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CLINICAL STUDY

Investigation of post-vaccinal canine distemper involving the Rockborn-like strain in nine puppies in New Zealand

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ABSTRACT

Case history: This report details investigations into nine cases of neurological disease and/or sudden death in 8–13-week-old puppies between 2021 and 2024. Aside from two pairs of littermates, cases were unrelated. The puppies had an onset of clinical signs 9–23 days following at least one "on-label" dose of a commercially available quadrivalent vaccine containing live attenuated canine distemper virus (CDV).

Clinical findings: Eight of the nine cases displayed signs typical of "classic distemper," including seizures, circling, tremors, hypersalivation, progressive neurological deficits, pyrexia, and/or respiratory and gastrointestinal signs. Pathological and molecular investigations were undertaken in eight cases. Mononuclear/lymphohistiocytic encephalitis or meningoencephalitis with or without neuronal intranuclear inclusion bodies was present in seven cases. Five cases had bronchopneumonia. Other lesions included poliomyelitis, necrotising enteritis and myocardial necrosis or myocarditis. PCR for CDV was positive on tissues from seven cases, and immunohistochemistry for CDV was positive on neural tissues in six cases. Whole genome sequencing of PCR amplicons demonstrated a Rockborn-like strain with 99.9% homogeneity between samples from four cases and a vial of vaccine.

Diagnosis: Based on the combination of case history, pathological findings, molecular test results and/or whole genome sequencing, a diagnosis of post-vaccinal canine distemper was confirmed in six cases and presumed in two.

Clinical relevance: Outbreaks of canine distemper have been stemmed by widespread vaccination starting in the mid-twentieth century. Consequently, confirmed cases of natural CDV have not been reported in New Zealand since an outbreak in the 1980s, and CDV is considered a "notifiable organism" as per the Biosecurity Act 1993. This is the first case series to report genomic investigation of post-vaccinal canine distemper in New Zealand puppies and highlights a rare adverse event associated with routine vaccination. Our results suggest that puppies with neurological, respiratory and/or gastrointestinal disease with an onset within 6 weeks of vaccination with live attenuated CDV should be reported and investigated accordingly.

Abbreviations: CAV: Canine adenovirus; CDV: Canine distemper virus; CNS: Central nervous system; FFPE: Formalin-fixed paraffin embedded; IHC: Immunohistochemistry; MPI: Ministry for Primary Industries; RT-PCR: Reverse transcription real-time PCR

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Introduction

Canine distemper virus (CDV) is a negative-sense, single-stranded RNA virus of the genus *Morbillivirus* and family *Paramyxoviridae*. Distemper-like disease was first described as a cause of morbidity and mortality in dogs in the Americas in the eighteenth century, from where it spread to Europe and afar and was eventually attributed to a virus in 1905 (Bresalier and Worboys 2014). It has a worldwide distribution and wide host range, being able to infect and cause disease in a range of terrestrial and marine carnivores, including domestic and wild canids, felids, mustelids and phocids (Karki *et al.* 2022; Kennedy *et al.* 2022). It is similar to but genetically distinct from other morbilliviruses including phocine and cetacean morbilliviruses of marine mammals, peste de petits ruminants of sheep and goats, measles virus of humans, and the now eradicated rinderpest of cattle (Sykes and Vandevelde 2023).

CDV is a pantropic virus with a particular propensity to infect the central nervous system and epithelia of the respiratory and alimentary tracts and skin.

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"Classic distemper" occurs in infected puppies aged 12–16 weeks and coincides with the natural waning of maternal antibody. The initial clinical signs are characterised by pyrexia, diarrhoea, vomiting, cough, oculonasal discharge, anorexia, and acute death. Neurological signs are usually seen 1–3 weeks post-infection and may include myoclonus, seizures, vestibular ataxia and/or paresis. Dogs that do not die in the first few weeks may go on to develop enamel hypoplasia and hyperkeratosis of the nasal planum and/or footpads, secondary to infection of epithelial cells. Adult dogs that become infected tend to develop relatively milder signs including slowly progressive paresis and incoordination. The severity of clinical signs, lesions and outcome of infection depend on the level of host immunity and virulence of the viral strain (Sykes and Vandevelde 2023).

The first records of CDV in New Zealand dogs are from the 1950s (Hartley 1956; Smith 1956). Occasional case reports of natural ("wild-type") CDV infection have occurred across New Zealand including in Otago (Anonymous 1976a, 1981), Canterbury (Anonymous 1976b) and Manawatū-Whanganui (Anonymous 1979). The most recent recorded outbreak originated in the Auckland dog population in the early 1980s, spreading to dogs in Northland and the Bay of Plenty (Kearns 1984; Lifton 1984). The epidemic was believed to have resulted from low vaccination rates in the south Auckland dog population and the spread was stemmed with a widespread vaccination programme. Three cases of possible CDV in unrelated puppies occurred between 2018 and 2019. In these cases, a source of infection was not found and there was no evidence of an associated outbreak (Buckle and Chernyavtseva 2021). Currently, CDV is a notifiable organism under the New Zealand Biosecurity Act 1993 (Anonymous 2023), meaning that any suspected case must be reported to the Ministry for Primary Industries (MPI) via the Exotic Pest and Disease Hotline (0800 80 99 66) for investigation. Surveillance data collated through MPI have shown no convincing evidence that wild-type CDV is circulating in contemporary New Zealand (Buckle and Chernyavtseva 2021), and to the authors' knowledge, a wild-type case of distemper has not been confirmed in dogs in New Zealand since the outbreak in the 1980s.

Vaccination remains the core tool for preventing CDV in domestic dogs worldwide (Squires *et al.* 2024). The first vaccines were developed in the 1920s and became commercialised by mid-century. Early on, serum-based and inactivated vaccines were found to produce limited protection against CDV infection, leading to formulation of vaccines containing modified live or attenuated CDV strains (Haig 1953; Appel 1978). A rare side effect of some of these vaccines has been the occurrence of post-vaccinal distemper. Formally described for the first time in Australian dogs (Hartley 1974), post-vaccinal distemper has been described sporadically in dogs worldwide (Bestetti *et al.* 1978; Vandenberghe *et al.* 2021; Rätsep and Ojkic 2024). Some cases have occurred in littermates (Cornwell *et al.* 1988a; Fairley *et al.* 2015; Pekkarinen *et al.* 2024), leading to the suggestion, in some cases, that intrinsic genetic factors or heritable immunodeficiency may make some puppies more susceptible to developing disease. It has also been suggested that some vaccine strains may retain residual virulence (Appel 1978) and thus may become pathogenic within the host. Herein, we describe nine cases of disease in recently vaccinated puppies reported to MPI between 2021 and 2024, and investigation into its association with attenuated vaccine-derived CDV.

Clinical history

Nine puppies originating from seven locations around New Zealand were reported to the MPI Exotic Pest and Disease Hotline, and were subsequently investigated for having a clinical presentation, lesions and/or test results compatible with canine distemper. Seven of these cases, including two that were littermates, were notified between July 2021 and August 2022, and another two cases, also littermates, were notified in April 2024. All cases had originally presented to their veterinarian for a spectrum of respiratory, gastrointestinal and/or neurological signs that were persistent or progressive and led to eventual euthanasia (n = 8) or death (n = 1). Post-mortem examinations were performed at Massey University School of Veterinary Science (Palmerston North, NZ) (n = 4), Awanui Veterinary (formerly Gribbles) in Dunedin (n = 1) and Palmerston North (n = 1) or by a clinical veterinarian (n = 3).

Cases were 8–13 weeks of age and originated from either the North Island (n = 6) or the South Island (n = 3) of New Zealand. All nine puppies had been administered at least one dose of Vanguard Plus 5 (Zoetis New Zealand Ltd., Auckland, NZ) according to the manufacturer's instructions in the weeks (min 10, max 28 days) leading up to euthanasia or death. Vanguard Plus 5 is a quadrivalent vaccine containing modified live CDV, adenovirus type-2, parainfluenza virus and parvovirus. This was the sole vaccine formulation administered to these puppies, aside from Case 1b, which was administered Vanguard Plus 5 as a first vaccination alongside littermate Case 1a, followed by a booster 10 days later with Canigen DHA2PPi (Virbac, Hamilton, NZ), before developing clinical signs.

Clinical findings

The period between vaccination and onset of clinical signs was known for eight cases and ranged from 9 to 23 days. Neurological abnormalities were most common (8/9 cases), and included seizures, abnormal proprioception, tremors, muscle spasms, blindness

and disorientation. Five cases had respiratory signs which included cough, rattly chest, respiratory distress and oculonasal discharge. Diarrhoea and pyrexia were each seen in four cases.

Ante-mortem PCR testing was done at a commercial diagnostic laboratory (IDEXX, Palmerston North, NZ) on samples from two puppies. The IDEXX Canine Neurologic RealPCR panel was performed on cerebrospinal fluid collected from Case 6 and returned a positive result for CDV after the puppy was euthanised. Case 5 was originally presented for ongoing diarrhoea, and the IDEXX Canine Diarrhoea RealPCR panel was positive for CDV on a faecal sample. This was the only puppy not to have central nervous system lesions but was reported to MPI as it had received the same vaccine batch as Cases 3 and 4 and returned a positive CDV PCR result.

Cases 7a and 7b were from a litter of four in a shelter environment. Both puppies developed neurological signs and, following euthanasia of the second puppy, an investigation into post-vaccinal disease was initiated. The first affected puppy in the litter (Case 7a) was provided to the vaccine company for further investigation into the adverse event but given the concurrent onset of clinical signs and similarity in clinical presentation it is assumed the findings from its sibling (Case 7b) may be extrapolated to Case 7a.

A summary of case history and clinical findings is presented in Table 1.

Pathological findings

Gross findings were available for seven cases. The puppies were usually in good body condition, aside from Case 4, which was thin. Gross lesions included pulmonary consolidation or reddening (n = 5), watery large intestinal contents (n = 2), and focally extensive myocardial pallor (n = 1).

Histologic findings were available for eight cases. Mononuclear or lymphohistiocytic polioencephalitis was present in seven cases (Figure 1(a)). Intranuclear inclusion bodies were seen within neurons of the brain (n = 2) and spinal cord (n = 1) of two puppies (Figure 1(b)), and there was multifocal neuronal degeneration or necrosis with gliosis and rare neuronophagy in three cases (Figure 1(c)). Other central nervous system (CNS) findings included cerebral malacia (n = 2) and poliomyelitis (n = 2).

Respiratory tract lesions were seen in six cases and included bronchopneumonia (n = 3) and alveolar histiocytosis (n = 3). Necrotising enteritis was diagnosed in two puppies although notably the intestinal tract was too poorly preserved to interpret in several cases

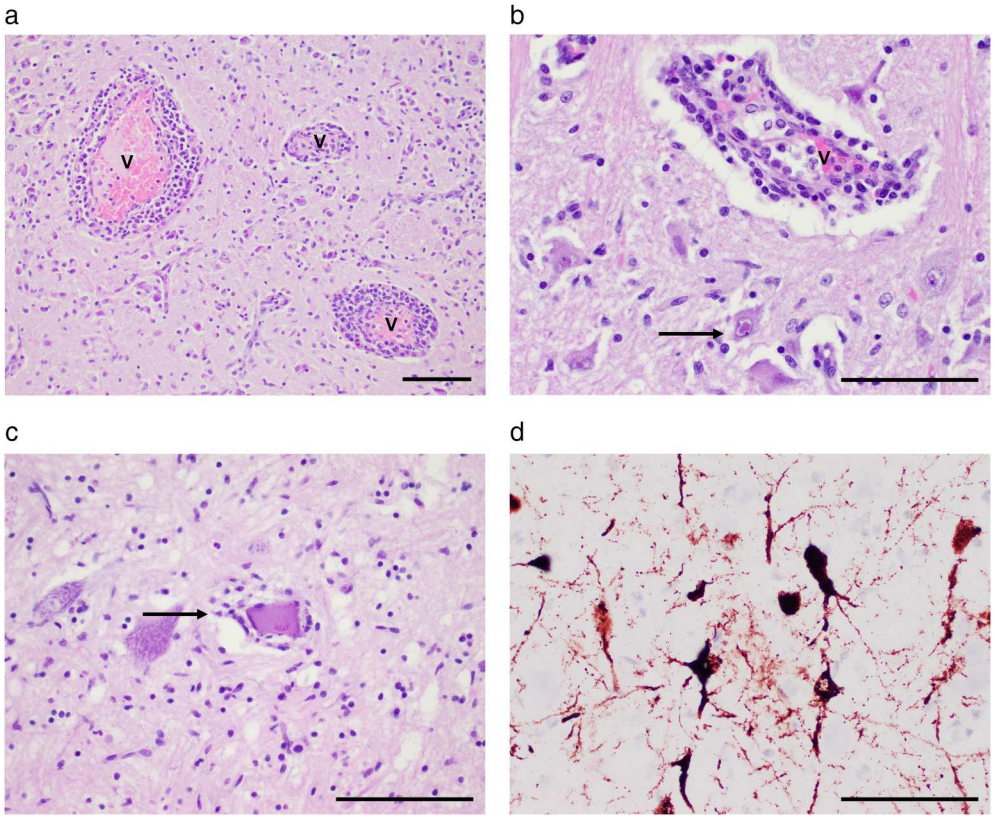

Figure 1. a–c: Photomicrographs of sections of brain from puppies with post-vaccinal distemper showing (a, b) encephalitis with gliosis and dense mononuclear perivascular cuffing in the grey matter of the brain; (b) occasional intranuclear eosinophilic inclusion within neurons (arrow); and (c) scattered neuronal degeneration with gliosis (arrow); H&E, V = blood vessel. (d) Immunohistochemistry showing strong positive immunoreactivity for canine distemper virus antigen in neurons and neuronal processes in the cerebral grey matter of Case 7b. Scale bar = 20 µm.

(n = 3). Four puppies had lymphocytic to suppurative myocarditis (n = 4) which in one case was accompanied by significant fibrosis. Myocarditis was considered to reflect bacterial sepsis secondary to bronchopneumonia in one case that also had multisystemic suppurative inflammation. Lymphocytolysis was seen in the lymph node of one puppy.

Laboratory findings

Given the implications of a CDV outbreak in New Zealand, further diagnostics were deemed appropriate and tissue samples from eight cases were submitted to the MPI Animal Health Laboratory (AHL; Upper Hutt, NZ) for further testing. The ninth case (7a) was provided to Zoetis for pathological and molecular investigations, which were pending at the time of writing.

PCR methodology

A range of fresh, fresh-frozen and formalin-fixed paraffin-embedded (FFPE) tissue scrolls from eight cases were submitted for RNA extraction and PCR (summarised in Table 2).

Nucleic acid extraction was performed using commercial kits. The MagMAX CORE Nucleic Acid Purification Kit (Applied Biosystems, Waltham, MA, USA) was employed to extract nucleic acid from fresh or fresh-frozen samples, while the NucleoSpin totalRNA FFPE XS (Macherey Nagel, Düren, Germany) was used for RNA extraction from FFPE tissue scrolls. Reverse transcription real-time PCR (RT–PCR) for CDV detection was conducted using primers and a probe from Elia *et al*. (2006) with the SuperScript III Platinum One-Step qRT-PCR Kit (Invitrogen, Waltham, MA, USA).

Six cases returned strong PCR-positive results on at least one tested tissue. One tested weakly positive on multiple tissues (Case 5) and one tested negative (Case 1b) (Table 2). Brain, liver and lung tissue from Case 1b were subsequently tested for canine herpesvirus-1, canine parainfluenza virus and canine adenovirus-2, all of which returned a negative result.

Immunohistochemistry

Immunohistochemistry for CDV was performed at the University of Guelph (Guelph, ON, Canada), using an automated staining platform (Dako autostainer; Dako/Agilent, Mississauga, ON, Canada). Tissue sections were incubated with anti-CDV monoclonal antibody and a brown chromogen (Vector Laboratories, Burlington, ON, Canada), and counterstained with H&E. Tested tissues were compared against known positive controls of lung. For negative reagent controls, duplicate sections of each positive control and tested tissue were subjected to the same immunohistochemical procedure with the substitution of antibody diluent for the primary antibody.

Six cases showed strong cytoplasmic immunoreaction of neurons and neuronal processes in the brain (Figure 1(d)), along with spinal cord neurons in one case. Cytoplasmic immunoreaction was also present in macrophages in the meninges, lung (alveolar spaces and interstitium) and lymph node, and in bronchiolar epithelial cells (Table 2).

Whole genome sequencing

Total RNA was extracted from fresh-frozen tissue samples of four cases (2, 3, 4 and 7b) and a reconstituted vial of Vanguard Plus 5 vaccine (batch 627184A, expiry 21 May 2024) using the QIAamp Viral RNA Mini kit (Qiagen, Hilden, Germany). The complete CDV genome was amplified by tiled RT–PCR from total RNA using published primers (Zhigang *et al*. 2021). Tiled RT–PCR amplicons were assessed for quality (TapeStation 4200 using High Sensitivity D5000 ScreenTape; Agilent, Santa Clara, CA, USA), purified (1.8X AMPure XP beads; Beckman Coulter Ltd., Brea, CA, USA); and pooled at equimolar concentrations. Each pool was prepared in quadruplicate for Oxford Nanopore sequencing on a MinION instrument using the Rapid Barcoding Kit 24 v14 and the manufacturer's software (Oxford Nanopore Technologies, Oxford, UK). The CDV genome sequence (NCBI accession NC_001921) was chosen as reference, and reads were mapped using the long read protocol of BBMap[1] and a consensus sequence generated using SAMtools (Danecek *et al*. 2021).

Complete genome assemblies (15,690 nucleotides) were obtained from the vaccine and samples from four puppies. A whole genome alignment using MAFFT (Katoh and Standley 2013) showed 99.87% identity with only 25 nucleotides of difference between the vaccine and puppy's assemblies, which we attribute to sequencing noise. In comparison, an alignment between the tested samples and the closest public reference sequence (NCBI accession KU666057), has 96.7% identity with 525 nucleotides of difference between them.

Whole genome sequencing of PCR-amplicons revealed a Rockborn-like strain with 99.9% homogeneity between samples from all four puppies and the tested vial of vaccine. In order to place these genomes within the context of known CDV sequences, an extended set of 15 genomes from diverse geographical origins were downloaded from NCBI[2] and,

[1] https://sourceforge.net/projects/bbmap/
[2] https://www.ncbi.nlm.nih.gov/

Table 1. Summary of case signalment, location, vaccination history, clinical presentation and pathologic lesions of nine puppies investigated for post-vaccinal distemper-like disease in New Zealand, 2021–2024.

Case	Signalment[a]	Location	Total number of vaccinations[b]	VG5 batch[c]	Days to onset of signs; death[d]	Clinical signs	Post-mortem lesions
1a	10-week-old F Huntaway	Southland	1	467769A	13; 28	Pyrexia (40.8°C), hypersalivation, seizures, diarrhoea, respiratory distress.	Non-suppurative encephalitis with malacia and intranuclear inclusion bodies (neurons and astrocytes). Necrotising myocarditis and enteritis. Severe fibrinosuppurative bacterial pneumonia.
1b	10-week-old M Huntaway	Southland	2	467769A	Unknown; 35	Tremors, oculonasal discharge, respiratory distress, pyrexia (39.4°C), lethargy, anorexia, weight loss, peripheral lymphadenomegaly, diarrhoea.	Lymphohistiocytic encephalitis with malacia. Lymphohistiocytic to suppurative myocarditis. Bronchointerstitial pneumonia. Necrotising enteritis. Nodal lymphocytolysis.
2	9-week-old Poodle cross	Waikato	1	5501109a	13; 13	Seizures, vomiting, respiratory signs.	Severe lymphohistiocytic meningoencephalitis. Alveolar histiocytosis.
3	2-month-old M English Springer Spaniel	Christchurch	1	501449	9; 10	Seizures, head tremor, muscle spasms, pyrexia (39.8–41.8° C), rattly respiration, hypersalivation.	Mild lymphohistiocytic meningoencephalitis. Lung too autolysed to interpret.
4	12-week-old M Kangal	Wellington	Uncertain, 1 known	501449	13; 15	Diarrhoea, progressive circling to the right.	Thin condition. Lymphohistiocytic encephalitis with scattered neuronophagy and malacia with Gitter cells. Alveolar histiocytosis.
5	10-week-old F Boxer	Auckland	1	501449	20; 20	Diarrhoea, acute collapse, unable to use hindlimbs, death.	Chronic lymphocytic myocarditis with fibrosis. Alveolar histiocytosis.
6	13-week-old F Rottweiler	Taranaki	1	5503078	23; 26	Altered proprioception, worsening head tremor, cough, seizures.	Meningoencephalitis and poliomyelitis, with gliosis, neuronal necrosis, neuronophagy and intranuclear inclusion bodies (neurons). Severe Gram-negative bacterial bronchopneumonia. Multifocal histiocytic-to-eutrophilic myocarditis, hepatitis and anterior uveitis (sepsis).
7a	8-week-old crossbreed	Northland	1	627184A	9; 10	Circling, tremors, blindness, hypersalivation	Not available[e]
7b	8-week-old crossbreed	Northland	1	627184A	10; 10	Mucopurulent ocular discharge, disorientation, pyrexia (40.3°C)	Mild non-suppurative meningoencephalitis, acute pulmonary oedema.

[a]As recorded at time of death.
[b]The total number of vaccinations of any brand administered.
[c]Batch refers to the most recently administered dose of Vanguard Plus 5.
[d]All puppies except Case 5 were euthanised.
[e]Puppy given to Zoetis Inc. for further work-up.
F = female; M = male; VG5 = Vanguard Plus 5.

including the sequenced samples, were used to build a cladogram with the UPGMA method on MEGA11 (Tamura *et al.* 2021), which places the vaccine and puppy samples together (Supplementary Figure 1).

Additional details on the methodology used are provided in Supplementary Information 1.

Discussion

For this case series, the following definition of a confirmed case of post-vaccinal distemper was used: puppies that had received at least one dose of vaccine containing live attenuated CDV administered according to manufacturers' guidelines, and which had molecular and/or immunohistochemical evidence of viral presence as well as one or more of encephalitis, poliomyelitis, pneumonia or myocarditis. By this definition, post-vaccinal distemper was confirmed in six puppies (Cases 1a, 2, 3, 4, 6 and 7b). Presumptive cases included two littermates of confirmed cases (1b and 7a), who had received the vaccine and developed clinical disease but where presence of vaccine was not definitively linked to post-mortem lesions. To the authors' knowledge, this is the first published study describing whole genome sequencing of a Rockborn-like strain and the first to link post-vaccinal distemper with the Rockborn-like CDV strain in New Zealand dogs.

Historically, proving the involvement of a vaccine in the development of CDV-like disease has relied on

Table 2. Summary of laboratory results for canine distemper virus PCR, immunohistochemistry and whole genome sequencing (WGS) on samples from nine puppies investigated for post-vaccinal distemper-like disease in New Zealand, 2021–2024.

	PCR		Immunohistochemistry		
Case	Tissues tested	Results	Tissues tested	Results	WGS tissue sample
1a	Conjunctival swabs, whole blood (EDTA)	Weak positive (swabs); negative (EDTA)	Brain, lung, liver	Positive in neurons, bronchiolar epithelial cells, alveolar macrophages	
1b	Brain, lung, liver, whole blood (EDTA)	Negative[a]	Brain	Negative	
2	Lung, brain, liver, spleen, kidney, colon, faeces	Positive (brain, faeces, pooled tissues); weak positive (lung, colon)	Spleen, lung, thymus, myocardium, kidney, liver, GIT, pancreas, brain	Positive in neurons (cerebellum, anterior and posterior colliculus, hippocampus, cortex)	Brain
3	Brain (FFPE), liver, kidney, stomach contents	Positive (all tissues)	Brain	Positive in neurons (cerebral gyrus, brainstem)	Stomach contents
4	Brain (FFPE), liver, lung, kidney, spleen, stomach contents	Positive (all tissues)	Brain, spinal cord	Positive in neurons (brain)	Spleen
5	Heart (FFPE), liver, lung, kidney, large intestine, small intestine, stomach contents; faeces[b]	Positive (faeces); negative (small intestine); weak positive (all other tissues)	Heart, liver, brain	Negative (all tissues)	
6	Brain (FFPE), heart, lung, spleen, liver, kidney, stomach contents; CSF[c]	Positive (brain, spleen, CSF); weak positive (lung, kidney); negative (heart, liver)	Brain	Positive in neurons (brain, spinal cord), meningeal macrophages	
7a	Not performed	Not available	Not available	Not available	
7b	Brain, lung, lymph node, conjunctiva, large intestine, small intestine, liver, CSF	Positive (all tissues)	Spleen, lymph node, kidney, heart, haired skin, brain	Positive in neurons and astrocytes (grey matter) and glial cells (white matter); scattered staining of macrophages in the lung, spleen and lymph node	Brain

[a]These tissues were also PCR-negative for canine herpesvirus-1, canine adenovirus and canine parainfluenza virus.
[b]Tested as part of IDEXX Canine Diarrhoea RealPCR panel (IDEXX Laboratories Pty. Ltd., Hamilton, NZ).
[c]Tested as part of IDEXX Canine Neurologic RealPCR panel (IDEXX Laboratories Pty. Ltd., Hamilton, NZ).
CSF = cerebrospinal fluid; FFPE = formalin-fixed, paraffin-embedded; GIT = gastrointestinal tract.

epidemiology and a temporal association with vaccine administration, although environmental factors and the possibility of wild-type disease can make interpretation of some cases difficult. In dogs with naturally acquired CDV infection, an ante-mortem clinical diagnosis can often be made by correlation of signalment and compatible clinical signs with demonstration of CDV genetic material within body fluids or tissues, usually done using commercially available RT–PCR. The optimal sample for this is an oropharyngeal or conjunctival swab due to early viral replication and persistence at these sites (Kim *et al.* 2006; Nemeth *et al.* 2018), but CDV RNA may also be detected in blood, cerebrospinal fluid and faeces (Frisk *et al.* 1999; Kim *et al.* 2006). Relying on RT–PCR positive results becomes difficult in cases of suspected post-vaccinal disease, as CDV RNA can be detected in similar samples following vaccination with attenuated virus for up to 2–3 weeks (Adaszek *et al.* 2023). Genomic sequencing allows differentiation of vaccine-derived viral strains from field ("wild-type") strains and was used here to demonstrate the same viral strain in fresh tissues from four cases and within a vial of vaccine, confirming implication of the vaccine strain. These findings were combined with immunohistochemistry, the gold standard test for CDV-induced disease (Nemeth *et al.* 2018), to demonstrate CDV within lesional tissues.

Some assumptions have been made with the two cases of littermates (Cases 1a and 1b, 7a and 7b). In both situations, each set of littermates had received the same vaccine on the same day, and each presented with similar signs to one another, although other littermates were unaffected. One of each pair was confirmed to have post-vaccinal disease with the approach outlined above (Table 2). Case 1b tested negative on PCR and IHC, and as well as receiving a primary dose of Vanguard Plus 5, had received a second vaccine booster with a different vaccine formulation 10 days prior to euthanasia. Given the confirmation of post-vaccinal disease in this puppy's sibling following vaccination solely with Vanguard Plus 5, extrapolation of the evidence suggests this may have also caused the similar clinical signs and lesions seen in Case 1b, and that false negative test results are possible in this case. Retrospective repeated testing in light of the additional cases was not possible for Case 1b due to a lack of available samples. At the time of writing, Case 7a was pending post-mortem examination and further investigation led by Zoetis.

In this case series, Case 5 may be an outlier. This puppy presented clinically for persistent diarrhoea and was determined to have died from myocardial failure secondary to myocarditis. This case was included in this case series as a positive CDV PCR result was obtained on a faecal sample in the week prior to death; the signalment and temporal distribution of signs was consistent with possible post-vaccinal disease; and the puppy had received the same

vaccine batch as two other affected puppies. Clinically, the positive PCR result on a faecal sample was suspected to merely represent post-vaccinal shedding; however, myocardial necrosis and/or myocarditis was seen in three other cases presented here and has been previously described in both dogs with naturally acquired CDV (Higgins *et al*. 1981) and mustelids with post-vaccinal distemper (Gill *et al*. 1988). We have considered the possibility of vaccine-derived CDV having caused Case 5's myocardial lesions, however this has not been confirmed, and an alternative underlying factor such as previous parvovirus infection was not excluded (Molesan *et al*. 2019).

Commercially available modified live vaccines contain attenuated strains of CDV which tend to differ from those found in a natural setting ("wild-type" strains) (da Fontoura Budaszewski *et al*. 2016; Anis *et al*. 2018). There have been several strains utilised in vaccines, including Rockborn-like, Onderstepoort, Snyder Hill and Convac (Anis *et al*. 2018), although the first two are most widely used. Currently, there are three brands of CDV-containing vaccine available in the New Zealand market: Nobivac Puppy DP, DHP and DHPPi (MSD Animal Health/Schering-Plough Animal Health Ltd., Upper Hutt, NZ), Canigen DHA2PPi (Virbac New Zealand Ltd., Hamilton, NZ) and Vanguard Plus 5 (Zoetis New Zealand Ltd.). Of these, only the Nobivac vaccines stipulated the CDV strain used on the label at the time of product registration. Following initial genomic investigations into these cases in 2022, an application was made by MPI to amend the product registration information for Vanguard Plus 5 to include that it contains an attenuated Rockborn-like strain of CDV (Zinzley 2022).

The composition of vaccines associated with cases of post-vaccinal CDV varies, as does the availability of genomic sequencing to implicate certain strains. Attenuated vaccines containing the Rockborn-like strain are considered highly immunogenic and are an effective immunisation strategy against natural disease. A Rockborn-like strain was reported to revert to virulence after multiple passages in laboratory conditions (Appel 1978) and has been associated with sporadic cases of post-vaccinal encephalitis in dogs since the 1980s. A recent report from Canada described post-vaccinal CDV in a 14-week-old puppy, with 99.9% homogeneity of the H gene to the Candur-Rockborn-like strains (Rätsep and Ojkic 2024), although the vaccine used was not stated. In 1995, a vaccine recall notice was issued in the USA for increased vaccine-associated reactions in puppies, all of which at least partly manifested as "CNS disturbance" (Gloyd 1995) and were attributed to a Rockborn-like strain (Martella *et al*. 2011). A report from the UK describing cases of post-vaccinal disease in greyhound littermates was initially linked with a Rockborn-like strain and suggested to be a possible batch issue (Cornwell *et al*. 1988a), although the association with a Rockborn-like strain was later retracted (Cornwell *et al*. 1988b). Some of the earlier reports of post-vaccinal CDV encephalitis were associated with use of vaccines that also contained attenuated canine adenovirus (CAV) type-1, the causative agent of infectious canine hepatitis (Hartley 1974; Bestetti *et al*. 1978). Attenuated CAV-1 has been linked with other adverse post-vaccinal events and has since been replaced with CAV-2, which has different tissue tropism but produces adequate cross-reactivity with much lower risk of adverse events (Appel 1999).

A previous 2015 report on post-vaccinal distemper encephalitis in New Zealand described two littermates who had received initial vaccinations with a brand that is no longer commercially available in NZ (Canvac 4, Pfizer Animal Health, Auckland, NZ) (Fairley *et al*. 2015) and anecdotally contained a different strain (CSL-Masterseed) to that implicated here (K. Brownlie,[3] pers. comm.) One of the littermates had developed disease following routine puppy vaccinations, and the other presented a year later following annual booster vaccine with Vanguard Plus 5 (then produced under the Pfizer Animal Health brand). While some sources state that disease does not occur with the Ondeersteport strain (Appel 1999), that strain has been associated with sporadic case reports (Keawcharoen *et al*. 2005), including a recent report on confirmed post-vaccinal disease in two litters of purebred dogs in Finland (Pekkarinen *et al*. 2024). The two affected litters had temporal and pathologic features that differ to the puppies described here, and multiple related purebred dogs being affected raises the possibility of a genetic or familial immunologic factor making them more susceptible to disease. As suggested by Fairley *et al*. (2015), the genetic makeup of individual dogs and littermates may affect their inherent susceptibility to infectious disease and may be relevant when multiple puppies from one litter develop post-vaccinal disease.

The host response to challenge with an attenuated virus can be influenced by a multitude of factors, including genetics, immuno-naivety, immunosuppression, or immunodeficiency; presence of comorbidities; and vaccine-dependent factors including the strain used and level of attenuation (Martella *et al*. 2011). With natural CDV infection, puppies may clear the virus with neutralising antibodies derived from prior challenge with natural infection or vaccination, or from maternally derived antibodies. Common to the puppies in this case series are their age and the vaccine used, whereas their geographic location and breed varied. The exception to this is Case 1b, who had received a more recent booster with a different

[3]K. Brownlie, Zoetis NZ, Auckland, NZ.

vaccine. Aside from Case 1b, lymphoid necrosis was not a common feature and there was no suggestion from gross or histological examination of the lymphoid tissues that any of these puppies had a congenital immunodeficiency, although functional assessment of this was not practical in any case. Relevant co-morbidities including co-infections were not evident from clinical, epidemiological and pathological investigations, however cannot be completely ruled out in all cases. A vaccine-specific factor must be considered, and while several puppies received the same batch, this was inconsistent and cannot explain all cases over the relevant period. Whether there could be differences in the manufacturing of the vaccine is uncertain and, at the time of writing, further investigation by the vaccine company is underway as a requirement of registration of a veterinary medicine in New Zealand (Anonymous 2022). It should also be considered that the notifiable nature of CDV in New Zealand may have prompted more in-depth investigation than would otherwise have been done in a country in which wild-type CDV still circulates, and in which post-vaccinal disease may be overlooked.

By and large, serious vaccine-associated disease is considered a very rare occurrence (Edwards *et al.* 2004; Valli 2015) but equivalent data has not been collated in New Zealand. Information on the number of different vaccines sold and administered to New Zealand dogs is not publicly available, making it difficult to comment on disease prevalence and relative risk. Zoetis has provided comment that "*Vanguard Plus 5 sales for the period July 2021 to June 2024 averaged 79.93% of total canine core (distemper, hepatitis, parvovirus, parainfluenza) vaccine sales in New Zealand*" (K. Brownlie[4], pers. comm.). It is important to note that all canine vaccines available in New Zealand satisfied regulatory bodies with regard to safety studies and documentation prior to their registration. The Agricultural Compounds and Veterinary Medicines Act 1997 (Anonymous 1997) stipulates that any reported adverse event must be investigated by the product registrant, who must work with MPI to reach a satisfactory resolution. In August 2024, following these reports, MPI commenced a review into the risks and benefits associated with the use of Vanguard Plus 5 in dogs in New Zealand (Narayan 2024).

Case 6 was the only one to receive extensive supportive care in hospital and included intensive care with artificial ventilation; the others were primarily managed as outpatients but euthanised due to deteriorating neurological signs. There are no specific antiviral treatments available for natural CDV and infected dogs are generally provided with supportive care based on clinical signs. This may include prophylactic antibiotics to control secondary infections, and anticonvulsant therapy to limit further systemic damage caused by neurological disturbances. Unfortunately, CDV-induced neurological signs are unanimously difficult to treat and are often progressive, although corticosteroids may be useful to reduce CNS oedema (Sykes and Vandevelde 2023). Owing to its rarity, there is little information published on managing CNS signs secondary to vaccine-induced disease.

In a contemporary setting, wild-type CDV is considered rare in well-vaccinated dog populations, although breakthrough cases are seen where there is crossover with wild reservoirs accompanied by lapses in vaccine coverage and herd immunity (Ek-Kommonen *et al.* 1997; Wyllie *et al.* 2016; Feijóo *et al.* 2021). There is increasing concern for the emergence of new wild-type strains of CDV and cross-species spread overseas, especially in recent years (Kennedy *et al.* 2022; Karki *et al.* 2022), exemplified by the emergence of a new wild-type strain associated with a disease outbreak in Australian ferrets (George *et al.* 2022). New Zealand has a feral mustelid population that is not actively surveyed, however the lack of confirmed wild-type CDV cases in dogs suggests CDV may not be circulating in wild reservoirs, but further research into this area may be warranted and continued monitoring is justified. Canine parvovirus and CAV-1 are similarly associated with high morbidity and mortality in dogs, and, like CDV, are largely controlled with widespread vaccination, although reports still occur in New Zealand (Hardcastle 2020). Immunisation against these three potentially lethal canine diseases continues to be recommended as part of core vaccines in dogs worldwide, and veterinarians are referred to the World Small Animal Veterinary Association vaccination guidelines for further information on current best practices (Squires *et al.* 2024).

The apparent lack of wild-type CDV in New Zealand and its notifiable status placed us in a unique position to promptly recognise these cases of post-vaccinal distemper and to distinguish it from wild-type CDV. Our results suggest that puppies with neurological, respiratory and/or gastrointestinal disease with an onset within 6 weeks of vaccination with live attenuated CDV vaccine should be considered as possible vaccine-associated cases and reported and investigated accordingly.

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No potential conflict of interest was reported by the author(s).

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