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Influence of maternally-derived antibodies in 6-week old dogs for the efficacy of a new vaccine to protect dogs against virulent challenge with canine distemper virus, adenovirus or parvovirus

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ABSTRACT

The results from three studies determining the efficacy of a canine multivalent vaccine in the presence of maternal antibodies are reported. Each study used 15 six week old dogs; five dogs were sero-negative; the remaining 10 had maternally derived antibodies to CDV, CAV and CPV. The five MDA-negative dogs and five of the MDA-positive dogs were vaccinated twice with the vaccine while the remaining 5 MDA-positive dogs were administered sterile water. According to EU guidelines for MDA studies dogs were challenged when maternally-derived antibodies in non-vaccinated dogs had greatly diminished or disappeared (3–5 weeks after second vaccination); clinical observations and rectal temperatures were recorded, and sera and faecal samples (CPV study only) were collected throughout the study.

After challenge, non-vaccinated dogs showed clinical signs of infection while none of the vaccinated dogs did. MDA-negative vaccinated dogs sero-converted with increases in titre observed after each vaccination, and further increases observed after challenge. MDA-positive vaccinated dogs showed declining antibody titres following the first vaccination, but increases after the second vaccination and further increases after challenge. In all vaccinated dogs the immune responses generated were protective, irrespective of the presence of maternal antibodies, as demonstrated by heterologous viral challenge.

In conclusion, two doses of the DHPPi/L4R vaccine administered to dogs from six weeks of age in the presence of maternal antibodies aided in the protection against virulent challenge with CDV, CAV-1 or CPV.

Introduction

For over a decade canine vaccines have been categorised into core, non-core and non-recommended groups [7], with canine distemper, parvovirus and adenovirus considered core vaccine components. These categories have been further developed and currently form the basis of the World Small Animal Veterinary Association (WSAVA) Guidelines for the Vaccination of Dogs and Cats [16].

Active immunisation of dogs is essential at reducing the risk of contracting infectious diseases and in particular viral infections [3]. As vaccine administration has become more routine and widespread, the incidence of most commonly observed diseases has been reduced, although there are occasional outbreaks in vaccinated animals [10]. Vaccine technology has also evolved in line with new disease agents to provide improved performance or broader efficacy [1].

Maternally derived immunity is considered the primary cause of vaccine failure in young dogs [6,8,12]. To overcome interference by maternally derived antibodies (MDA), and ensure protection when maternal antibody levels wane, it is recommended to vaccinate puppies repeatedly between 6 and 16 weeks of age. However, this is logistically demanding and most products now have a single or double vaccination regimen depending on the age of dog and whether MDA are expected to be present. Although MDA was thought to have more of an impact on live vaccine components, recent studies have demonstrated that maternal antibodies can

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have a negative influence on the generation of immune responses following administration of vectored [11] or adjuvanted killed antigen vaccines [14,15]. What these studies, and others in dogs [2] have shown is that the level of maternal antibodies has a significant influence on the ability of a vaccine to generate a passive immune response, with decreasing maternal antibody levels permitting more response from the vaccine.

In this paper we describe the efficacy of a new multivalent vaccine (DHPPi/L4R), containing the core viral components, when administered to dogs from six weeks of age in the presence of maternally derived antibodies. Dogs were challenged following vaccination and the impact of vaccination on clinical variables and serology was examined by comparing MDA-positive and MDA-negative vaccinated dogs to MDA-positive non-vaccinated dogs in each study.

Materials and methods

This study reports the results of three European Pharmacopeia monograph compliant trials investigating the efficacy of canine distemper virus (CDV; monograph 01/2008:0448), canine adenovirus type 2 (CAV-2; monograph 01/2008:1951) and canine parvovirus (CPV; monograph 01/2008:0964) in a new multivalent vaccine for dogs. The studies were conducted in accordance with the Act on Animal Health and Animal Welfare of The Czech Republic, and had been approved by Bioveta a.s. and Zoetis ethical review committees. Day 0 was when dogs received the first administration of vaccine or sterile water.

Animals

In each study fifteen 6-week old Beagle dogs were enrolled. Five dogs were sero-negative (MDA−) with the remaining ten dogs, randomly allocated to two groups, being sero-positive to CDV, CPV, CAV-1 and CAV-2 (MDA+), at titres comparable to those observed in the field; MDA titres prior to first vaccination are shown in Table 1. The MDA-negative pups were derived from SPF dams, while the MDA-positive pups were derived from conventional health status dams which had been vaccinated with the test vaccine described below. All dogs were of good general health and free from infection with the viral agents contained within the vaccine. Dogs from the MDA− group and one MDA+ group were vaccinated with DHPPi/L4R. Dogs from the second MDA+ group served as controls and were administered sterile water. After the second test material administration, all vaccinated dogs (MDA− and MDA+) and two non-vaccinated dogs (MDA+), with greatly diminished or no MDAs and selected at random by a company biometrician, were challenged with the relevant challenge virus.

Vaccine

An experimental vaccine batch was produced which contained modified live CDV, canine parainfluenza virus (CPiV), CAV-2, CPV-2b (DHPPi), inactivated *Leptospira interrogans* serovars Canicola, Icterohaemorrhagiae and Bratislava, *Leptospira kirschneri* serovar Grippotyphosa, and rabies virus (L4R). The DHPPi component was freeze-dried while the L4R component was a liquid containing adjuvant (aluminium hydroxide). The control product was sterile water. Administration (1 ml) was by the subcutaneous route behind the left shoulder blade on day 0 and behind the right shoulder blade on day 21, using standard aseptic technique.

Challenge

CDV isolate Snyder Hill was obtained from the American Type Culture Collection (ATCC); the CAV-1 isolate Mirandola was obtained from the Animal and Plant Health Inspection Services, Centre for Veterinary Biologics (APHIS, CVB); and the CPV-2b isolate 212/98 was obtained from the University of Bari, Italy. For the CDV (10^{-1} dilution of an unknown titre virus stock) and CAV-1 ($10^{6.3}$ $TCID_{50}$/mL) studies 1 mL of challenge material was administered by the intravenous route on day 42; for CPV ($10^{6.6}$ $TCID_{50}$/mL) a 2 mL dose was administered with 1 mL orally and 1 mL intranasally (0.5 mL per nostril) on day 56. The day of CPV challenge was postponed by 2 weeks from day 42 to day 56, because the MDA+, non-vaccinated control dogs still had detectable maternal antibodies on day 28 and day 35.

Observations and samples

Rectal temperatures (°C) of all animals were recorded daily for a period of seven days after each vaccination, and from prior to challenge strain administration until the end of the study. Clinical observations were performed daily from day-2 until the end of the study. Additional general health observations were performed at least once daily at times distinct from clinical observations. Any dogs which exhibited signs of disease, such that in the opinion of the examining veterinarian their welfare was seriously affected, were euthanased as appropriate to avoid unnecessary suffering.

Table 1
Maternal derived antibody titres prior to first vaccination. All results shown are virus neutralisation titres where the end point was assessed as the serum dilution where more than 50% of the characteristic cytopathic effect was attenuated. Different groups of dogs were used in each of the three studies.

Animal	Treatment	Study one		Study two		Study three
		CAV-1	CAV-2	CPV-2	CPV-2b	CDV
1	MDA-negative; vaccinated	<2	<2	<5	<5	<2
2		<2	<2	<5	<5	<2
3		<2	<2	<5	<5	<2
4		<2	<2	<5	<5	<2
5		<2	<2	<5	<5	<2
1	MDA-positive; vaccinated	64	32	320	5120	4
2		64	64	80	640	8
3		64	128	320	640	4
4		⩾256	128	320	2560	2
5		64	64	640	2560	2
1	MDA-positive; controls	128	64	640	1280	8
2		128	128	160	1280	16
3		64	64	320	2560	8
4		128	128	160	5120	4
5		128	128	80	1280	8

Blood samples were collected from each animal prior to test material (vaccine or control) administration on day 0, and then weekly until challenge with a final sample the end of the study. For the CPV study further blood samples for white blood cell (WBC) counts were collected before challenge administration on day 52, 54 and 56, and then 3, 5, 7, 10, 12 and 14 days post-challenge.

To determine virus shedding in the CPV study, faecal swabs were collected into sterile tubes on day 56, before challenge administration, and then 3, 5, 7, 10, 12 and 14 days post-challenge.

Laboratory analysis

Sera samples collected were examined for the presence of antibodies to CDV, CPV-2, CPV-2b, CAV-1 and CAV-2 by serum-neutralisation test. Briefly, duplicate twofold dilutions were made in cultivation medium and approximately 100 $TCID_{50}$ of the respective virus (vaccine strains) was added followed by incubation at 37 °C for 1 h in 5% CO_2. Following incubation susceptible cells (VERO, MDCK or CRFK) were added and incubated at 37 °C for 3–7 days in 5% CO_2. The end point was assessed as the serum dilution where more than 50% of the characteristic cytopathic effect was attenuated. For the CPV study the end point was determined following 5–7 days cultivation using a haemagglutination with porcine red blood cells. For the CPV study, whole blood samples were analysed for leucocyte counts by staining cells with Tűrk's solution and counting them in a standard counting chamber. Faecal samples were examined for virus presence and titre by haemagglutination assay, as described previously [4].

Statistical analysis

Body temperatures were classified into hypothermic (<37.0 °C), normal (37.0–39.5 °C) and hyperthermic (>39.5 °C). Descriptive statistics for antibody titres against relevant antigens including the geometric mean, minimum and maximum were calculated for each group of vaccinates and controls at each time point. For each animal in the CPV study the arithmetic mean of WBC counts taken up to 4 days pre-challenge was calculated to obtain the baseline value and post-challenge WBC counts were compared with the baseline value thereby calculating the percentage reduction. Leucopoenia was defined as a decrease of WBC greater than 50% of the baseline value. The geometric mean of the maximum titres excreted in faeces of control animals were calculated and compared to the maximum titre excreted in faeces of each vaccinated animal.

Results

Canine distemper

After challenge rectal temperatures in non-vaccinated animals became elevated, up to 40 °C. Non-vaccinated dogs also demonstrated clinical signs due to distemper virus, including vomiting, diarrhoea, ocular discharge and apathy; both dogs were euthanased ten or eleven days after challenge. None of the vaccinated animals, in either the MDA− or the MDA+ groups showed any abnormal clinical signs following challenge.

Serological examinations confirmed that MDA− animals did not have antibodies to CDV before the first vaccination (Fig. 1). On day 0, when animals were six weeks of age, titres had declined in MDA+ vaccinated animals (geometric mean 3.5) and in MDA+ non-vaccinated animals (geometric mean 8.0). The titres of MDA + non-vaccinated animals continued to decrease until seven days after the second test material administration when, at 10 weeks of age, all control animals were sero-negative. MDA+ non-vaccinated animals were not examined for antibody levels after challenge, because they were both euthanased prior to the end of the study.

In MDA+ vaccinated animals, antibody titres decreased until 21 days after the first vaccination (geometric mean 1.1). Titres increased 7 days after the second vaccination in one animal (geometric mean 1.3) and 7 days later in the remaining four animals (geometric mean 3.5). Titres of all animals were boosted by the challenge (geometric mean 4.6). In MDA− vaccinated animals, the first measurable increases in virus-neutralising antibodies were detected in three animals 14 days after the first vaccination (geometric mean 3.5). All five vaccinated animals had sero-converted 21 days (geometric mean 24.3) after the first vaccination, with peak titres 7 (geometric mean 42.2) and 14 days (geometric mean 42.2) after the second vaccination. After challenge, anamnestic responses in antibody titres were observed in all MDA− vaccinated animals.

Canine adenovirus type 1 and 2

After challenge, dogs in the MDA− vaccinated group showed normal rectal temperature, while two of five MDA+ vaccinated dogs and both of the MDA+ non-vaccinated animals showed increases with a maximum of 40.3 °C observed. Abnormal clinical signs due to canine hepatitis were observed in one control dog with diarrhoea, anorexia and abdominal tenderness starting five days post challenge. Conjunctivitis and subsequently bilateral corneal opacity (blue eye) were observed from eight days post challenge. The second control dog showed no abnormal clinical signs, but died suddenly five days after challenge. Vaccinated dogs showed no abnormal clinical signs after challenge.

Serological examinations (Fig. 2) confirmed that MDA− vaccinated animals did not have antibodies to CAV-1 before the first vaccination. On day 0, when animals were six weeks of age, titres had declined in MDA+ vaccinated animals (geometric mean 84) and in MDA+ non-vaccinated animals (geometric mean 111). Antibody titres of MDA+ non-vaccinated animals continued to decrease until challenge (12 weeks of age) when one animal had low titres and the second dog was sero-negative. Following challenge, the one surviving dog with low MDA titres before challenge showed a substantial increase. In MDA+ vaccinated animals, antibody titres decreased until 14 days (geometric mean 4.0) after the second vaccination. Titres then showed an increase 21 days after the second vaccination (geometric mean 8.0) before titres were boosted by the challenge. In MDA− vaccinated animals, first measurable increases in virus-neutralising antibodies were detected in all but one animal against CAV-1 seven days (geometric mean 2.6) after the first vaccination; all five MDA− vaccinated animals had sero-converted by 7 days later (geometric mean 7.0). Antibody titres peaked 14 days (geometric mean 128.0) after the second vaccination and then declined until challenge (geometric mean 111.4). After challenge, anamnestic responses in antibody titres were observed in all MDA− vaccinated animals.

The development of antibody titres to CAV-2 (Fig. 3) mirrored that of antibodies to CAV-1 except in two points. Both MDA+ non-vaccinated animals were sero-negative (<2) on the day of challenge on day 42. In MDA+ vaccinated animals, antibody titres to CAV-2 decreased until seven days after the second vaccination and then started to rise from 14 days after the second vaccination.

Canine parvovirus

Following challenge with CPV-2b normal rectal temperatures were observed in dogs from both vaccinated groups. However, one MDA+ non-vaccinated dog showed hyperthermia between 9

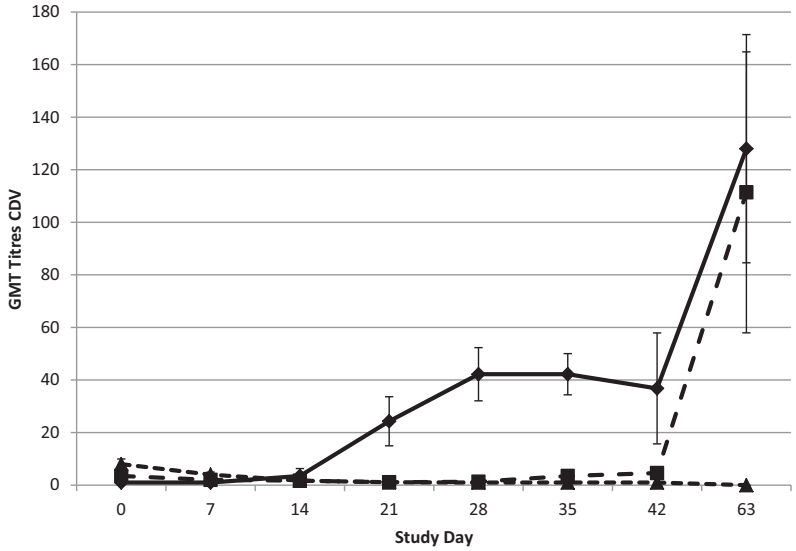

Fig. 1. Geometric mean CDV antibody titres at each sampling time point by treatment group. ♦ = MDA− vaccinated; ■ = MDA+ vaccinated; ▲ = MDA+ non-vaccinated. Dogs were vaccinated on days 0 and 21, and challenged on day 42. Error bars are SEM.

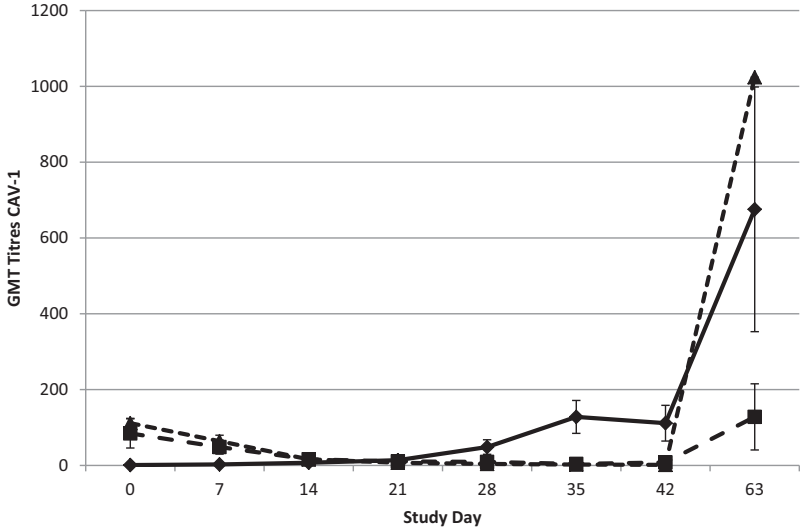

Fig. 2. Geometric mean CAV-1 antibody titres at each sampling time point by treatment group. ♦ = MDA− vaccinated; ■ = MDA+ vaccinated; ▲ = MDA+ non-vaccinated. Dogs were vaccinated on days 0 and 21, and challenged on day 42. Error bars are SEM.

and 12 days after challenge, while the second dog showed hypothermia 12 days post challenge. Abnormal clinical signs due to canine parvovirus infection were observed eight days post challenge with anorexia and apathy, followed 1–3 days later with vomiting and diarrhoea in both dogs. The vaccinated dogs from both MDA− and MDA+ groups showed no abnormal clinical signs.

The profile of serological responses against CPV-2 was the same as for CPV-2b (Fig. 4) with titres generally lower (data not shown). Serological examinations confirmed that MDA− vaccinated animals did not have antibodies to CPV before the first vaccination. On day 0, when animals were six weeks of age, titres had declined in MDA+ vaccinated animals (CPV-2 geometric mean 279; CPV-2b geometric mean 1689) and in MDA+ non-vaccinated animals, (CPV -2 geometric mean 211; CPV-2b geometric mean 1940). Antibody titres of MDA+ non-vaccinated animals continued to decrease until all control animals were sero-negative at 12 weeks of age against CPV-2 and 13 weeks of age against CPV-2b. Following challenge, both control animals survived and showed an increase in antibody titres against CPV-2 (905) and CPV-2b (3620). In MDA+ vaccinated animals, antibody titres decreased in two animals at 7 days (geometric mean 80) and in three animals at 14 days (geometric mean 69.6) after the second vaccination. Titres then increased until challenge (CPV-2 geometric mean 640; CPV-2b geometric mean 2941). After challenge, anamnestic responses in antibody titres were observed in at least four of five MDA+ vaccinated animals. In MDA− vaccinated animals, that were negative at the start of the study, all five animals had sero-converted seven days after the first vaccination (geometric mean 139.3). Geometric mean titres against CPV-2b stabilised 21 days after second vaccination until challenge (CPV-2 geometric mean 1470; CPV-2b geometric mean 5881). After challenge, anamnestic responses in antibody titres were observed in at least two of five MDA− vaccinated animals.

Examination of white blood cell counts showed that none of the vaccinated dogs showed a decline in counts below 50% of baseline pre-challenge values, this being the study definition of leucopoenia. However, both of the MDA+ non-vaccinated dogs did show a

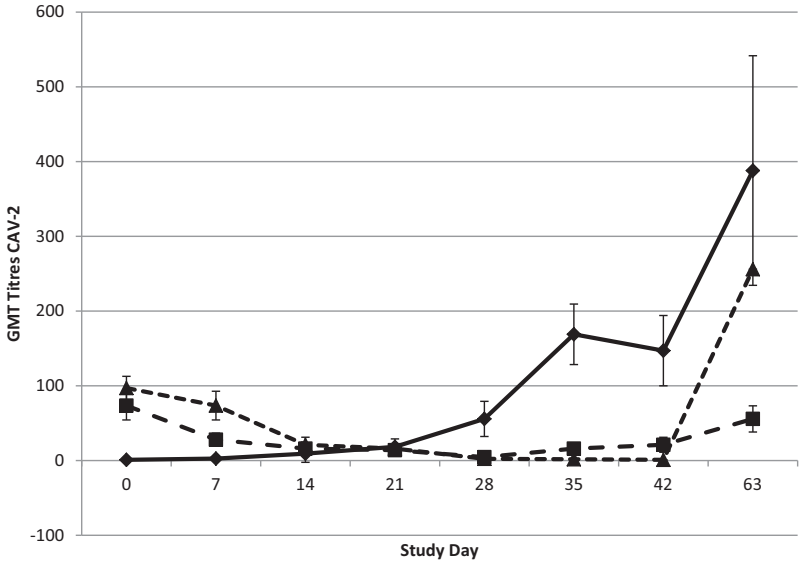

Fig. 3. Geometric mean CAV-2 antibody titres at each sampling time point by treatment group. ♦ = MDA− vaccinated; ■ = MDA+ vaccinated; ▲ = MDA+ non-vaccinated. Dogs were vaccinated on days 0 and 21, and challenged on day 42. Error bars are SEM.

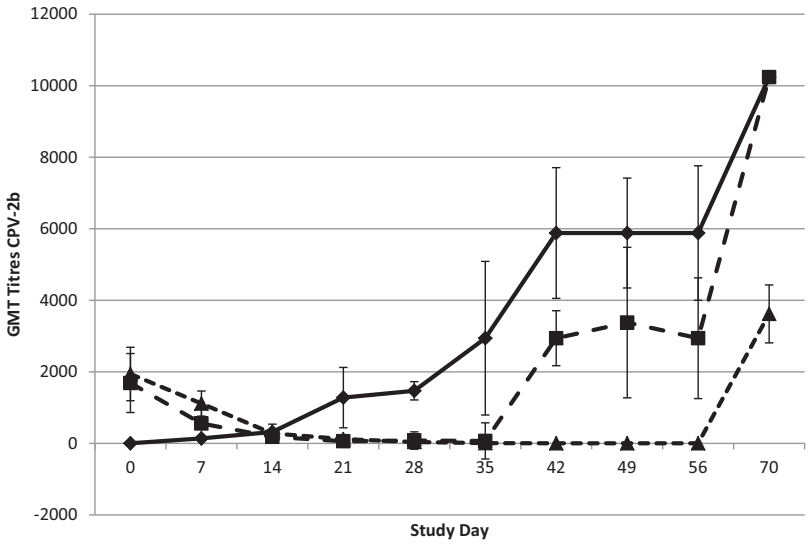

Fig. 4. Geometric mean CPV-2b antibody titres at each sampling time point by treatment group. ♦ = MDA− vaccinated; ■ = MDA+ vaccinated; ▲ = MDA+ non-vaccinated. Dogs were vaccinated on days 0 and 21, and challenged on day 56. Error bars are SEM.

reduction in counts greater than 50% and were defined as leucopoenic (data not shown). Examination of the faecal samples by haemagglutination assay (Table 2) indicated small amounts of excreted CPV ranging from 4 to 16 HAU were detected in two of five vaccinated MDA-negative animals on one or two days between three to five days after challenge. In three of five vaccinated MDA-positive animals small amounts of CPV ranging from 8 to 32 HAU were detected for one or two days from three to seven days after challenge. No virus excretion was observed in the remaining vaccinated animals and in any of the vaccinated animals from ten days after challenge. Both control animals excreted CPV from three to fourteen days after challenge.

Discussion

In this paper we evaluated the efficacy of a new canine multivalent vaccine in the presence of maternally derived antibodies, demonstrating that administration of the two dose vaccination regimen to dogs at minimum age aids in their protection following virulent challenge with CDV, CAV-1 and CPV.

From six weeks of age, a rapid decline in antibody titres was noted in the MDA-positive, non-vaccinated dogs, and the majority of puppies were sero-negative at the point of challenge when they were 12 (CDV and CAV-1) or 14 (CPV) weeks of age, that is 3 and 5 weeks after the second vaccination. The half life of antibodies to canine distemper and canine infectious hepatitis has been demonstrated to be 8.4 days [5], with maternal antibodies to distemper in puppies declining to levels deemed insignificant by 10–12 weeks of age [6]. Maternal antibodies against CPV tend to persist for longer and can in some cases still interfere with vaccination between 10 and 14 weeks of age [9,13]. The profile of maternal antibody decline in the non-vaccinated MDA-positive dogs we observed correlates well with previous work and is therefore likely to be reflective of a field situation.

All of the MDA-negative dogs increased antibody titres by three weeks following the first vaccination. Further increases were observed following the second vaccination, when titres were

Table 2
Examination of faeces samples – haemagglutination test for CPV (HAU/ml).

Treatment	Day 56	Day 59	Day 61	Day 63	Day 66	Day 68	Day 70
MDA− vaccinated	<2	<2	<2	<2	<2	<2	<2
	<2	<2	<2	<2	<2	<2	<2
	<2	16	<2	<2	<2	<2	<2
	<2	<2	<2	<2	<2	<2	<2
	<2	4	4	<2	<2	<2	<2
GMT	<2	2	<2	<2	<2	<2	<2
MDA+ vaccinated	<2	<2	8	8	<2	<2	<2
	<2	<2	<2	<2	<2	<2	<2
	<2	4	32	<2	<2	<2	<2
	<2	<2	<2	<2	<2	<2	<2
	<2	<2	<2	8	<2	<2	<2
GMT	<2	<2	3	2	<2	<2	<2
Controls	<2	32	256	1024	⩾4096	⩾4096	256
	<2	32	512	2048	1024	⩾4096	⩾4096
GMT	<2	32	362	1448	2048	4096	1024

clearly of a greater magnitude than those seen in MDA-positive vaccinated dogs. Further increases in antibody titres were observed again after challenge indicating successful experimental infection. The vaccinated MDA-positive dogs showed limited responses to the first vaccination but distinct responses to the second vaccination; these responses were comparable to those seen after the first vaccination in MDA-negative vaccinated dogs. After challenge, all MDA-positive vaccinated puppies showed further elevated responses indicating successful challenge infection and immunological memory response, and therefore the ability of the dogs' immune system to respond to vaccination in the presence of maternal antibodies. Despite the lower magnitude of antibody responses in the MDA-positive, vaccinated dogs compared to the MDA-negative, vaccinated group the former were successfully protected against virulent challenge.

The negative impact of maternal antibodies on vaccination is well known [6] and it is why vaccines are recommended to be administered on a number of occasions to neonatal dogs. Certainly for canine parvovirus, any haemagglutination inhibition (HI) titres greater than 1:20 have been demonstrated to result in dogs failing to respond to vaccination [13]. As the antibody titres to CPV in the vaccinated MDA-positive dogs in our investigation declined steadily following the first vaccination, it could be assumed that the initial vaccination was suppressed by maternal antibodies and that only once MDA serum-neutralisation titres had decreased sufficiently to titres between 1:20 and 1:40 was the second vaccination able to induce a protective immune response in the neonatal dogs.

Similar scenarios are also probable with the other antigens examined. In our investigation antibody titres to CDV in the vaccinated MDA-positive dogs were at or below the limit of quantification (<1:2) prior to second vaccination having shown a rapid decline over the preceding weeks. In the three weeks after second vaccination titres increased to similar levels as found two to three weeks after the first vaccination in MDA-negative dogs. In the CAV-1 study, MDA-positive dogs showed antibody titres between 1:8 and 1:16 against CAV-1 and 1:4 to 1:32 against CAV-2 prior to second vaccination. These titres were sufficiently low to allow the second vaccination to induce protective responses. The presence of maternal antibody clearly limits the initial impact of vaccination on young animals, but subsequent boosting with a second vaccination even in the presence of some residual maternal antibodies increases the responses to all the vaccine antigens examined here; CPV, CAV-1, CAV-2 and CDV.

Conclusions

In conclusion, we have demonstrated that administration of a minimum titre, multivalent vaccine to dogs of six weeks of age is efficacious in the presence of maternal antibodies; preventing mortality and reducing clinical signs of CAV-1 and inducing protective serological responses to CAV-2; preventing mortality and clinical signs caused by CDV and preventing clinical signs, leucopoenia and viral excretion caused by CPV.

Conflict of interest

All authors are either employees (S.M.W., A.T., V.K., C.S., J.S. and G.S.) or technical consultants (E.S.) of Zoetis or employees of Bioveta (E.P.), and the vaccine described in this paper is marketed by Zoetis.

S.M.W., E.S., C.S., E.P., A.T. and V.K. contributed to experimental design; V.K. performed data review and analysis; J.S. and G.S. provided project mentorship and support; SMW prepared the manuscript; all authors have read and approved the content.

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