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Are vaccine strain, type or administration protocol risk factors for canine parvovirus vaccine failure?

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ABSTRACT

Canine parvovirus (CPV) is a highly contagious and worldwide cause of serious and often fatal disease in dogs, despite the widespread availability of vaccines. Which vaccine-related factors are associated with vaccination failure is largely unknown, and there are no reports from Australia. In this study – the first national population-level CPV study of its kind ever conducted – we analysed data on 594 cases of apparent CPV vaccination failure reported from an Australian national surveillance system to determine whether vaccine strain, type or administration protocol are risk factors for vaccination failures. The strain of CPV used in vaccine manufacture was not significantly associated with vaccination failure in clinical practice. The vaccine type (killed versus attenuated vaccine) for puppies diagnosed with CPV was associated with a lower mean age at time of vaccination ($P = 0.0495$). The age at administration of the last CPV vaccination a puppy received prior to presenting with disease was a significant ($P = 0.0334$) risk factor for vaccination failure, irrespective of whether the vaccine was marketed for a 10-week or 12-week or greater vaccination finish protocol. There was also a strong negative correlation between age at last vaccination prior to disease and vaccination failure ($P < 0.0001$): the later a puppy received this last vaccination, the lower the risk of vaccination failure. This supports the hypothesis that the use of final vaccination in puppies at less than 16 weeks of age predisposes to vaccination failure and warrants a final age for vaccination recommendation to be at least 16 weeks for all canine parvovirus vaccines, especially in outbreak situations. The large number of cases identified in this study confirms that CPV vaccination failure is occurring in Australia. Veterinarians should consider CPV as a differential diagnosis in cases with appropriate clinical presentation, regardless of the reported vaccination status of the dog.

1. Introduction

Canine parvovirus (CPV) is a highly contagious and commonly diagnosed infection of dogs. Prognosis is poor without treatment; survival rates of only 9% have been reported (Goddard and Leisewitz, 2010).

CPV is transmitted through the faecal-oral route and after an incubation period of three to seven days presents most commonly as acute haemorrhagic enteritis with severe leukopaenia in young dogs up to six months of age (Decaro and Buonavoglia, 2012; Decaro et al., 2007; Goddard and Leisewitz, 2010). A number of factors have been associated with CPV infection and disease including insufficient immunity, geographical region and socioeconomic status, the presence of co-pathogens, and stressors such as weaning, overcrowding and increased parasite load (Brady et al., 2012; Cavalli et al., 2008; Goddard and Leisewitz, 2010; Kalli et al., 2010; Ling et al., 2012).

Much research has been conducted into the emergence of CPV in the late 1970s, and into the evolution of CPV strains, leading to a current understanding that three predominant strains circulate worldwide currently, and these are termed CPV-2a, CPV-2b and CPV-2c (Decaro and Buonavoglia, 2012; Goddard and Leisewitz, 2010; Meers et al., 2007; Mittal et al., 2014; Truyen, 2006). Debate continues regarding the clinical significance of these subtypes, their virulence and their ability to evade vaccination (Truyen, 2006; Pratelli et al., 2001; Goddard and Leisewitz, 2010). It is possible for dogs to be co-infected with more than one virus strain (Vieira et al., 2008).

Prophylactic vaccination for CPV is common practice around the world and is a component of the core vaccinations recommended for all dogs in Australia. Attenuated live virus vaccines are considered the most effective and thus preferable choice for CPV prophylaxis; however killed vaccines are available and have also been proven to stimulate an adequate antibody response (Buonavoglia et al., 1992; Decaro et al., 2007; Goddard and Leisewitz, 2010; Hoare et al., 1997). The vaccines available in Australia and elsewhere are made using either the original CPV or the CPV-2b variant (Larson and Schultz, 2008). A multivalent

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attenuated live vaccine used at 6–9 weeks of age and repeated every 3–4 weeks until the puppy is 14–16 weeks old has been until recently considered best practice (Davis-Wurzler, 2014); however vaccines reporting effective immunity with a 10-week and 12-week finish are also registered for use in Australia. Follow-up immunisation one year after completing the initial puppy series has also been a common recommendation, with some authors advocating subsequent triennial vaccinations with extended duration of immunity vaccines, although annual vaccines are still commonly available and utilised (Davis-Wurzler, 2014; Mouzin et al., 2004). In Australia, vaccines are registered for re-vaccination either on a 12-month basis ('annual vaccines') or every 3 years ('triennial vaccines') although veterinarians might also use vaccines 'off-label' in a manner different to the prescribed label (Australian Veterinary Association, 2013). CPV vaccines in Australia are almost all trivalent modified live vaccines and also include Canine Distemper and Canine Adenovirus type 2 components. Recently, the WSAVA Vaccine Guidelines Group (Day et al., 2016) has tightened their recommendations to now state that final puppy vaccination should take place at sixteen weeks of age or older, and for most effective immunity that the follow-up immunisation can be brought forward to between six months and twelve months of age. No information is currently available on veterinarians' actual vaccine usage patterns.

Although vaccination failure rates have not been quantified, their occurrence is well established and has been reported in the literature (Decaro et al., 2008). The most common cause of vaccination failure for all young animals is understood to be the interaction with maternally derived antibodies (MDA) preventing the onset of effective immunity (Buonavoglia et al., 1992; Decaro et al., 2005). MDA are predominately transferred to puppies through the ingestion of colostrum, although passive transfer through the placenta and the ingestion of CPV antibodies in milk is suggested to play some role (Davis-Wurzler, 2014; Decaro et al., 2005; Goddard and Leisewitz, 2010). While maternal immunisation is effective in protecting neonates for up to the first sixteen weeks of life it can interfere with CPV vaccination. The exact titre of maternal antibody that is capable of neutralising a CPV vaccination – while still unable to allow complete protection against CPV infection – is in dispute and likely varies between individuals. Original studies showed that circulating MDA titres ≥ 20 and < 80 were able to cause immunisation to be ineffective in stimulating antibodies whilst still allowing CPV infection (Pollock and Carmichael, 1982). Further studies have shown successful subclinical infection of puppies with titres of > 80 (Decaro et al., 2005). The window of MDA interference was reported to be between the ages of 40 and 69 days in one study (Iida et al., 1990). Interference of MDA with active immunisation against CPV infection has been reported to have been partially overcome under laboratory conditions by using either high-titre vaccinations (Buonavoglia et al., 1992; De Cramer et al., 2011; Decaro et al., 2005; Hoare et al., 1997) or intranasal vaccination (Buonavoglia et al., 1994; Decaro et al., 2007; Martella et al., 2005). No studies demonstrating an increased efficacy of these categories of vaccine under field conditions have been reported. Currently, intranasal CPV vaccines are not commercially available in Australia and while some available brands of vaccines are promoted as high-titre, there have been no studies demonstrating better efficacy in breaking through MDA in Australian puppies.

Another reported potential cause of vaccination failure is the difference between the strains of CPV used to produce vaccines and the strains circulating in the field (Mittal et al., 2014; Pratelli et al., 2001). Many of the vaccines available in Australia are based on the original virus variant CPV-2 that is now considered to be extinct in the field (Parrish et al., 1991). The remaining vaccines are based on the CPV-2b variant and no vaccines exist that have been developed from CPV-2a – the dominant strain currently reported in Australia (Meers et al., 2007) – or from CPV-2c variants. CPV-2b vaccines have been found to effectively produce antibodies against the heterologous CPV virus variants (Truyen, 2006; Wilson et al., 2014). Conversely, the CPV-2 vaccine has been suggested in one study (Pratelli et al., 2001) to stimulate a significantly lower and shorter immunity against the CPV-2b variant, and its efficacy with other variants has also been called into question. The clinical significance of this has not yet been demonstrated.

The large number of CPV-2 variants that have been discovered suggests a tendency for future virus mutation and variant development and has considerable potential implications for vaccination efficacy (Truyen, 2006). A review paper published in 2015 concluded that due to limitations in study design, small sample sizes, failure to test vaccines in the presence of MDA, and a lack of field trials, that the cross-protection of available vaccines for the new CPV-2c strain has not yet been conclusively proven and further trials are required (Hernández-Blanco and Catala-López, 2015).

Another commonly recommended prophylaxis to reduce CPV infection is to minimise the exposure of dogs potentially lacking immunity to high-risk environments. The suggested period of isolation varies; however, not exposing puppies to grassed areas or animals with unknown vaccination status prior to finishing the course of puppy vaccinations is a common recommendation. Further prophylaxis involves good hygiene practices with disinfection of all potential CPV exposed surfaces and equipment, and changing clothes and shoes if contact with contaminated environment is considered likely (Goddard and Leisewitz, 2010; Prittie, 2004; Scott, 1983).

To try and combat pathogens such as CPV, a voluntary disease surveillance program – *Disease WatchDog* – was launched in January 2010 in Australia with the aim of monitoring the prevalence, occurrence, transmission and risk factors of important companion animal diseases (Ward and Kelman, 2011). Registered veterinarians and their staff are encouraged to report a variety of disease cases and the resulting surveillance database has been used for a range of research purposes. The *Disease WatchDog* database has improved the epidemiological analysis of companion animal disease in Australia.

The objective of this study was to determine the association between CPV vaccination failure and vaccine strain, vaccine type and vaccination protocol. The findings of this study will aid veterinarians in their decision on the correct vaccine and protocol to give to an individual dog to help prevent CPV disease.

2. Materials and methods

2.1. Data source

All data were acquired from the *Disease WatchDog* database, which relies on veterinary practitioners and nurses entering disease case details. In exchange, submitters gain access to real-time maps and data specific to their practice area, enabling them to make more informed decisions regarding vaccination schedules and health prevention protocols for their patients.

Records of all CPV disease cases reported between 21 January 2010 and 4 June 2015 were extracted. All cases were screened for duplicate entries to ensure that case reports were only included once in analyses. Records were allocated a case identification number and contained the following generic data fields: clinic name, veterinarian name, case occurrence date, patient name, suburb, postcode, state, species, breed, age (years, months, weeks), gender (female, male or unknown), neuter status (neutered, entire or unknown), disease diagnosed, method of case diagnosis, case outcome, vaccination status, vaccine type and vaccination date. In the disease-reporting system, any vaccinations the patient had received were able to be recorded, however only the last vaccination prior to disease was used in the analysis. Any cases affecting multiple littermates were recorded concurrently through the use of a 'litter' checkbox and additional 'animals in litter' category in order to prevent repetitive data entry.