgG.[24] Following entry of a pathogen and colonisation of the respiratory mucosa, tissue damage and inflammation allows IgG to be exuded to the luminal surface where it can contain and limit the infection. This systemic immune response is able to reduce the severity or duration of clinical signs. Immunity is not expected until at least 7-10 days after the second dose in the primary course of an injectable *B. bronchiseptica* vaccine.[30]

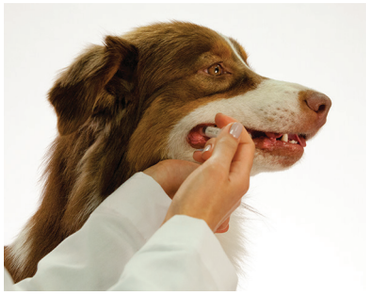


Figure 8. Administration of Protech® Bronchi-Shield® Oral into the buccal cavity.

Boehringer Ingelheim Animal Health recommends using a mucosal CIRDC vaccine (oral or intranasal) whenever possible in both puppies and adult dogs, because they provide robust, local mucosal immunity. The current WSAVA vaccination guidelines state that intranasal or oral vaccines are preferred for protection against *B. bronchiseptica*, and they are strongly recommended in high risk environments such as shelters.[31]

Protech® Bronchi-Shield® Oral

Proven efficacy
Robust protection against the primary cause of CIRDC *(B. bronchiseptica)*, with efficacy against this pathogen equivalent to intranasal Bronchi-Shield® III.[27,32]

Easy administration
Simple, no-fuss administration can reduce stress for both the dog and owner. Simply trickle 1 ml of vaccine into the buccal cavity.

Early protection
12 months protection against *B. bronchiseptica* with a single dose from 8 weeks of age.

Mucosal vaccination for puppies and adults
Intranasal administration can be challenging in some dogs, leading many vets to use them only in puppies and switch to injectable vaccines for adult dogs. Bronchi-Shield® Oral's easy administration means that both puppies and adult dogs can benefit from mucosal vaccination against *B. bronchiseptica*.

Fits easily into annual and triennial vaccine protocols
See page 15 for suggested protocols.
Bronchi-Shield® Oral is available in cost-effective convenience packs with Protech® C4, Duramune Adult® C4 or Protech® Pi2.

Protech® Bronchi-Shield® III (intranasal)

Broad mucosal protection
The only Australian mucosal vaccine to protect against three important CIRDC pathogens (*B. bronchiseptica*, canine adenovirus type 2 and canine parainfluenza virus), providing the broadest mucosal protection available.

Early protection
12 months protection with a single dose from 8 weeks of age.

Protech® BB and Protech® Pi2 (injectable)

If mucosal vaccination is assessed not to be possible, then injectable options are available as an alternative for this small proportion of dogs. Canine parainfluenza virus is also included in Protech® C4 and Duramune Adult® C4. Protech® BB can be used as a diluent for Protech® C4, Duramune Adult® C4 or Protech® Pi2.

For more information on suggested vaccine protocols please see page 15.

Leptospirosis

How important is the pathogen?

Risk

Leptospirosis is a bacterial disease caused by pathogenic serovars of *Leptospira interrogans*, a member of the spirochaete family. Over 200 serovars have been identified, of which only a limited number have been demonstrated to cause disease in dogs. Based on serology, serovars Copenhageni and Australis are the most frequently identified leptospira serovars infecting dogs in Australia.[33,34,35] **Leptospirosis is one of the most common zoonoses in the world, and is a notifiable disease in Australia.**

Leptospiral organisms are maintained in a primary host species (which varies depending on serovar) where infection may be asymptomatic. Spillover into incidental hosts may occur, and this may be associated with severe illness and mortality. **In Australia, the maintenance host of serovar Copenhageni is believed to be introduced rats.**[34] Direct exposure may occur from exposure of mucous membranes to infected urine, bite wounds or ingestion of infected tissue. Indirect exposure may occur from contaminated water, food, soil or bedding.

Consequence

Dogs with leptospirosis may be misdiagnosed as they can present with a wide range of clinical signs of varying levels of severity. Classically, infection results in acute to subacute haemorrhagic, renal and hepatic disease.[37] Mortality rates have been reported to be approximately 50% of hospitalised cases in dogs.[34] **Leptospirosis should be considered a differential diagnosis in any dog exhibiting signs of a non-specific illness or signs of haemorrhagic, renal or hepatic disease.**[38]

A serological survey of 956 shelter dogs in Australia revealed an overall seroprevalence for leptospiral antibodies of 1.9%, with state-based variation.[33] Seroprevalence was greatest in Victoria (2.8%), Queensland (2.5%) and New South Wales (2.3%). **Serovar Copenhageni was the most prevalent serovar detected in this study.** There is geographical variation in the predominant serovars affecting dogs in Australia. Serovar Copenhageni (of the icterohaemorrhagiae serogroup) is the most prevalent serovar in southern and eastern Australia, while serovar Australis is more prevalent in North Queensland.[34,35,36]

All Australian dogs could be considered at risk of infection given the potential for exposure to infected rodents. The American College of Veterinary Internal Medicine (ACVIM) Small Animal Consensus Statement on Leptospirosis states, *"In geographic locations in which infection occurs in urban, backyard dogs, all dogs may be at risk, and the vaccine may be considered part of a core vaccination protocol".*[38]

How effective is the vaccine?

Protech® C2i is a bivalent vaccine containing *Leptospira interrogans* serovar Copenhageni, the most prevalent canine serovar in Australia.[33] Protech® C2i also contains canine coronavirus, a potential cause of gastroenteritis (refer to page 11). The vaccine elicits serogroup specific immunity and does not offer cross-protection against leptospira serovars not included in the vaccine. In clinical trials involving the leptospiral component of Protech® C2i, puppies vaccinated at 6 and 9 weeks of age were challenged 3 weeks and 57 weeks later with virulent serovar Copenhageni.[39,40] **In both trials the vaccinated puppies showed a statistically significant reduction ($p<0.05$) in post-challenge thrombocytopenia, clinical scores and serologic responses versus the controls.** Challenge at 57 weeks resulted in 60% mortality of the control group, whereas all vaccinated dogs survived.

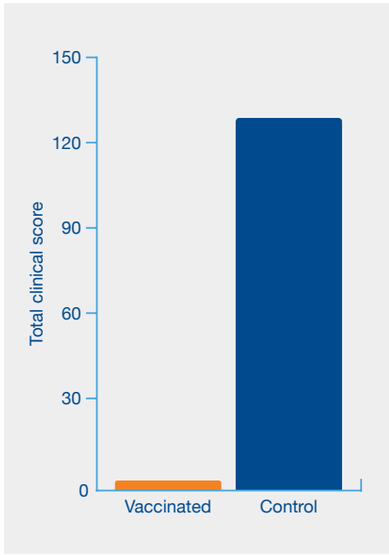


Figure 9. Efficacy of the leptospiral fraction of Protech® C2i. Total clinical score of pups challenged with virulent serovar Copenhageni 3 weeks post-vaccination (vaccinates vs controls).[39]

Protech® C2i is available as a convenient and cost effective combination pack with Protech® C3 and C4, and can be used on its own or as a diluent for Protech® and Duramune Adult® C3 and C4.

Canine enteric coronavirus

How important is the pathogen?

Risk

Canine enteric coronavirus (CCoV) is a common enteropathogen of dogs. Australian studies have assessed prevalence of infection based on electron microscopy of faecal samples from healthy and diarrhoeic dogs, with positive samples reported in 7.1% (n=156)[41] and 2.9% (n=104)[42] of dogs.

An Australian serological survey tested samples from 1,396 dogs to investigate the prevalence of anti-CCoV antibodies.[43] In this study the samples were divided into two groups based on the number of animals housed together: the open population consisted of suburban or rural pet dogs that were housed in groups of three or less (n=1,107); and the kennel population was composed of group-housed dogs e.g. in shelters (n=289). The presence of antibodies indicated that the dogs were currently or previously infected, as this study was performed prior to the introduction of CCoV vaccines in Australia. The results showed that 15.8% of the open population had IgG antibodies to CCoV. In the kennel population, overall prevalence was 40.8%, with antibodies detected in 10 of the 11 tested populations. There was state-based variation as shown in Figure 10.

CCoV is highly contagious and spreads rapidly through susceptible dog populations. Viral shedding typically lasts a few weeks but has been documented to continue for as long as 6 months after clinical signs have resolved.[44]

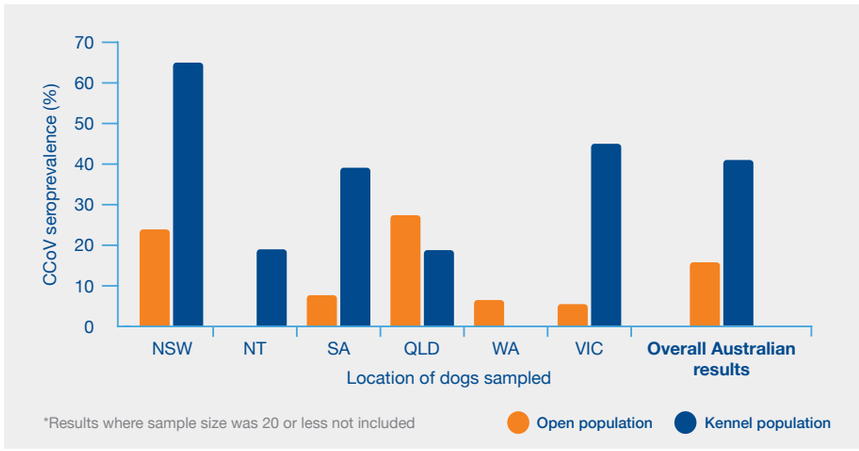


Figure 10. Percentage of Australian dogs seropositive to CCoV. Adapted from Naylor et al 2001.[43]

Consequence

Infection results in lysis, desquamation, and shortening of the small intestinal villi.[2] Infection with CCoV alone typically results in mild or asymptomatic enteritis, although severe and fatal disease has been reported.[45] In general, disease in young dogs is more severe than in adults. Clinical signs may include lethargy, inappetence, vomiting, diarrhoea and dehydration. Infected adults are usually asymptomatic, however they will shed the virus and be a source of infection for other dogs.[2]

Co-infection with CCoV and canine parvovirus (CPV) has been shown to result in more severe disease, both experimentally and under natural settings.[2,46,47] As these viruses infect different regions of the villi, co-infections result in more widespread epithelial damage than with either virus alone.

In a study examining concurrent CCoV and CPV infections, eight of nine dogs became moribund and were euthanised between seven and nine days post-infection.[46] In contrast, all dogs infected with either CCoV or CPV alone developed less severe disease and recovered.

How effective is the vaccine?

Protech® C2i is a bivalent vaccine containing inactivated canine enteric coronavirus and *Leptospira interrogans* serovar Copenhageni. Inactivated canine enteric coronavirus vaccination has been shown to reduce the severity and duration of clinical signs, and the duration of viral shedding, however it does not provide sterilising immunity.[48]

The use of CCoV vaccines is considered by some to be controversial because CCoV usually causes only mild or subclinical disease. However, dual infection with CCoV and other enteropathogens, such as CPV, can result in increased morbidity and mortality. Vaccination may therefore be of clinical benefit, in much the same manner as vaccination against canine parainfluenza virus (CPiV) is used to control canine infectious respiratory disease (CPiV rarely causes severe disease alone but can act synergistically with other respiratory pathogens to cause more severe disease).[30]

Protech® C2i is available as a convenient and cost effective combination pack with Protech® C3 and C4, and can be used on its own or as a diluent for Protech® and Duramune Adult® C3 and C4.

Puppy vaccination protocols

The challenge of optimising a primary vaccination protocol for puppies is that there are two competing priorities in the first few months of a puppy's life. The first is protecting them from infectious disease – puppies are immunonaive and particularly vulnerable to infectious disease, and isolating them until they have completed a course of vaccinations reduces their risk of infection from preventable diseases. However, this isolation has a negative impact on the second priority, ensuring adequate socialisation. Exposing puppies to as many novel stimuli and environments in the first 3-4 months of life is important for their normal development. Failure to adequately socialise puppies may result in a range of behavioural difficulties, including aggression, fear and anxiety conditions, and phobia development, which may result in dogs being surrendered and euthanased.[49,50]

Weighing up the risk of infectious disease versus poor socialisation for your patients is not simple, and this risk assessment will depend on a range of circumstances, such as the practice philosophy, and the prevalence of disease in the local area. Regardless of the circumstances, the optimal solution is to use vaccines and vaccination protocols that provide protection at the earliest possible age.

Maternally derived antibody interference

Maternally derived antibodies (MDA) provide passive immunity for the neonate in the critical first few weeks to months of life. MDA can be acquired either *in utero* via the placenta, or via the ingestion of colostrum within the first 24 hours of life. In puppies up to 98% of MDA is acquired via colostrum.[51] Although of great benefit to the neonate, when it comes to vaccination, the protection afforded by MDA comes at a cost as they can also bind to and neutralise vaccine antigens and thus prevent stimulation of an appropriate adaptive immune response.

Although MDA interference can occur with all injectable vaccine antigens, the impact on canine parvovirus (CPV) vaccination is of particular interest given that this pathogen is highly prevalent in many parts of Australia, and that infection is potentially fatal. For CPV, the minimum MDA titre that is able to prevent replication of a vaccine strain of the virus is lower than the titre that can protect the pup from virulent field viruses, meaning that a pup's MDA titre must drop into the non-protective range before a vaccine can work.

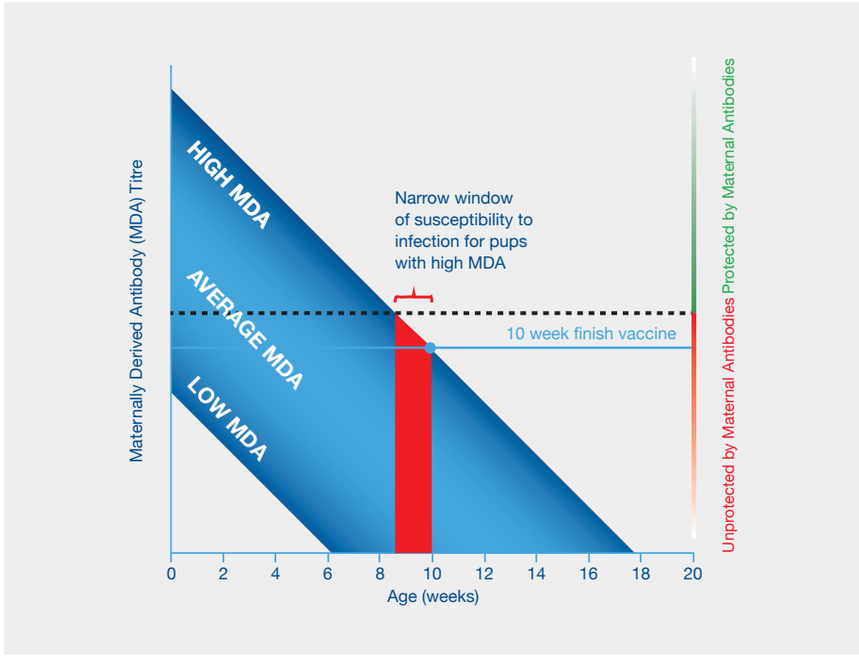


Figure 11. Newer generation high titre low passage vaccines are able to break through high levels of maternal antibodies, meaning pups can be protected sooner.

All puppies, irrespective of their starting maternal antibody titre or the specific vaccine or vaccination protocol used, will therefore be susceptible to infection for a time prior to being able to respond to vaccination. Although this "window of susceptibility" cannot be avoided, it can be minimised by choosing a potentiated vaccine (e.g. a Protech® or Duramune® core vaccine) that is better able to overcome MDA.

Potentiated vaccines (high titre, low passage)

Protech® and Duramune® core vaccines are potentiated, early finish vaccines. The two key features of potentiated vaccines that allow successful immunisation in the face of high MDA titres are the passage level of the vaccine strain and the titre of the vaccine. Attenuation is the process by which the virulence of an organism is reduced such that it is no longer capable of causing disease, but is still able to replicate, and therefore trigger an appropriate immune response. Attenuation of viruses for vaccine seed stock is commonly performed by repeatedly growing a virulent virus in cell culture, a process known as passaging. Highly passaged organisms replicate less well in the animal, are less immunogenic, and are less able to overcome MDA. In contrast, low passage vaccines are better able to replicate in the host and overcome higher MDA levels, with a resulting decrease in the minimum age for final vaccination. The other feature of vaccine technology which influences the ability to overcome MDA is the number of virus particles (titre) contained in the vaccine. As might be expected, in general, higher titre vaccines are better able to overcome MDA than low titre vaccines.

How many doses are required to stimulate immunity?

Only a single dose of a modified live core canine vaccine is required to stimulate adequate immunity in the absence of MDA interference (in an immunocompetent animal). Puppies with low MDA titres may be vulnerable to infectious disease, and also capable of responding to vaccination, at an early age. Pups with high levels of MDA may not be able to respond to vaccination until a later vaccine is given. MDA titres can vary considerably, both between litters and even within a litter, and it is not practically possible to establish when an individual pup will be able to respond to vaccination. Giving a course of vaccines ensures protection at the earliest opportunity.

What is the best interval to have between vaccinations?

Vaccination protocols should aim to allow a pup the opportunity to respond to vaccination at the earliest opportunity (i.e. after MDA has decreased below the critical level). A standard inter-vaccination interval would be 2-4 weeks. It is recommended that vaccines of any type are not given closer than two weeks apart, because the non-specific immune response to a vaccine may inhibit the response to subsequent vaccines. The maximum vaccination interval should be based on consideration of the risk of exposure to infectious disease during the primary vaccination course (e.g. for a breeder with a history of CPV on their property, minimising the inter-vaccination interval to two weeks is recommended).

When should the last dose of core vaccine be given?

Protech® and Duramune® core vaccines are registered for final vaccination from 10 weeks of age onwards. This registered early finish is based on challenge studies which demonstrate excellent protection in puppies with varying levels of MDA when vaccinated at 10 weeks of age. As previously discussed, the early socialisation of puppies is beneficial to reduce the risk of behavioural problems. However, a later finishing protocol minimises the chance of a pup failing to respond to vaccination through MDA interference, which may occur in exceptional circumstances. When deciding on a vaccination protocol for a particular animal, the epidemiology of each disease, the likely persistence of MDA and the dog's history and environment should all be considered.

Some veterinarians may choose to align the puppy vaccination protocol with international vaccination guidelines, regardless of the local disease risk. The current World Small Animal Veterinary Association (WSAVA) vaccination guidelines recommend that the final core vaccine is administered at 16 weeks of age or later.[1] Protech® and Duramune® core vaccines can be used in both early and later finishing protocols.

The downside to a protocol finishing at 16 weeks is that, traditionally with such a protocol, pups would not start being socialised until at least 17 weeks of age (to allow time for immunity to develop). The use of an early finish vaccine, such as the Protech® and Duramune® core vaccines, can allow for a useful compromise to maximise protection and to minimise potential future behavioural problems. In this scenario, pups may be allowed to socialise 7 to 10 days after a vaccine is given at 10 weeks or later, as it is known that the vast majority of pups will be protected at this time. A later final dose can still be recommended to provide protection in the rare circumstance that a pup does not respond to the earlier vaccine, and to align with international vaccination guidelines.

How long after vaccination is the pup protected?

In the absence of interfering levels of MDA, there is a rapid onset of immunity following vaccination with modified live core vaccines. The speed of onset is antigen dependent. Immunity to CPV may develop as soon as 3 days after vaccination, and is usually present within 5 days, with immunity to canine distemper occurring more rapidly, and canine adenovirus being a little slower.[1] To take into account individual animal variation, reasonable standard advice would be to isolate pups for 7 to 10 days after vaccination.

For more information on suggested vaccine protocols please see page 15.

Vaccine safety

Modern vaccines are extremely safe when used as intended in healthy animals, but like all medicines, they have the potential to result in side effects. But just how common are adverse reactions to vaccination? A large retrospective study conducted in the US looked at adverse events reported by owners following vaccination in 1.2 million dogs, given over 3.4 million doses of vaccine.[52] In this cohort, 4,678 suspected adverse reactions (of any kind, including very minor reactions) were reported within 3 days of vaccination, equating to a reported rate of 38 cases per 10,000 dogs vaccinated. In this study it is important to note that all reports were included in the analysis, regardless of the likely relationship with vaccination. **The adverse event rate was shown to correlate with the number of individual vaccines received during the visit. The study also revealed that the rate of suspected adverse events was inversely related to a dog's body weight (as shown in Figure 12).**

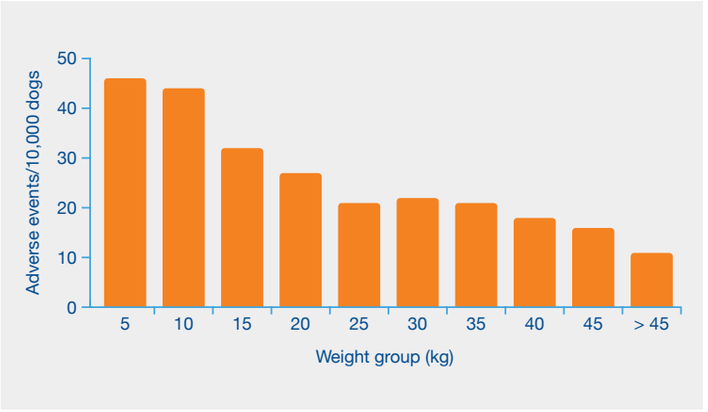


Figure 12. Suspected adverse event rate within 3 days of vaccination by weight group of dogs. Adapted from Moore et al 2005.[52]

Types of adverse reactions

A broad range of cytokines and other inflammatory mediators are activated as part of the normal immune response to a vaccine, therefore it is expected that a small proportion of animals will develop transient **systemic reactions.**[53] Signs associated with this type of reaction may include lethargy, pyrexia and anorexia. These signs typically resolve within 24-48 hours without treatment. Transient **injection site reactions** (e.g. pain, swelling and erythema) may occur in a small proportion of animals receiving an injectable vaccine.

Type I hypersensitivity (anaphylactic) reactions can occur after administration of any vaccine.[51] Mild anaphylactic reactions may result in signs such as facial oedema, erythema and pruritus, and treatment with a glucocorticosteroid and/or antihistamine is indicated.[1] Severe anaphylactic reactions are very rare but in these cases signs such as dyspnoea, hypotension and collapse may develop. Treatment options for such cases may involve supportive therapy to restore blood pressure and perfusion using intravenous fluids, oxygen supplementation and adrenaline.[51]

A small proportion of dogs given mucosal canine cough vaccines (intranasal or oral) may develop mild, transient **upper respiratory signs** (e.g. coughing) which results from an inflammatory response to the replicating vaccine organisms. Antibiotic therapy is not usually indicated and may prevent or reduce a normal immune response if given within 7 days of a live mucosal *B. bronchiseptica* vaccine.

"There is a realisation that on rare occasions, vaccination of a dog or cat might lead to an unexpected clinical reaction. Such reactions are for the most part mild and inconsequential and a simple* *risk benefit* *analysis will always suggest that the benefit obtained from having solid immunity to potentially lethal disease far outweighs the small risk of a vaccine associated adverse event." **2015 WSAVA Vaccination Guidelines.**[54]

Why might a dog fail to respond to vaccination?

Canine core (C3) vaccines are among the most effective of the veterinary vaccines and it is very rare for fully vaccinated dogs to develop signs of disease. However no vaccine, whether for veterinary or human medicine, can protect 100% of the population. Possible explanations for why a dog may not respond as expected to core vaccination include:

- Maternal antibody interference. Although rare, this is the most common reason for a puppy to fail to respond to core vaccination.[1]
- Genetic factors. A small proportion of dogs are genetically incapable of responding to vaccination because their immune system does not recognise a particular vaccine antigen. This is estimated to occur in approximately 1 in 1,000 dogs for canine parvovirus vaccination and 1 in 5,000 dogs for canine distemper virus vaccination.[1]
- Stress, immunosuppression or an underlying illness at the time of vaccination can affect the ability of the immune system to respond appropriately to a vaccine.
- Vaccine administration or storage factors.

Suggested vaccination protocols

Annual C5 Protocol 1

Vaccine	Puppy			Adult
	6-8 weeks	10-12 weeks*	14-16 weeks (optional)**	Annual
Protech® C4	●	●	●	●
Bronchi-Shield® ORAL		ORAL		ORAL

Annual C5 Protocol 2

Vaccine	Puppy			Adult
	6-8 weeks	10-12 weeks*	14-16 weeks (optional)**	Annual
Protech® C3	●	●	●	●
Bronchi-Shield® III		●		●

Triennial C5 Protocol 1

Vaccine	Puppy			Adult			
	6-8 weeks	10-12 weeks*	14-16 weeks (optional)**	Year 1	Year 2	Year 3	Year 4
Protech® C4	●	●	●				
Duramune® C4 Adult				●			●
Bronchi-Shield® ORAL		ORAL		ORAL	ORAL	ORAL	ORAL
Protech® Pi2					●	●	

Triennial C5 Protocol 2

Vaccine	Puppy			Adult			
	6-8 weeks	10-12 weeks*	14-16 weeks (optional)**	Year 1	Year 2	Year 3	Year 4
Protech® C3	●	●	●				
Duramune® C3 Adult				●			●
Bronchi-Shield® III		●		●	●	●	●

*Protech® C3 and Protech® C4 are registered for final vaccination from 10 weeks of age. Protech® Bronchi-Shield® III and Protech® Bronchi-Shield® Oral require a single dose from 8 weeks of age.

**Protech® C3 and Protech® C4 may be used in later finishing protocols e.g. when high environmental risk exists or to align with international vaccination guidelines. Please see pages 12-13 for more information on puppy vaccination protocols.

Protech® C2i may be used as a diluent for Protech® C3, Protech® C4, Duramune Adult® C3 or Duramune Adult® C4. Two doses 2-4 weeks apart from 6 weeks of age with annual revaccination will protect against *Leptospira interrogans* serovar Copenhageni and canine enteric coronavirus.

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