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Risk factors for death from canine parvoviral-related disease in Australia

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ABSTRACT

Canine parvovirus (CPV) is a highly contagious cause of serious and often fatal disease in dogs worldwide despite the availability of safe and efficacious vaccines. Although a number of studies have focussed on identifying risk factors in disease development, risk factors associated with death from CPV are largely unknown. In this study we analysed a total of 1451 CPV cases reported from an Australian surveillance system – using univariate and multivariate techniques – to determine significant risk factors associated with death and euthanasia. A crude case fatality rate of 42.3% was estimated – higher than has been reported previously. We found that 3.3% of CPV cases had a history of vaccination in the previous 12 months, despite having completed the primary puppy vaccination course. The majority (89.5%) of these cases occurred in dogs <12 months of age, indicating failure of the primary vaccination course to provide protective immunity (most likely due to interference of the vaccine antigen with maternal antibodies but other reasons are discussed). Extending the age at which the final puppy vaccination is administered might be one of several strategies to consider. The final multivariate model showed that in non-litter CPV cases, risk of death was significantly associated with season of diagnosis (summer) and pedigree type (hounds and non-sporting dogs). Euthanasia in non-litter CPV cases was significantly associated with season of diagnosis (summer), state of residence (Northern Territory/South Australia/Tasmania combined), age (<six months) and vaccination status (unvaccinated and unknown). No significant risk factors associated with death were identified in cases in which there was more than one puppy in a litter infected. The risk factors identified in this study can be used as prognostic indicators for veterinarians faced with CPV cases. The possible explanations for the associations identified and their clinical relevance to CPV case outcome are discussed

1. Introduction

Canine parvovirus (CPV) is a major cause of morbidity and mortality in dogs worldwide, particularly in puppies (Goddard and Leisewitz, 2010). The virus is transmitted via the faeco-oral route and preferentially infects rapidly dividing cells, showing a tropism for small intestinal epithelium, lymphoid tissue, bone marrow, and occasionally the myocardium if the puppy is less than three weeks of age (Prittie, 2004). Death of myeloproliferative cells and thymic lymphocytolysis causes immunosuppression. Malabsorption, vomiting and diarrhoea from damaged intestinal lining and villous atrophy, can rapidly progress to shock and death due to continual fluid and protein losses, bacterial sepsis and endotoxaemia. Occasionally myocarditis or pneumonia is observed (Goddard and Leisewitz, 2010).

Estimated case fatality rates have varied between studies, but mostly range between 25% and 35% (Brinke and Neiger, 2010; Glickman et al., 1985; Horner, 1983;

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Kalli et al., 2010). In the absence of treatment, case fatality rates approach 91%. However, with prompt and aggressive treatment, survival rates can reach 80–95% (Prittie, 2004).

The most commonly reported risk factor predisposing to CPV related disease is lack of protective immunity. This may be due to failure of passive transfer of antibodies via colostrum, incomplete or ineffective primary vaccination course, or failure of vaccination to induce immunity because of interference by maternal antibodies (Smith-Carr et al., 1997). Unvaccinated puppies aged between six weeks and six months are at greatest risk of developing CPV-related disease, and the incidence of disease is also greater in the warmer months of the year (Godsall et al., 2010; Horner, 1983; Smith-Carr et al., 1997). The reported predisposition of certain breeds – including Rottweiler, Doberman pinscher, German shepherd, American pit bull terrier, Labrador retriever, Springer spaniel and Yorkshire terrier (Day, 1999; Glickman et al., 1985; Goddard and Leisewitz, 2010; Godsall et al., 2010; Smith-Carr et al., 1997) – suggests genetic susceptibility to disease.

Case fatality rates associated with CPV-related disease in Australia have not been recently documented, and very little information is available on the risk factors associated with death. It has been suggested that younger age and non-current vaccination status adversely affect disease outcome, however, this has not been formally investigated in Australia (Godsall et al., 2010; Horner, 1983; Houston et al., 1996).

Few recent studies on the epidemiology of infectious diseases in pet populations have been published. Surveillance of the canine population for infectious disease in Australia is rare, and most examples of surveillance systems elsewhere have focussed on zoonotic diseases, notably rabies and parasitic infections (*Trichuris*, *Isospora*, *Toxascaris*, *Ancylostoma* and *Toxocara*). In January 2010 Virbac Animal Health in Australia launched Disease WatchDog, a national companion animal health surveillance system (Ward and Kelman, 2011). The aim was to provide information on occurrence, transmission and risk factors for CPV-related disease (and other infectious diseases in dogs and cats). This surveillance project has provided the first dataset of information available on the epidemiology of CPV infection in Australia. The aim of the current study was to estimate the case fatality rate for canine parvoviral-related disease in Australia during the period 1st January to 31st December 2010, and to identify those risk factors – including age, sex, vaccination status, pedigree type, reproductive status, season and state of residence – associated with death. These factors can be used as prognostic indicators by veterinarians when treating diagnosed CPV cases, as well as providing insights into the effectiveness of current vaccination practices.

2. Materials and methods

2.1. Data collection

Data was collected using Disease WatchDog, a real-time online canine and feline infectious disease surveillance system developed and maintained by Virbac Animal Health (Ward and Kelman, 2011). The Disease WatchDog database was created for veterinary practitioners across Australia to log epidemiological data and provide real-time updates on infectious disease occurrences, notably canine parvovirus, canine distemper virus, feline herpesvirus, feline calicivirus, feline infectious peritonitis, and feline leukaemia virus (www.diseasewatchdog.org). Awareness of the Disease WatchDog initiative within the veterinary profession has been promoted via the Australian Veterinary Association and several diagnostic laboratories, notably IDEXX Laboratories, Gribbles Veterinary Pathology and Vetnostics (Ward and Kelman, 2011).

Registration to apply for access to the Disease WatchDog database is voluntary, completed online, and restricted to veterinarians and veterinary nursing staff so as to maximise reliability of recorded data. Continued participation from registered participants is encouraged by provision of written resources mailed to the practice and monthly email reminders to log cases for the previous month. Representatives from Virbac Animal Health regularly conduct visits at participating clinics to promote continued awareness and provide support.

Case information recorded by practitioners in the Disease WatchDog database includes identification of the veterinarian, patient and veterinary clinic; disease; method of case diagnosis (CPV faecal antigen test, clinical presentation, polymerase chain reaction, immunofluorescence, other); date of diagnosis; postcode of patient's residence; patient signalment (age, breed, reproductive status); and case outcome (died, euthanased, survived, or treatment ongoing). Multiple cases affecting littermates are entered simultaneously by means of a 'litter' checkbox to prevent repetitive data entry. Data entered online is immediately visible on maps that registrants can view, thereby providing real-time information about disease cases and outbreaks in particular geographical areas.

2.2. Data management

Data was extracted from the Disease WatchDog database, filtering for CPV cases with a reported case diagnosis date between 1st January and 31st December 2010. Case date, method of diagnosis (CPV antigen test, clinical, PCR, immunofluorescence, other), state of patient's residence, breed (specific breed or mixed), age (in years and months), sex (male, female), reproductive status (entire, neutered), vaccination status (vaccinated, unvaccinated, unknown), litter infected (yes, no), number in litter infected, and case outcome (died, euthanased, survived, treatment ongoing) were extracted from the database for each record for analysis.

Cases were not included in data analysis if the record contained date discrepancies (for example if the vaccination date preceded date of birth, or if date of diagnosis preceded vaccination date) or if the record had incomplete information. Duplicate entries were also removed prior to analysis.

Case outcome information was recorded as death, euthanasia, survived or treatment ongoing. For analysis, 'survived' or 'treatment ongoing' cases were combined to create an outcome variable 'survived'. The categories 'death' and 'euthanasia' were retained.

Predictor variables were categorised for statistical analysis. Method of diagnosis was categorised as CPV faecal antigen test, clinical presentation, or other (polymerase chain reaction, immunofluorescence, contact with diagnosed case, unspecified CPV test). Within Disease Watch-Dog, generic drop-down menus are present for the entry of 'method of diagnosis' regardless of which disease is being logged. Cases diagnosed via immunofluorescence were placed in the 'other' category in this situation due to lack of reliability of positive results for CPV: it was not specified whether these were antibody tests (not useful for CPV diagnosis) or antigen tests. Cases diagnosed via PCR, contact with a diagnosed case and unspecified CPV tests were also grouped as 'other' due to small numbers in each category.

Recorded date of diagnosis was used to classify cases according to season (summer – December, January, February; autumn – March, April, May; winter – June, July, August; and spring – September, October, November). Sex was male, female or unknown. Vaccination status was classified as unknown; unvaccinated; incomplete primary vaccination course; or vaccinated within the previous 12 months (with completed primary puppy course of vaccinations). Completion of the primary course of vaccinations was defined as those puppies who received their last vaccination at greater than 14 weeks of age, as per vaccination guidelines of the World Small Animal Veterinary Association (WSAVA) (Day et al., 2010). Incomplete primary vaccination course was defined as those puppies who received one or more vaccinations prior to 14 weeks of age.

Reproductive status was neutered or entire. Breed information (specific breed or mixed breed) was extracted and cases were categorised as either pedigree or mixed breed; pedigree dogs were then further classified as gundog, hound, non-sporting, terrier, toy, utility or working dog. State of residence was New South Wales, Queensland, Victoria, Western Australia or other (Tasmania, Northern Territory, South Australia combined). Age for non-litter cases was categorised into <six months of age, six to <12 months, 12 to <18 months, 18 to <24 months, and 24 months and older.

For cases with a litter diagnosis of CPV, age was categorised into one to <two months of age, two to <three months, three to <four months, four to <five months, and five months or more. Number of infected animals in each litter was categorised as one or two infected littermates, three or four infected littermates, and five or greater.

CPV cases were subdivided into three categories for statistical analysis to determine significant risk factors; litter cases, non-litter cases that died, and non-litter cases that were euthanased. Positive litter diagnosis cases were analysed separately to non-litter cases because potential risk factors associated with death – such as greater environmental virus contamination and greater opportunities for increased faeco-oral transmission due to mixing of cases within the litter – could not be accounted for in non-litter cases. Risk factors for non-litter cases were analysed separately for cases that died and for cases that were euthanased, because it is likely that additional risk factors contributed to euthanasia (such as restriction of owner finances affecting willingness to proceed with treatment) other than disease severity.

Identification of risk factors for death in non-litter cases was restricted to those with a positive CPV faecal antigen test result because of the high specificity of this diagnostic method (Decaro et al., 2005, 2010; Desario et al., 2005; Esfandiari and Klingeborn, 2000; Kumar et al., 2010). Those cases diagnosed with clinical presentation were excluded from the analysis because of the possibility that some of these cases may not have been true CPV cases. Cases categorised in the 'other' category were not included due to small numbers and likely poor positive predictive value.

Identification of risk factors for death (died or euthanased combined) in litter cases was not restricted to a particular diagnostic method because of the limited case numbers. In addition it was assumed that each recorded case in the litter had a positive CPV diagnosis via the specified test, thereby increasing specificity of results for the diagnostic methods.

Potential predictor variables for death in non-litter cases who died or were euthanased included age, sex, reproductive status, vaccination status, mixed breed or pedigree, pedigree type, season and state of patient's residence. Predictor variables for death in litter cases included age, vaccination status, number in litter affected, mixed breed or pedigree and season. Other recorded variables were not included for litter animals due to insufficient number of cases.

2.3. Data analysis

Crude case fatality rate and group-specific case fatality rates were calculated as (numerator) the number of cases that died, or the number of cases that were euthanased, as a proportion of (denominator) the total number of cases. This total represents the number of cases that survived (survived and treatment ongoing categories) and those that either died or were euthanased. Confidence intervals were calculated assuming a binomial distribution.

The association between case outcome (died or euthanased, versus survived and treatment ongoing) and age, sex, reproductive status (neutered or entire), vaccination status (unknown; unvaccinated; vaccination within previous 12 months; incomplete primary vaccination course), breed (mixed breed or pedigree), pedigree type, and season was estimated by unadjusted odds ratios. This was only done for associations that were statistically significant ($P < 0.05$), determined using the chi-squared test for independence.

Following univariate analysis, the covariates (potential risk factors) that best predicted the odds of the outcome variable (death or euthanasia) were identified by fitting logistic regression models to the dataset. Variables that were statistically associated with the outcome at a P-value of 0.20 or less were selected for analysis and a multivariate logistic regression model was created using a forward stepwise algorithm. Likelihood ratio tests were used to select variables. The final multivariate model only included variables significant at $P < 0.05$. Odds ratios and 95% confidence intervals were calculated to interpret the relationship between these predictor variables and the outcome. The overall goodness of fit of the final logistic

regression model was assessed using the Hosmer and Lemeshow test. Microsoft Excel 2008 was used for all data management and SPSS v. 19 (SPSS Inc., 2010) was used for all data analysis.

3. Results

Between 1st January and 31st December 2010, 166 veterinary clinics across Australia recorded CPV cases in the Disease WatchDog database. In total there were 1198 individual CPV events reported during this period. Forty nine reports (4.1%) were removed prior to analysis: eight reports as non-identical copies, 16 incomplete reports, 24 reports with date discrepancies, and one report that cited a 'negative parvo test' as the case diagnosis. The remaining 1149 reports included 126 litter diagnoses reported as single events. When each dog within a litter was counted as a single event, this resulted in a total of 1451 individual CPV cases.

Of the 1149 reports, 873 (76%) were diagnosed via CPV faecal antigen test, 220 (19%) via clinical presentation, and 56 (4.9%) via other methods (PCR, immunofluorescence, unspecified CPV test). The majority of reports involved dogs less than one year of age: 691 reports (60.1%) were dogs less than six months of age, 289 (25.2%) were six to less than 12 months of age, 85 (7.4%) were 12 to less than 18 months of age, 22 (1.9%) were 18 to less than 24 months of age, and 67 (5.8%) were 24 months and older. The mean and median age of reported cases were 236 and 133 days (approximately 7.5 and 4.5 months), respectively.

There were 38 cases (3.3%) with a history of vaccination in the previous 12 months (having completed primary puppy course), compared with 195 cases (17.0%) with an incomplete primary vaccination course, 916 dogs (58.3%) that were unvaccinated and 246 (21.4%) that had an unknown vaccination status. The majority (89.5%) of dogs reported as CPV cases that had a history of vaccination within the previous 12 months were under 12 months of age.

Mixed breed dogs comprised 527 (45.9%) reports and pedigree dogs comprised 622 (54.1%) reports. Of the 622 reports in pedigree dogs there were 33 (5.3%) gundogs, 32 (5.1%) hounds, 56 (9.0%) non-sporting dogs, 214 (34.4%) terriers, 53 (8.5%) toy dogs, 55 (8.8%) utility dogs and 179 (28.8%) working dogs. There were 249 (21.7%) reports made in summer, 365 (31.8%) in autumn, 217 (18.9%) in winter and 318 (27.7%) in spring.

Of the 1023 non-litter cases, 449 (43.9%) were female, 566 (55.3%) were male, and 8 (0.7%) were of unknown sex; 960 (93.8%) were entire and 63 (6.2%) were neutered.

3.1. Crude case fatality rate

Of the 1451 cases recorded, there were 614 mortalities (died and euthanased) resulting in a crude case fatality rate of 42.3% (95% CI 39.8–44.9%). Of the mortalities, 264 (43%) cases died and 350 (57%) were euthanased.

3.2. Non-litter cases

There were 776 reported non-litter cases diagnosed by CPV faecal antigen test; for these reports the case fatality rate was 35.8% (95% CI 32.5–39.3%).

3.2.1. Risk factors for death in non-litter cases

Risk factor analysis for death in non-litter cases (Table 1) was restricted to reports in which CPV was determined to be the cause of disease using the CPV faecal antigen test ($n = 776$). Age was not a significant risk factor for death from CPV ($P = 0.13$), however, group-specific fatality rates were highest in dogs less than six months of age (19.1%, 95% CI 15.1–23.8%) and dogs 18 months to less than 24 months of age (23.1%, 95% CI 6.2–54.0%). There was no significant association between the risk of death and vaccination status ($P = 0.94$), sex ($P = 0.82$) or reproductive status ($P = 0.56$).

Breed (mixed breed versus pedigree) was not a significant risk factor for death ($P = 0.48$), however, there was a significant association with pedigree type ($P = 0.0005$). Group-specific case fatality rates were highest in hounds (43.8%, 95% CI 20.8– 69.4%), gundogs (29.2%, 95% CI 13.4–51.2%) and non-sporting dogs (34.6%, 95% CI 17.9–55.6%). Death was 4.5 times more likely in hounds, 2.4 times more likely in gundogs, and 3.1 times more likely in non-sporting dogs, compared to mixed breed dogs. Terriers and working dogs had a reduced risk of death compared to mixed breed dogs.

The season in which a CPV case was reported was significantly associated with the risk of death ($P = 0.007$). The group-specific case fatality rate was highest for cases reported in summer (24.8%) compared to autumn (15.8%), winter (16.7%) and spring (9.6%). Cases diagnosed in summer were 3.1 times more likely to die compared to cases diagnosed in spring.

State of residence was a significant risk factor for death from CPV ($P = 0.03$). The highest case fatality rate was estimated for New South Wales (20.1%), followed by Queensland (15.0%) and Victoria (14.6%). Cases in Western Australia were at least risk of dying, with a fatality rate of only 5.7%.

The following variables were associated ($P < 0.2$) with the outcome of death in non-litter cases: season, state of residence, pedigree type and age. As shown in Table 2, the final best-fitting multivariate logistic regression model included two variables: season ($P = 0.013$) and pedigree type ($P = 0.002$). Cases reported in summer were at greatest risk of death (OR 3.09; 95% CI 1.57–6.05, $P = 0.01$) compared to spring. Compared to mixed breed dogs significant increased risk of death was found for hounds (OR 4.26; 95% CI 1.45–12.53, $P = 0.008$) and non-sporting dogs (OR 3.33; 95% CI 1.36–8.14, $P = 0.008$). The final model fitted the data adequately (Hosmer and Lemeshow chi-squared statistic = 1.816, $P = 0.99$).

3.2.2. Risk factors for euthanasia in non-litter cases

Risk factor analysis for euthanasia in non-litter cases (Table 3) was restricted to reports in which CPV was diagnosed using the CPV faecal antigen test ($n = 776$). There was no significant association between the risk of euthanasia and sex ($P = 0.19$), reproductive status ($P = 0.51$), breed ($P = 0.66$) or pedigree type ($P = 0.73$).

Vaccination status was significantly associated with the risk of euthanasia ($P = 0.0009$). The likelihood of death was higher for unvaccinated dogs (31.9%) and dogs with an unknown vaccination status (26.7%) compared to dogs vaccinated within the previous 12 months (20.8%). Of

Table 1
Risk factors for death from canine parvovirus in Australian dogs (non-litters) reported in the Disease WatchDog database from 1st January to 31st December 2010. Odds ratios were only calculated for significant ($P < 0.05$) risk factors.

Variable	Category	Died	Survived	Case fatality (%)	95% CI	X^2 statistic	*P*-value	OR
Age	<6 m	63	267	19.1	15.1–23.8	7.2	0.13	NA
	6–12 m	18	151	10.7	6.6–16.5			
	12–18 m	5	36	12.2	4.6–27.0			
	18–24 m	3	10	23.1	6.2–54.0			
	>24 m	5	34	12.8	4.8–28.2			
Vaccination status	Vaccinated <12 m	3	19	13.6	3.6–36	0.43	0.94	NA
	Unvaccinated	49	250	16.4	12.5–21.2			
	Unknown	26	132	16.5	11.2–23.4			
	Incomplete primary vaccination	16	97	14.2	8.6–22.3			
Sex	Female	40	220	15.4	11.3–20.5	0.05	0.82	NA
	Male	53	277	16.1	12.4–20.6			
Reproductive status	Neutered	8	34	19.0	9.1–34.6	0.34	0.56	NA
	Entire	86	464	15.6	12.8–19.0			
Breed	Mixed breed	39	226	14.7	10.8–19.7	0.48	0.49	NA
	Pedigree	55	272	16.8	13.0–21.4			
Pedigree type	Gundog	7	17	29.2	13.4–51.2	25. 9	0.0005	2.4
	Hound	7	9	43.8	20.8–69.4			4.5
	Non-sporting	9	17	34.6	17.9–55.6			3.1
	Terrier	11	96	10.3	5.5–18.0			0.7
	Toy	6	25	19.4	8.1–38.1			1.4
	Utility	7	28	20.0	9.1–37.5			1.4
	Working	8	80	9.1	4.3–17.6			0.6
	Mixed breed	39	226	14.7	10.8–19.7			1
Season	Summer	29	88	24.8	17.5–33.8	12.2	0.007	3.1
	Autumn	31	165	15.8	11.2–21.9			1.8
	Winter	17	85	16.7	10.3–25.6			1.9
	Spring	17	160	9.6	5.9–15.2			1
Australian state	New South Wales	56	223	20.1	15.6–25.4	10.7	0.03	1.6
	Queensland	16	91	15.0	9.0–23.4			1.1
	Victoria	13	76	14.6	8.3–24.0			1.1
	Western Australia	5	82	5.7	2.1–13.5			0.4
	Other	4	26	13.3	4.4–31.6			1

CI, confidence interval; OR, odds ratio; NA, not applicable.

those dogs with an incomplete primary vaccination course, only 12.6% died or were euthanased.

The season in which a CPV case was reported was significantly associated with the risk of euthanasia ($P = 0.01$). The proportion of dogs euthanased was highest for cases reported in summer (36.7%) compared to autumn (28.3%), winter (22.0%) and spring (21.6%).

State of residence was also a significant risk factor for euthanasia ($P = 0.003$). The highest proportions of euthanasia were recorded in Queensland (37.2%) and Tasmania/

Table 2
Final multivariate logistic regression model for risk factors associated with death from canine parvovirus in Australian dogs (non-litters) reported in the Disease WatchDog database from 1st January to 31st December 2010.

Variable	Category	*b*	S.E.	*P*-value	OR	95% CI
Season	Spring	0	–	–	1	–
	Winter	0.72	0.38	0.06	2.05	0.98–4.32
	Autumn	0.67	0.33	0.04	1.95	1.02–3.71
	Summer	1.13	0.34	0.001	3.09	1.57–6.05
Pedigree type	Mixed	0	–	–	1	–
	Working	−0.58	0.41	0.16	0.56	0.25–1.26
	Utility	0.41	0.46	0.38	1.50	0.61–3.72
	Toy	0.22	0.50	0.66	1.25	0.47–3.29
	Terrier	−0.36	0.37	0.33	0.70	0.34–1.44
	Non-sporting	1.20	0.46	0.01	3.33	1.36–8.14
	Hound	1.45	0.55	0.01	4.26	1.45–12.53
	Gundog	0.89	0.49	0.07	2.44	0.93–6.38

CI, confidence interval; OR, odds ratio; NA, not applicable.

Table 3
Risk factors for euthanasia from canine parvovirus in Australian dogs (non-litters) reported in the Disease WatchDog database from 1st January to 31st December 2010. Odds ratios were only calculated for significant ($P < 0.05$) risk factors.

Variable	Category	Euthanased	Survived	Case fatality (%)	95% CI	X^2 statistic	*P*-value	OR
Age	<6 m	118	267	30.6	26.1–35.6	8.44	0.08	NA
	6–12 m	36	151	19.3	14.0–25.8			
	12–18 m	14	36	28.0	16.7–42.7			
	18–24 m	3	10	23.1	6.2–54.0			
	>24 m	13	34	27.7	16.1–42.9			
Vaccination status	Vaccinated <12 m	5	19	20.8	7.9–42.7	16.57	0.0009	1.0
	Unvaccinated	117	250	31.9	27.2–37.0			1.64
	Unknown	48	132	26.7	20.5–33.9			
	Incomplete primary vaccination	14	97	12.6	7.3–20.6			0.55
Sex	Female	70	220	24.1	19.4–29.6	1.70	0.19	NA
	Male	111	277	28.6	24.2–33.4			
Reproductive status	Neutered	10	34	22.7	12.0–38.2	0.43	0.51	NA
	Entire	174	464	27.3	23.9–30.9			
Breed	Mixed breed	87	226	27.8	23.0–33.2	11.24	0.66	NA
	Pedigree	97	272	26.3	21.9–31.1			
Pedigree type	Gundog	3	17	15.0	4.0–38.9	4.39	0.73	NA
	Hound	5	9	35.7	14.0–64.4			
	Non-sporting	6	17	26.1	11.1–48.7			
	Terrier	41	96	29.9	22.6–38.4			
	Toy	9	25	26.5	13.5–44.7			
	Utility	6	28	17.6	7.4–35.2			
	Working	27	80	25.2	17.6–34.7			
	Mixed breed	87	226	27.8	23.0–33.2			
Season	Summer	51	88	36.7	28.8–45.3	11.24	0.01	2.1
	Autumn	65	165	28.3	22.6–34.6			1.4
	Winter	24	85	22.0	14.9–31.2			1.0
	Spring	44	160	21.6	16.3–28.0			1.0
Australian state	New South Wales	70	223	23.9	19.2–29.3	15.80	0.003	0.5
	Queensland	54	91	37.2	29.5–45.7			0.9
	Victoria	21	76	21.6	14.2–31.4			0.4
	Western Aust	22	82	21.2	14.0–30.5			0.4
	Other	17	26	39.5	25.4–55.6			1.0

CI, confidence interval; OR, odds ratio; NA, not applicable.

South Australia/Northern Territory [combined] (39.5%), compared to New South Wales (23.9%), Victoria (21.6%) and Western Australia (21.2%).

Proportions of euthanasia were highest in puppies less than six months of age (30.6%), dogs 12–18 months (28.0%) and dogs over 24 months of age (27.7%), however, these differences were only marginally significant ($P = 0.08$).

The following variables were associated ($P < 0.2$) with the outcome of euthanasia in non-litter cases: season, state, age, sex and vaccination status. As shown in Table 4, the final best-fitting multivariate logistic regression model included four variables: season ($P = 0.005$), residential state ($P = 0.010$), age ($P = 0.025$) and vaccination status ($P < 0.001$). Cases reported in summer were at greatest risk of euthanasia (OR 2.33; 95% CI 1.40–3.87, $P = 0.001$) compared to spring. Dogs in New South Wales (OR 0.42; 95% CI 0.21–0.86, $P = 0.02$) and Western Australia (OR 0.43; 95% CI 0.19–0.96, $P = 0.04$) had a reduced risk of euthanasia compared to Tasmania/Northern Territory/South Australia combined. Dogs aged less than six months of age were at greatest risk of euthanasia compared to dogs in all other age categories. Unvaccinated dogs (OR 1.66, 95% CI 0.58–4.76, $P = 0.34$) and those with unknown vaccination status (OR 1.45, 95% CI 0.49–4.29, $P = 0.51$) were at greater risk of euthanasia compared to dogs vaccinated within the previous 12 months. Dogs with an incomplete primary vaccination course were 0.48 times less likely to be euthanased (95% CI 0.15–1.55, $P = 0.22$) compared to dogs vaccinated within the previous 12 months. The final model fitted the data adequately (Hosmer and Lemeshow chi-squared test = 4.44, $P = 0.73$).

3.3. Risk factors for death in litter cases

There were 126 litters reported as CPV cases in Disease WatchDog between 1st January and 31st December 2010. Of these litters, 59 (46.8%) had one or two affected puppies, 39 (31.0%) had three or four affected puppies, and 28 (22.2%) had five or more affected puppies. There were 58 litters (46.0%) of mixed breed and 68 litters (54.0%) of pure breed puppies. Of the 126 litters, 64 litters (50.8%) were unvaccinated, 19 litters (15.1%) had an unknown recorded vaccination status, 39 litters (31.0%) had received an incomplete primary vaccination course, and 4 litters (3.1%) had been vaccinated in the previous 12 months (having completed the primary puppy course of vaccinations).

Table 4
Final multivariate logistic regression model of risk factors associated with euthanasia due to canine parvovirus in Australian dogs (non-litters) reported in the Disease WatchDog database from 1st January to 31st December 2010.

Variable	Category	*b*	S.E.	*P*-value	OR	95% CI
Season	Spring	0	–	–	1	–
	Winter	−0.01	0.31	0.97	0.99	0.54–1.80
	Autumn	0.31	0.24	0.20	1.37	0.85–2.20
	Summer	0.85	0.26	0.001	2.33	1.40–3.87
Australian state	Northern territory/South Australia/Tasmania	0	–	–	1	–
	WA	−0.86	0.42	0.04	0.43	0.19–0.96
	Victoria	−1.03	0.42	0.01	0.36	0.16–0.81
	Queensland	−0.27	0.38	0.48	0.77	0.37–1.61
	New South Wales	−0.86	0.36	0.02	0.42	0.21–0.86
Age	<6 m	0	–	–	1	–
	6 to <12 m	−0.75	0.23	0.001	0.47	0.30–0.74
	12 to <18 m	−0.28	0.37	0.45	0.76	0.37–1.56
	18 to <24 m	−0.52	0.69	0.45	0.60	0.15–2.30
	>24 m	−0.23	0.36	0.51	0.79	0.40–1.59
Vaccination status	Vaccinated <12 m	0	–	–	1	–
	Unvaccinated	0.51	0.54	0.34	1.66	0.58–4.76
	Unknown	0.37	0.55	0.51	1.45	0.49–4.29
	Incomplete primary vaccination	−0.74	0.60	0.22	0.48	0.15–1.55

CI, confidence interval; OR, odds ratio; NA, not applicable.

There was an approximately equal distribution of cases across seasons: 35 (27.8%) litters in autumn, 31 (24.6%) in winter, 31 (24.6%) in spring and 29 (23.0%) in summer.

As shown in Table 5, no significant association was found between age ($P = 0.11$), vaccination status ($P = 0.36$), number of puppies in litter affected ($P = 0.33$), breed ($P = 0.36$) or season ($P = 0.08$) and death from CPV-related disease.

Increasing age of puppies in infected litters was associated with a reduced risk of death, although overall this trend was non-significant ($P = 0.11$). Puppies in litters aged one to less than two months of age had an estimated case fatality rate of 77.8%; the case fatality rate reduced progressively with increasing age to the point where case fatality rate of puppies over five months of age was 28.0%.

The case fatality rate was higher in unvaccinated litters (57.8%), litters with unknown vaccination status (47.4%) and litters that had received an incomplete primary vaccination course (43.6%), compared to puppies in those litters which had completed the primary course of vaccinations (25.0%), although this difference was non-significant ($P = 0.36$). The highest case fatality rate was

Table 5
Risk factors for death from canine parvovirus in Australian dogs (litters) reported in the Disease WatchDog database from 1st January to 31st December 2010. Odds ratios were only calculated for significant ($P < 0.05$) risk factors.

Variable	Category	Died and euthanased	Survived	Case fatality (%)[a]	95% CI	X^2 statistic	*P*-value	OR
Age	1 m to <2 m	14	4	77.8	51.9–92.6	7.53	0.11	NA
	2 m to <3 m	28	27	50.9	37.2–64.5			
	3 m to <4 m	12	14	46.2	27.1–66.3			
	4 m to <5 m	5	9	35.7	14.0–64.4			
	>5 m	5	8	28.0	15.1–67.7			
Vaccination status	Vaccinated <12 m	1	3	25.0	1.3–78.1	2.07	0.36	NA
	Unvaccinated	37	27	57.8	44.8–69.8			
	Unknown	9	10	47.4	25.2–70.5			
	Incomplete primary vaccination	17	22	43.6	28.2–60.2			
Number in litter infected	1–2	26	33	46.1	31.4–57.5	2.2	0.33	NA
	3–4	23	16	59.0	42.2–74.0			
	5 or more	15	13	53.6	34.2–72.0			
Breed	Mixed breed	32	26	55.2	41.6–68.0	0.82	0.36	NA
	Pedigree	32	36	47.1	35.0–59.5			
Season	Summer	14	15	48.3	29.9–67.1	6.7	0.08	NA
	Autumn	24	11	68.6	50.6–82.6			
	Winter	14	17	45.2	27.8–63.7			
	Spring	12	19	38.7	22.4–57.7			

CI, confidence interval; OR, odds ratio; NA, not applicable.
[a] Death and euthanasia.

recorded in autumn (68.6%) and the lowest in spring (38.7%).

4. Discussion

This study reports the first population-based estimate of case fatality rate from naturally acquired CPV in the Australian canine population. In non-litter cases, pedigree type, season and state of residence were risk factors for death from CPV; vaccination status, season, state of residence and age were risk factors for euthanasia. No significant risk factors for death from CPV-related disease were found for litter cases.

Risk factors for death and euthanasia were analysed separately due to the presence of unmeasured confounding factors – such as financial status of the owner, the strength of the bond between an owner and their dog, and availability of treatment options within veterinary facilities – that may influence the decision to euthanase an animal with clinical disease. Significant risk factors for death from CPV were therefore assumed to be more accurate predictors of disease severity.

Reliability of results for risk factor analysis was maximised by only using cases diagnosed via positive CPV faecal antigen tests, since the high specificity (reportedly 95.9–99.7%) of this diagnostic method reduces the number of false positive cases included in the analysis (Decaro et al., 2005, 2010; Desario et al., 2005; Esfandiari and Klingeborn, 2000; Kumar et al., 2010). False positives may occur if the test is performed four to ten days following administration of a modified-live vaccine (the test is unable to discriminate between field and vaccine antigens). The presence of vaccine antigen in the faeces is likely due to the replication of live vaccine virus within lymphoid tissue or epithelial cells of the gastrointestinal tract and subsequent faecal shedding of antigen (Lamm and Rezabek, 2008; Patterson et al., 2007; Pollock and Coyne, 1993). This issue is most relevant for puppies receiving their primary course of vaccinations, since vaccination and susceptibility to CPV infection occur concurrently.

The estimated case fatality rate (43.2%) in this study is higher than reported elsewhere, with studies in New Zealand, the United States of America and Europe documenting case fatality rates between 26% and 36% (Glickman et al., 1985; Horner, 1983; Kalli et al., 2010). In our study, selection bias is likely to be a factor when using data to estimate case fatality rates. Although all participating veterinary clinics are encouraged to report all cases of parvovirus (and other diseases), it is possible that at least for some clinics, only the more severe clinical cases (which are more likely to die or be euthanased) were reported. This would result in an overestimation of the case fatality rate.

Seasonality was a significant risk factor for death in non-litter cases, with dogs diagnosed in summer most at risk of death and euthanasia compared to other seasons. There is reportedly a higher incidence of CPV in warmer months of the year, proposed to be due to greater opportunities for viral particle transmission associated with peak breeding season, greater movement of dogs, increased mixing of dogs at recreational facilities, and greater use of boarding and kennel facilities over the holiday period – although it is uncertain whether these same factors also influence death rates (Kalli et al., 2010; Smith-Carr et al., 1997). It could be hypothesised that ingestion of a greater number of virion particles (secondary to increased environmental contamination) increases disease severity resulting in high death rates, however, this is difficult to prove in a field study due to the difficulty of measuring the size of the viral inoculum ingested.

State of residence was a significant risk factor for death in non-litter cases, with New South Wales recording the highest case fatality rate (20.1%) and Western Australia recording the lowest (5.7%). One recently published study demonstrated the occurrence of mutation and recombination of CPV strains – termed antigenic shift – in Japan (Mochizuki et al., 2008). It is plausible that this might also be occurring in Australia, resulting in differences between strains present in particular geographical areas. Subsequently, there might be reduced protection from maternally derived antibodies and reduced effectiveness of vaccination, whereby immunonaivety to newly evolving strains in particular states may increase susceptibility to infection and reduce a dog's ability to mount an effective immune response against the virus. Consequentially, there would be greater infection severity and higher death rates (Lamm and Rezabek, 2008). Dogs in Western Australia are likely geographically isolated from the dog population in eastern Australia, hence the evolution of different CPV strains is plausible.

Population density should also be considered as a factor influencing death in different states. In this study the Australian states that recorded the highest case fatality rates (New South Wales, followed by Victoria and Queensland) have a higher human population density than states recording the lowest case fatality rates (Western Australia and Northern Territory/South Australia/Tasmania combined) (Australian Bureau of Statistics, 2010). It could be hypothesised that more populated areas with a higher density of dogs experience more severe disease and therefore higher case fatality rates, possibly due to ingestion of a greater number of virions secondary to increased environmental contamination, however, this is yet to be documented.

Differences in herd immunity could also be considered an important factor contributing to the higher case fatality rate from CPV-related disease in Australia compared to other countries, and also differences across Australian states. Dogs living in geographical regions with low herd immunity experience greater infection incidence, most likely due to greater opportunities for transmission secondary to a higher volume of circulating parvovirus virions within their given population, in combination with the presence of an adequate number of susceptible hosts. For CPV, the presence of susceptible hosts depends largely on the proportion of animals that are vaccinated, since vaccination has proven efficacy in protecting dogs against infection with field strains (Truyen, 2006). It could be hypothesised that geographical regions with low herd immunity experience greater disease severity and higher case fatality rates, however, this has not been documented (Woolhouse et al., 1997). Future studies investigating the rate of vaccination uptake and the level of herd immunity

in Australia would contribute significantly to our understanding of the risk factors for CPV-related disease and death, and guide future prevention strategies.

The higher case fatality rate in Australian dogs compared with other countries may also be due to differences in strain virulence. A recent study found that the predominant antigenic variant in Australia, CPV-2a, differed from other common strains in some countries in Europe and the United States (CPV-2b and CPV-2c) (Meers et al., 2007; Truyen, 2006). Different antigenic CPV strains have varied clinical effects based on animal signalment, immunocompetence, viral dosage and route of transmission, hence it is plausible that the CPV-2a strain in Australia may overall be more virulent and produce more severe disease than the 2b and 2c strains. If this were true, infection in immunonaive dogs in Australia (most likely due to either lack of adequate vaccination or vaccine failure due to interference with maternal antibodies) may be more likely to result in death from CPV than infection in immunonaive dogs elsewhere, resulting in a higher overall case fatality rate (Goddard and Leisewitz, 2010; Lamm and Rezabek, 2008). The level of immunocompetence against CPV in any canine population is affected largely by vaccination status (Smith-Carr et al., 1997), which is discussed further below.

Breed of dog (mixed or pedigree) was not a significant risk factor for death or euthanasia in this study. Pedigree dogs have previously been reported to be at increased risk of developing CPV compared to mixed breed dogs, however, results of the current study showed that once infected, there was a similar prognosis for survival between mixed breed and pedigree dogs (Kalli et al., 2010). However, there was a significant effect within pedigree dogs: the highest case fatality rates were estimated for hounds, non-sporting dogs and gundogs, and the lowest fatality rates were estimated for terriers and working dogs. This trend may be due to differences in immune competence between specific breeds as immunological nonresponsiveness is thought to be controlled genetically, although interestingly pedigree types at greater risk of death in this study do not correlate with those specific breeds previously reported to be at greatest risk of CPV infection (Rottweiler, Doberman pinscher, German shepherd, American pit bull terrier, Labrador retriever, Springer spaniel, and Yorkshire terrier) (Day, 1999; Glickman et al., 1985; Goddard and Leisewitz, 2010; Godsall et al., 2010; Smith-Carr et al., 1997). An estimated 0.1% of dogs in general are non-responsive to CPV vaccines and whilst this lack of response is genetically controlled it is seen across breeds (Welbon et al., 2011). This may account for some of the deaths reported in vaccinated dogs in this study.

Surprisingly vaccination status was not a significant risk factor for death from CPV (Table 1), even though lack of protective immunity is the most reported risk factor predisposing to disease (Smith-Carr et al., 1997). One explanation is selection bias: if more severe clinical cases are reported and if these cases are also more likely to have vaccination status recorded within Disease Watchdog, this could result in vaccination status appearing as less of a risk factor. Equally, this finding may simply demonstrate the multifactorial nature of this disease, with other factors such as co-infection, stress, parasites and nutrition, potentially influencing the outcome in these cases. Vaccination against CPV with a live attenuated vaccine is reported to prevent the development of clinical signs, reduce viral shedding, limit disease severity and reduce hospitalisation time, all together resulting in significantly lower case fatality rates in vaccinated dogs compared to unvaccinated dogs (Meunier et al., 1985; Spibey et al., 2008). These patterns were not found in the present study (Table 1): there was no significant difference in case fatality rates between dogs that were unvaccinated (16.4%) and those dogs that had received a vaccination within the previous 12 months. Age should be considered as a potential confounding factor for this result; however, the majority (89.5%) of dogs that had a history of vaccination within the previous 12 months that developed disease due to CPV were less than 12 months of age. In addition, exposure to parvovirus was not measured in this study and might account for the lack of association between veterinary clinic reported vaccination status and risk of parvovirus death. It is likely that vaccination still remains an essential factor in providing immunity and therefore reduced disease and overall case fatality rates.

There were 38 CPV cases (3.3%) that had a history of vaccination within the previous 12 months despite having received a complete course of primary puppy vaccinations, indicating apparent vaccine failure. This result questions the typical presentation of a parvovirus case as an unvaccinated animal, and indicates that CPV should be on the list of differential diagnoses for any dog presenting with vomiting or diarrhoea regardless of vaccination status. Of these 38 cases, 23 (60.5%) contracted CPV within 14 days of the last vaccination. The incubation period for CPV is three to seven days and it takes up to two weeks for dogs to establish protective immunity following vaccination depending on the success of previous boosters in the primary series; hence it is plausible that a proportion of these cases developed disease due to an insufficient time interval between vaccination and exposure to CPV (Day et al., 2010). This possibility highlights the need to keep puppies isolated from other dogs and parvovirus-contaminated public areas until at least two weeks following the final vaccination to allow sufficient immunity to develop prior to potential exposure. In addition a small proportion of the cases diagnosed within 14 days of vaccination may represent false positive test results in the CPV faecal antigen test, due to the inability of the test to discriminate between field and modified-live vaccine antigens for four to ten days following vaccination (Lamm and Rezabek, 2008; Patterson et al., 2007; Pollock and Coyne, 1993).

Lack of cross-protection between vaccine strains and newly emerging field strains could also be considered as a cause of vaccine failure, however, strong cross protection between strains is well reported in literature (Truyen, 2006). It is possible that vaccination status might have been misreported in some cases in Disease WatchDog. However, this is unlikely because reports came from veterinary clinics in which veterinarians and staff are expected to be familiar with the true vaccination status of patients (or else would have indicated uncertainty by reporting vaccination status as ‘unknown’).

Interestingly the majority of dogs (89.5%) that had a history of vaccination within the previous 12 months that developed disease due to CPV were under 12 months of age. This finding largely points towards failure of the primary puppy course of vaccinations to provide protective immunity. It is recommended that the final vaccine in the puppy course be given at 14–16 weeks, since at this age maternal antibodies are reported to have declined to a level at which vaccination should be effective in allowing development of acquired immunity to protect against field infection (Day et al., 2010). However, it is plausible that a small percentage of puppies at this age still have maternally derived antibodies capable of inactivating the vaccine antigen. This means that a large window of opportunity for infection exists in these particular dogs as maternal antibodies continue to decline below protective levels and their next vaccination is not for another 12 months. This trend certainly is an argument against the 'early finish' vaccination protocol, in which the final primary puppy vaccination is given at 10 or 12 weeks of age (Day et al., 2010). It may even be pertinent to consider a later finish for the final primary vaccination than at 14–16 weeks of age, in order to ensure those puppies with prolonged maternal immunity are able to fully respond to vaccination. Alternatively, the presence of CPV in vaccinated dogs may result from vaccination failure due to vaccine, procedural or patient factors. Vaccination of immunocompromised dogs may also be a cause of vaccine failure, due to the inability of the immune system to mount an effective response against the vaccine antigen. As discussed earlier, genetic non-responder state is thought to occur in 0.1% of dogs and may account for some of these cases in this study.

The potential presence of co-infections in CPV cases should also be considered as an influence on case outcome regardless of vaccination status. Development of a secondary bacterial infection reportedly increases the case fatality rate from CPV-related disease, often related to overgrowth of commensal bacteria in the gastrointestinal tract and invasion by *Salmonella*, β-haemolytic *Escherichia coli*, *Campylobacter* and *Clostridium difficile* resulting in septicaemia or endotoxaemia (Lamm and Rezabek, 2008; Prittie, 2004). Concurrent infection with coronavirus and endoparasites (such as hookworm, roundworm, *Giardia*, coccidia) are also reported to negatively affect outcome (Goddard and Leisewitz, 2010; Lamm and Rezabek, 2008; Prittie, 2004).

Vaccination status emerged as a significant risk factor for euthanasia (Table 3), with those dogs that were unvaccinated (31.9%) or had an unknown vaccination status (26.7%) having a higher rate of euthanasia than dogs with recent (20.8%), incomplete or non-recent (12.6%) vaccination status. Reasons influencing the owner's decision not to vaccinate their dog may be similar to factors influencing the owner's decision to euthanase their dog (such as insufficient finances to pay for veterinary services or lack of a strong emotional bond between pet and owner affecting their willingness to proceed with treatment).

Another unexpected finding was that age did not have a significant influence on death from CPV. One explanation is selection bias: if more severe clinical cases of parvovirus are reported within Disease Watchdog, and these cases over-represent older age categories within the source population, an age effect might not have been detected. Humoral immunity does not reach full adult capacity until one year of age in dogs: adult levels of serum IgM are reached at two to three months of age, adult serum IgG levels are not reached until six to nine months of age, and adult serum IgA levels are often not present until one year of age (Felsburg, 2002). Cell-mediated immunity is also compromised in younger animals, as adult numbers and proportions of T and B lymphocytes are not reached until 12 months of age (Day, 2007). This immaturity of humoral and cell-mediated immunity is thought to compromise the ability of younger animals to respond to immunogenic challenge, thereby resulting in increased severity of infection and higher case fatality rate from infectious disease in animals less than 12 months of age. In this study, however, prognosis for survival from CPV related disease was similar for non-litter dogs regardless of age, which may point towards a high level of virulence of Australian CPV strains.

Although younger dogs were no more likely to die from CPV than older dogs, a significantly higher rate of euthanasia was recorded for dogs less than six months of age compared to older dogs. It is hypothesised that this trend is less likely related to infection severity and more likely related to emotional and financial factors influencing the decision to euthanase an animal. It is possible that there is less of a human–animal bond between owners and younger dogs due to the shorter period of ownership, thereby negatively affecting willingness to proceed with veterinary treatment.

Small numbers of litter cases in this study means that interpretation of risk factors associated with death should be done with caution. The most noticeable trends in litter cases (aged under five months) were a higher case fatality rate in unvaccinated puppies, and higher case fatality rates associated with puppies of younger age (Table 5). This higher case fatality rate perhaps reflects the importance of herd immunity in protecting these puppies that are too young to vaccinate. The results of litter risk factor analysis were not statistically significant – most likely due to the relatively small number of litter cases ($n = 126$) in the study – and further research into these patterns with a larger study population is required to make reliable conclusions.

The clinical manifestations of CPV infection are multifactorial with elements of the host, pathogen and environment affecting infection severity and outcome, hence further research should be directed at identifying additional factors that may influence death. Presence of clinical signs on presentation associated with systemic inflammatory response syndrome (heart rate >140 beats/min, respiratory rate >30 breaths/min, temperature >39.2 °C or <37.8 °C) has been reported as a negative prognostic indicator, and it is also reported that presence of severe leukopaenia with the absence of a left shift negatively impacts survival rates (Goddard et al., 2008; Kalli et al., 2010). Hypercortisolaemia and low serum thyroxine concentrations are also strongly associated with non-survival (Schoeman et al., 2007).

Development of a secondary bacterial infection resulting in septicaemia and endotoxaemia is also reported to increase the risk of death, and as mentioned previously concurrent infection with other viruses, bacteria and endoparasites may also adversely affect infection outcome (Lamm and Rezabek, 2008; Macintire and Smith-Carr, 1997; Prittie, 2004). It would be useful to repeat these studies in a population of Australian dogs to determine whether similar patterns emerge.

One limitation of this study is that the current demographics of the canine population from which the data was collected is unknown. Documentation of the size and signalment of the base canine population in Australia as part of a national animal health surveillance system would enable calculations of infection prevalence to be made, as well as identification of risk factors for infection. These factors could then be compared to risk factors for death to enable a full description to be made of the epidemiology of canine parvovirus in Australia, with the ultimate aim of developing practices to lead to the eradication of CPV infection in dogs.

5. Conclusion

The high case fatality rate from CPV documented in this study is evidence that the infection continues to be an important cause of death in Australian dogs. Identification of risk factors associated with death provides prognostic information for veterinarians when faced with CPV cases, thereby allowing strategic preventive and treatment protocols to be developed. Such an understanding of the epidemiology of CPV and identification of the factors that influence outcome is necessary for making a step towards elimination of the disease from the Australian canine population.

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