

In canine acute diarrhoea with no identifiable cause, does daily oral probiotic improve the clinical outcomes?

A Knowledge Summary by

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PICO question

In canine acute diarrhoea with no identifiable cause, does a daily probiotic supplement in diet, compared to no probiotic supplement, provide better clinical outcomes?

Clinical bottom line

Five placebo-controlled trials suggested a daily oral probiotic supplement provides better clinical outcomes to dogs that have acute diarrhoea (present < 14 days) without an identifiable cause. However, the strength of the evidence is limited and there is uncertainty around the clinical relevance of the studies to some of the outcomes. The probiotic agents, dose, dosing interval, the feeding methods, diets and the duration of treatment were varied in these studies. These variations can lead to different clinical outcomes.

Clinical scenario

A dog with acute diarrhoea has been brought to your clinic and no cause is identified. The owners suggest the feeding of a probiotic to shorten the recovery time, based on their findings on the Internet. You have no experience in recommending a probiotic supplement as diarrhoea management. You wish to find out if the suggestion is scientifically supported.

The evidence

Five randomised, blinded, placebo-controlled trials (Herstad et al., 2009; Kelley et al., 2009; Ziese et al., 2018; Gomez-Gallego et al., 2016; and Nixon et al., 2019) have been found fully or partially relevant to the PICO. The trials studied the effects of probiotic use on indices of the clinical improvement of acute diarrhoea with no identifiable cause. They measured the time to diarrhoea resolution (Herstad et al., 2009; Kelley et al., 2009; and Nixon et al., 2019), improvement in diarrhoea severity (Ziese et al., 2018 and Gomez-Gallego et al., 2016), change in faecal microbiota (Ziese et al., 2018 and Gomez-Gallego et al., 2016) and the percentage of dogs requiring additional medical treatment, e.g. antibiotics (Kelley et al., 2009 and Nixon et al., 2019). Currently, there is no clear definition of acute diarrhoea. However, diarrhoea is classified as chronic when it lasts constantly, or intermittently for more than 14 days (Chandler, 2002). Based on the description of chronic diarrhoea, diarrhoea lasting less than 14 days is described as 'acute' in this Knowledge Summary.

Summary of the evidence

Ziese et al. (2018)	
Population:	<p>Dogs with acute haemorrhagic diarrhoea lasting < 3 days.</p> <p>They were recruited from the Clinic of Small Animal Medicine at University of Munich, from Oct 2013 to Mar 2015.</p> <p>Dogs were excluded if they had:</p> <ul style="list-style-type: none"> - drug treatment that might cause mucosal irritation - antibiotic treatment before diarrhoea or during hospitalisation - parasite or parvovirus infection - pancreatitis
Sample size:	84 dogs were recruited. 59 dogs were excluded due to the above mentioned reasons or the refusal to participate. 25 dogs completed the study. Signalment (age, breed, weight and sex) was comparable between probiotic and placebo group.
Intervention details:	<p>Probiotic group (n=13):</p> <ul style="list-style-type: none"> - Commercial product – Visbiome (ExeGi Pharma): <ul style="list-style-type: none"> o <i>Lactobacillus plantarum</i> DSM 24730 o <i>Lactobacillus plantarum</i> DSM 24731 o <i>Bifidobacterium breve</i> DSM 24732 o <i>Lactobacillus paracasei</i> DSM 24733 o <i>Pediococcus pentosaceus</i> DSM 24734 o <i>Lacto-bacillus plantarum</i> DSM 24735 o <i>Bifidobacterium animalis</i> DSM 24736 o <i>Lactobacillus paracasei</i>, <i>Lactobacillus acidophilus</i> and <i>Bifidobacterium animalis</i> DSM 24737 - Dose (of each strain): <ul style="list-style-type: none"> o < 10 kg: 225 billions colony forming units (cfu) o 10–20 kg: 450 billions cfu o > 20 kg: 900 billions cfu <p>Placebo group (n=12):</p> <ul style="list-style-type: none"> - Maltose with trace amounts of silicon dioxide. <p>Experimental setup:</p> <ul style="list-style-type: none"> - probiotic treatment was mixed with food for appetent dogs - probiotic was diluted in water and administered with 5 mL syringe for anorexic dogs - probiotic was fed every 24 hours for 21 days - gastrointestinal diet (Royal Canin) was fed to all dogs - canine haemorrhagic diarrhoea severity index (CHDSI) was measured from day 0 to day 8 - dogs were discharged if CHDSI was < 2 - faecal samples were collected on day 0, 7 and 21
Study design:	Randomised, blinded, controlled trial

<p>Outcome studied:</p>	<p>1. CHDSI</p> <ul style="list-style-type: none"> - It was assessed by the owners at home or clinicians during hospitalisation - Six parameters: <ul style="list-style-type: none"> • activity • appetite • vomiting • faecal consistency • defaecation frequency • blood admixture in stool - A score from 0 (normal) to 3 (severe) was given to each parameter - Cumulative score: <ul style="list-style-type: none"> • < 3: clinically insignificant • 4–5: mild presentation • 6–8: moderate presentation • ≥ 9: severe presentation • the maximum possible score was 18 - The score on each day was compared to the baseline (day 0) - The study measured the number of days taken for a statistically significant improvement (compared to its own baseline) in both groups <p>2. Faecal microbiota</p> <ul style="list-style-type: none"> - The data was measured on day 0, 7 and 21 - Dysbiosis index - the abundance of seven bacteria: <ul style="list-style-type: none"> • <i>Faecalibacterium</i> • <i>Turicibacter</i> • <i>Escherichia coli</i> • <i>Streptococcus</i> • <i>Blautia</i> • <i>Fusobacterium</i> • <i>Clostridium hiranonis</i> - The abundance of <i>Clostridium perfringens</i>, <i>C. perfringens</i> enterotoxin gene and netF toxin gene were measured - Quantification of enterotoxin and netF toxin gene may imply the abundance of enterotoxin expressing <i>C. perfringens</i> - The abundance of bacteria and genes were measured by quantitative Polymerase Chain Reaction (qPCR)
<p>Main findings: (relevant to PICO question):</p>	<p>1. CHDSI</p> <ul style="list-style-type: none"> - In the probiotic group, a statistically significant improvement was observed on day 3, compared to its own baseline (day 0) (mean: 5.0, standard deviation (SD): 3, P=0.008). A statistically significant improvement was not observed until day 4 in the placebo group, compared to its own baseline (mean: 5.2, SD: 2.8, P=0.002).

	<p>2. Faecal microbiota</p> <ul style="list-style-type: none"> - There was no significant difference in the dysbiosis index between the two groups. - The abundance of <i>C. perfringens</i>: <ul style="list-style-type: none"> • It was significantly lower (P=0.011) on day 7 in the probiotic group (mean: 5.80 logDNA/g faeces, SD: 1.15), compared to its own baseline (day 0) (mean: 6.98 logDNA/g faeces, SD: 1.17). • It was significantly lower (p < 0.05) on day 21 (mean: 4.79 logDNA/g faeces, SD: 1.41) in the probiotic group, compared to its own baseline (day 0). • Compared to its own baseline (day 0), there was no significant finding on day 7 and 21 in the placebo group. - Enterotoxin expressing <i>C. perfringens</i> <ul style="list-style-type: none"> • On day 7, the percentage of dogs positive for enterotoxin expressing <i>C. perfringens</i> was not significantly different between the two groups • On day 7, both probiotic group (P=0.016) and placebo (P=0.016) had a lower abundance of enterotoxin gene in comparison to their own baseline[†] • On day 21, the abundance of enterotoxin gene was significantly lower in the probiotic group than placebo group (P=0.028)[†] • On day 21, the percentage of dogs positive for enterotoxin expressing <i>C. perfringens</i> was significantly lower (P=0.019) in the probiotic group (1/10, 10%) than the placebo group (5/8, 62.5%) - There was no significant difference between the two groups in the abundance of netF gene or the percentage of dogs positive for netF toxin expressing <i>C. perfringens</i> on day 7 and 21 <p>† The data was not described here as the abundance of gene (log DNA) was presented graphically in the paper. The measure of variation was presented as error bars. Please refer to figure 4 of this paper for further detail.</p>
<p>Limitations:</p>	<ul style="list-style-type: none"> - CHDSI was evaluated by two groups of people with different knowledge backgrounds (i.e. clinicians and owners). It may have resulted in a different assessment - Risk of bias – one author received a travel fund from the probiotic provider (MENDES S.A.) to go to an international conference. Another author received a consultation fee from the probiotic manufacturer (ExeGi Pharma) - The authors did not explain the inconsistent number of faecal samples for microbiota analysis on days 0, 7 and 21. For instance, the number of faecal samples analysed on day 0, 7, and 21 in the placebo group was 10, 12 and 8 respectively

	<ul style="list-style-type: none"> - The dependent variable described in the abstract was different from the results of this paper. In the abstract, it was mentioned that a clinical recovery was observed on day 3 and day 4 in the probiotic and placebo group respectively. Yet, the study actually measured the number of days taken for a statistically significant improvement in CHDSI. A statistically significant improvement in CHDSI does not necessarily imply a clinical recovery (i.e. the mean score of the probiotic group on day 3 was 5.0, while score < 3 was classified as clinically irrelevant)
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Gomez-Gallego et al. (2016)	
Population:	<p>Dogs ≥ 6 months old with acute diarrhoea.</p> <p>They were recruited from clinics in southern Finland.</p> <p>Dogs were excluded if they had:</p> <ul style="list-style-type: none"> - systemic illnesses - diarrhoea lasting ≥ 2 weeks - hypoproteinaemia - antibiotic or corticosteroid treatment 30 days prior to the trial - recurrent vomiting - <i>Giardia</i> infection - probiotic administration or new medication, other than the experimental probiotic product, during the study - veterinary visit for diarrhoea medications other than the experimental probiotic product during the study
Sample size:	66 dogs were recruited. 44 dogs completed the study.
Intervention details:	<p>Probiotic group (n=25):</p> <ul style="list-style-type: none"> - 2 dL sour-milk probiotic product daily - 2 x 10⁹ cfu of each of the following strains: <ul style="list-style-type: none"> • <i>Lactobacillus fermentum</i> VET 9A • <i>Lactobacillus rhamnosus</i> VET 16A • <i>Lactobacillus plantarum</i> VET 14A - Owners might opt to split the daily probiotic treatment over two feeding times, or administer it in one feeding time <p>Placebo group (n=19):</p> <ul style="list-style-type: none"> - Sterilised water with 10% titanium (I.V) oxide (Sigma-Aldrich, Finland) <p>Experiment set-up:</p> <ul style="list-style-type: none"> - The participants visited one of the five study clinics in southern Finland to receive the test product - The treatment period was 7 days, with a 6-month follow-up period - Treatment period: <ul style="list-style-type: none"> • The diet consisted of a low-fat protein source (e.g. chicken, fish) and rice

	<ul style="list-style-type: none"> • The participants visited the same vets on day 0 and day 7 • The vets filled in a questionnaire on the physical exam for each visit • Faecal samples were collected on day 0 and day 7 • The owners filled in a validated questionnaire (Roine, Uusitalo and Hielm-Björkman., 2016) on stool consistency each day <p>- 6-month follow-up period:</p> <ul style="list-style-type: none"> • The dogs gradually returned to their normal diet • The owners filled in a questionnaire on recurrence of diarrhoea and other gastrointestinal signs, on day 14, 21, 28 and at 6 months
Study design:	Randomised, blinded, controlled trial
Outcome studied:	<ol style="list-style-type: none"> 1. Stool consistency (Waltham Faecal Scoring System) <ul style="list-style-type: none"> - From 1 (very hard stool) to 5 (watery diarrhoea) - The score was measured on day 0–7, 14, 21, 28 2. Faecal microbiota <ul style="list-style-type: none"> - The abundance of: <ul style="list-style-type: none"> • <i>C. perfringens</i> (alpha toxin or enterotoxin expressing strain) • Enterohaemorrhagic <i>E. Coli</i>/ Enteropathogenic <i>E. Coli</i> (EHEC/EPEC) • <i>Enterococcus faecium</i> • <i>S. aureus</i> • Total eubacteria - The faecal samples were collected and measured on day 0 and 7 by qPCR
Main findings: (relevant to PICO question):	<ol style="list-style-type: none"> 1. Stool consistency[#] <ul style="list-style-type: none"> - Compared to day 0, the mean score was reduced by 1.712 in the probiotic group and 1.279 in the placebo group on day 7. The difference was statistically significant (P=0.043) - During the first month post-treatment, the average reduction in the mean stool consistency score in the probiotic group was greater than the placebo group, with a difference of 0.271 (P=0.033) 2. Faecal microbiota[#] <ul style="list-style-type: none"> - The decrease in the number of <i>C. perfringens</i> alpha toxin producing strain (P=0.05) and <i>E. faecium</i> (P=0.032) was greater in the probiotic group than the placebo group, with statistical significance - The mean changes in the other bacteria from day 0 to day 7 were not statistically significant <p>[#] The measure of variation was reported graphically as error bars in the paper. Please refer to figure 1 (stool consistency) and figure 2 (faecal microbiota) for further detail.</p>

Limitations:	<ul style="list-style-type: none"> - The paper did not evaluate the baseline variations in age, sex, breed and weight between the two groups - The administration frequency (once daily or split into two feedings) were not tightly controlled in this study - The author intended to collect data on day 14, 21, 28 and at 6 months to evaluate the diarrhoea recurrence and other gastrointestinal signs. However, no data at 6 months was presented - It was not explicitly clear on how the authors executed two of the exclusion criteria – i.e. how they kept track of whether the participants had veterinary visits for other diarrhoea medication, or received medications and probiotics other than the experimental product during the study
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Herstad et al. (2009)	
Population:	<p>Dogs with acute gastroenteritis and diarrhoea.</p> <p>They were recruited from the small animal clinic at the Norwegian School of Veterinary Science.</p> <p>Dogs were excluded if they:</p> <ul style="list-style-type: none"> - had clinical signs for ≥ 2 weeks - received a probiotic 1 month before the trial - required supportive therapy during hospitalisation
Sample size:	36 dogs
Intervention details:	<p>Probiotic group (n=15):</p> <ul style="list-style-type: none"> - Probiotic product ZooLac Propaste - 2.85 billions/mL of each of the following: <ul style="list-style-type: none"> • <i>Lactobacillus farciminis</i> • <i>Pediococcus acidilactici</i> • <i>Bacillus subtilis</i> • <i>Bacillus licheniformis</i> - 1.35 billions/mL of thermos-stabilised <i>Lactobacillus acidophilus</i> - Dose: <ul style="list-style-type: none"> • 1–10 kg: 1 mL • 10–25 kg: 2 mL • 25–50 kg: 3 mL • started with a double dose <p>Placebo group (n=21)</p> <ul style="list-style-type: none"> - It contained the same base ingredient with the probiotic apart from the bacteria - The appearance was indistinguishable with the probiotic product

	<p>Experiment setup:</p> <ul style="list-style-type: none"> - The probiotic or placebo treatment was terminated when normal stool was observed - The probiotic or placebo was fed three times daily - The patients visited the vet on day 4 and day 8 after the treatment started - The owners commented about the quality of faeces, date of the first normal stool and last abnormal stool observed - 17 dogs were screened for parasite infection on day 0. No parasite infection was detected - 33 dogs were screened for <i>Salmonella</i> infection on day 0. No <i>Salmonella</i> infection was detected
Study design:	Randomised, blinded, controlled trial
Outcome studied:	<ol style="list-style-type: none"> 1. The time from day 0 to the last abnormal stools observed 2. The time from day 0 to the first normal stools observed 3. Number of stools during the first three days of the treatment
Main findings: (relevant to PICO question):	<ol style="list-style-type: none"> 1. A shorter time from day 0 to the last abnormal stools ($P=0.045$) was reported in the probiotic group (mean: 1.3 days, 95% CI: 0.5–2.1 days) than the placebo group (mean: 2.2 days, 95% CI: 1.3–3.1 days) 2. There was no statistically significant difference between the probiotic (mean: 2.9 days, 95% CI: 2.1–3.7 days) and the placebo (mean: 3.4 days, 95% CI: 2.6–4.2 days) from day 0 to first normal stool 3. The number of stools was reduced in both groups during the first three days ($P\leq 0.01$). No descriptive data (e.g. the mean number of reduction and measure of variation) was provided. The difference between groups was not statistically significant
Limitations:	<ul style="list-style-type: none"> - The paper did not evaluate the baseline variation in age, sex, breed and weight between the two groups - In the evaluation of clinical signs before the trial, the number of respondents did not add up to 36 (sample size) in the categories of fever ($n=29$), appetite ($n=34$), change in diet ($n=34$), antiparasitic treatment ($n=35$), vaccination ($n=35$) and consumption of spoiled food ($n=35$). The author did not explain the inconsistent number of respondents - Single-centre study - Faecal analyses on parasite and <i>Salmonella</i> infection before the trial were not performed in 19 dogs and three dogs respectively - Nine dogs in the probiotic group and four dogs in the placebo group consumed spoiled food before the trial. This may complicate the aetiologies of the diarrhoea of the participating dogs - The paper did not state explicitly who were blinded in the trial. - No clear and standardised definition of ‘abnormal stool’ was provided to the owners and clinicians

Kelley et al. (2009)	
Population:	<p>Young adult dogs with acute diarrhoea and no other medical condition.</p> <p>They received no prior treatment and were referred to vet clinics.</p>
Sample size:	<p>45 dogs were recruited and 31 dogs completed the study. Signalment (age, breed and weight) of the probiotic and placebo group was comparable.</p>
Intervention details:	<p>Probiotic group (n=13):</p> <ul style="list-style-type: none"> - <i>Bifidobacterium animalis</i> AHC7, 1 x 10¹⁰ cfu/dose <p>Placebo group (n=18):</p> <ul style="list-style-type: none"> - Same vehicle as the probiotic without the bacterium <p>Experiment setup</p> <ul style="list-style-type: none"> - All dogs were screened for <i>Giardia</i> and intestinal parasite infection - All dogs routinely received ivermectin or pyrantel to control internal parasites - Treatment was administered as a cocoa butter treat, twice daily - Treatment was administered for a maximum of 2 weeks or until the resolution of diarrhoea - Both groups received Eukanuba or Iams maintenance diet - Trained kennel staff monitored the behaviour and recorded the stool score daily - The administration of metronidazole was based on the following considerations: <ul style="list-style-type: none"> - number of abnormal stools - degree of diarrhoea - overall health - risk of outbreak to the neighbouring dogs
Study design:	Randomised, blinded, controlled trial
Outcome studied:	<p>Time to diarrhoea resolution</p> <ul style="list-style-type: none"> - Stool score <ul style="list-style-type: none"> • 1 = ideal • 2 = soft • 3 = viscous liquid with some particulate matter • 4 = watery - Diarrhoea resolution <ul style="list-style-type: none"> • score improved from 4 to ≤ 2, and • remained at ≤ 2 for at least 5 consecutive days <p>Percentage of dogs administered metronidazole during the study</p>

<p>Main findings: (relevant to PICO question):</p>	<ol style="list-style-type: none"> 1. A significantly shorter time ($P < 0.01$) to diarrhoea resolution was observed in the probiotic group (mean \pm SE: 3.9 ± 2.3 days) than the placebo group (6.6 ± 2.7 days) 2. A lower percentage of dogs in the probiotic group (5/13, 38.5%) received metronidazole than the placebo group (9/18, 50%). No statistical analysis was performed. However, a Fisher's Exact test* performed by the author of this Knowledge Summary found that this result was not statistically significant ($P = 0.72$) (GraphPad, 2018) 3. Excluding dogs receiving metronidazole, 3/9 (33%) in the placebo group and 7/9 (77%) in the probiotic group recovered from diarrhoea on day 4. No statistical analysis was performed. A Fisher's Exact test* performed by the author of this Knowledge Summary found that this result was not statistically significant ($P = 0.153$) (GraphPad, 2018) <p>*Fisher's Exact test is a statistical test to evaluate if there is non-random association between two categorical variables in a study with small sample size.</p>
<p>Limitations:</p>	<ul style="list-style-type: none"> - Dogs were recruited from one organisation only - Only one probiotic bacterium was included in the study - No statistical analysis was performed on the different percentage of dogs receiving metronidazole between the two groups - No statistical analysis was performed on the different percentage of dogs (without metronidazole treatment) recovered on day 4 between the probiotic and placebo group - An error in data presentation was suspected in the main findings (see point 3). The number of dogs in the probiotic group should be eight instead of nine, after the exclusion of the five dogs receiving metronidazole - Three dogs were identified as <i>Giardiasis</i> positive during the study. They continued the study and their data was included - The stool scoring system was not validated as it had no reference - The definition of acute diarrhoea (i.e. the duration of diarrhoea) was not specified in this study - The use of cocoa butter is not recommended due to the risk of theobromine toxicity

<p>Nixon et. al (2019)</p>	
<p>Population:</p>	<p>Dogs who had a faecal score of 5 or 6 (watery stool) for \geq one occasion within 24 hours before the veterinary visit. They were recruited from 11 units in the UK and three units in Ireland.</p>

	<p>Dogs were excluded if they:</p> <ul style="list-style-type: none"> - had diarrhoea for ≥ 7 days - received antibiotic or probiotic treatment < 4 weeks before the start of the study - required additional treatments other than the feed supplement - had diarrhoea known to be secondary to other diseases (e.g. endocrine disease) or a surgical condition
Sample size:	<p>148 dogs were recruited. 30 dogs were excluded due to dosing error, failure to accept the study diet or inappropriate inclusion (i.e. no recorded diarrhoea). 118 dogs were included in the study. 107 dogs completed the study with diarrhoea resolution. 11 dogs were withdrawn for additional medical intervention. Signalment (age, breed, weight, and sex) were comparable between the two groups.</p>
Intervention details:	<p>Probiotic group (n=57):</p> <ul style="list-style-type: none"> - <i>E. faecium</i> 4b1707, 2×10^8 cfu/g - Probiotic paste (Pro-Kolin Advanced) with Preplex prebiotic, combined kaolinite and montmorillonite clay, psyllium, pectin, and beta glucan - Two dogs were withdrawn for additional medical treatments. 55 dogs completed the study <p>Placebo group (n=61):</p> <ul style="list-style-type: none"> - Oral paste with indistinguishable taste, packaging and appearance - Nine dogs were withdrawn for additional medical treatments. 52 dogs completed the study <p>Experimental setup</p> <ul style="list-style-type: none"> - All dogs received Hills i/d - Probiotic and placebo paste was administered orally every 8 hours - The treatment was terminated on day 10 or when the dogs had normal defaecation consecutively three times - Dose: <ul style="list-style-type: none"> • < 5 kg: 2 ml • 2–15 kg: 3 ml • 15–30 kg: 5 ml • 30–45 kg: 7 ml • > 45 kg: 10 ml - Dogs with deterioration or no improvement were withdrawn from the study and were given additional medical intervention
Study design:	Randomised, blinded, controlled trial
Outcome studied:	<p>1. Duration of diarrhoea</p> <ul style="list-style-type: none"> - It was measured from the start of the first probiotic or placebo treatment to diarrhoea resolution

	<ul style="list-style-type: none"> - Diarrhoea was resolved when the dogs had normal defaecation three times consecutively - Faeces with a consistency score ≤ 3 was defined as normal. <ul style="list-style-type: none"> - The faecal consistency score was based on the Nestle-Purina scoring system - It ranged from 1 (firm) to 6 (watery) - Dogs withdrawn for additional medical treatments were censored from the analysis for the duration of diarrhoea <p>2. Rate of diarrhoea resolution</p> <ul style="list-style-type: none"> - It measured the proportion of dogs with diarrhoea against time (hours) <p>3. Additional medical intervention</p> <ul style="list-style-type: none"> - It measured the percentage of dogs withdrawn for the additional treatment
<p>Main findings: (relevant to PICO question):</p>	<ol style="list-style-type: none"> 1. The probiotic group (median: 32 hours, range: 2–118 hours, n=51) had a significantly shorter duration of diarrhoea (P=0.008) than the placebo group (median: 47 hours, range: 4–167 hours, n=58). The inter-quartile range was reported in the box plot (figure 3B of the paper) 2. Probiotic group had a 1.6 times faster rate of resolution than placebo group (P=0.02) 3. A significantly (P=0.04) lower percentage of dogs in the probiotic group (3.5%, 2/57) required additional medical treatments than the placebo group (14.8%, 9/61)
<p>Limitations:</p>	<ul style="list-style-type: none"> - Although dogs with diarrhoea secondary to other diseases or surgical conditions were excluded, the other causes of diarrhoea, such as viral and parasitic infection, were not investigated before the trial - Risk of bias – one author is employed by the probiotic manufacturing company (Protexin) - The number of dogs completed the study did not match with the number of dogs included in the analysis for the duration of diarrhoea. For instance, 52 dogs in the placebo group completed the study, and 58 dogs were involved in the analysis for the duration of diarrhoea

Appraisal, application and reflection

Five placebo-controlled studies (Herstad et al., 2009; Kelley et al., 2009; Ziese et al., 2018; Gomez-Gallego et al., 2016; and Nixon et al., 2019) have assessed the clinical outcomes of administering a daily oral probiotic supplement in dogs that have acute diarrhoea with no identifiable cause. The significant findings were reported for various outcome measures, namely the time to diarrhoea resolution (Herstad et al., 2009; Kelley et al., 2009; and Nixon et al., 2019), improvement in diarrhoea severity (Gomez-Gallego et al., 2016 and Ziese et al., 2018), change in the microbiota (Gomez-Gallego et al., 2016 and Ziese et al., 2018) and the percentage of dogs that required additional treatment (Nixon et al., 2019 and Kelley et al., 2009).

Herstad et al. (2009), Kelley et al. (2009) and Nixon et al. (2019) presented a shorter time to diarrhoea resolution in the probiotic group. The improvement ranged from 15 hours (Nixon et al., 2019) to 2.7 days (Kelley et al., 2009). All three studies were partially relevant to the PICO due to several reasons. Herstad et al. (2009) did not perform faecal analyses on 19 dogs and three dogs for parasite and *Salmonella* infection. The study also included dogs with spoiled food consumption. Meanwhile, although dogs with diarrhoea secondary to other diseases or surgical conditions were excluded, Nixon et al. (2019) did not investigate the other potential causes of diarrhoea in the participants, such as viral and parasitic infection. Thereby, it is uncertain if there was no identifiable cause of all the cases of diarrhoea in these two studies. Kelley et al. (2009) spotted three dogs were Giardiasis positive during the trial and included their data. It reduces the relevance of this study because not all of the participants suffered from diarrhoea with no known cause.

The limitations of these three studies (Herstad et al., 2009; Kelley et al., 2009; and Nixon et al., 2019) reduce the strength of the presented evidence. For example, Herstad et al. (2009) did not evaluate the baseline variations, such as sex, age and breed, between the probiotic and placebo group. The potential variations in signalment can lead to confounding analysis. No standardised definition of abnormal stool was given to the owners and clinicians, which may reduce the reliability. A competing interest is identified in Nixon et al. (2019). The study was at risk of bias, and double-blinding was applied to reduce the associated risk. However, there was a mismatch between the number of dogs that completed the study and the number of dogs included in the analysis of diarrhoea resolution. The authors did not explain the discrepancy. Kelley et al. (2009) did not use a validated stool scoring system, which reduces the clinical relevance. Due to the partial relevance to the PICO and the limitations, these studies may not be adequately strong enough to support a faster clinical recovery by the probiotic supplement.

Two studies (Gomez-Gallego et al., 2016 and Ziese et al., 2018) measured improvement in diarrhoea severity in the probiotic group. Gomez-Gallego et al. (2016) reported a greater improvement in stool consistency score in the probiotic group (-1.712) than the placebo (-1.279) on day 7. However, the improvement in the probiotic group differed from the placebo by 0.433 only. With a < 0.5 difference in the consistency score, it is questionable if there was an observable difference in the stool quality. The clinical relevance of the minor improvement in the consistency score (i.e. whether the clinical impact is noticeable in daily practice) was therefore debatable. Gomez-Gallego et al. (2016) did not evaluate the baseline variations, such as sex, age and breed, between the probiotic and placebo group. The potential baseline variations may confound the observed difference. Meanwhile, Ziese et al. (2018) reported that the probiotic group took one day less to achieve a statistically significant improvement in the Canine Haemorrhagic Diarrhoea Severity Index (CHDSI). The clinicians and owners may have different standards when they evaluate the costs and benefits of a one day improvement. It was then challenging to comment on the clinical relevance of Ziese et al.'s (2018) finding.

The probiotic group presented a greater decrease of faecal *C. perfringens* on day 7 (Gomez-Gallego et al., 2016), and a lower abundance of faecal *C. perfringens* (Ziese et al., 2018). Ziese et al. (2018) did not explain the inconsistent number of faecal samples analysed on day 0, 7, 21. The clinical relevance of these finding is affected by the undefined relationship between *C. perfringens* and acute diarrhoea. Guard et al. (2015) reported an association between increased *C. perfringens* in faeces and acute diarrhoea, whilst Duijvestijn et al. (2016) could not find an association between them. Hence, it remains controversial whether a reduction of *C. perfringens* in faecal samples can be regarded as a clinical benefit.

Nixon et al. (2019) and Kelley et al. (2009) showed a lower percentage of dogs in the probiotic group received additional treatment, such as antibiotics, than the placebo group. The data presented by Kelley et al. (2009) is

of limited strength as no statistical analysis was performed. In contrast, Nixon et al. (2019) offered fairly strong evidence by the inclusion of a large sample size (n=118). The signalment between the two groups was comparable. One issue with Nixon et al. (2019) is the partial relevance to the PICO (as discussed previously). Nonetheless, one study provided fairly strong evidence that there is a reduced requirement of additional treatment (e.g. antibiotics) in dogs administered a daily probiotic. Further studies are helpful to validate this suggested benefit and to completely address dogs that have acute diarrhoea with no identifiable cause.

In conclusion, five placebo-controlled trials partially or completely addressed the PICO. The participating dogs were recruited from clinics, which support the applicability of these studies. They all presented a better clinical improvement in the probiotic group than the placebo. This suggests a daily supplement of oral probiotic may provide better clinical outcomes to dogs having acute diarrhoea without an identifiable cause. However, the clinical relevance of the reduction in faecal *C. perfringens* and improvement in diarrhoea severity were uncertain. The strength of the studies supporting a shorter time to diarrhoea resolution was limited due to the partial relevance to the PICO and several limitations. Lastly, Nixon et al. (2019) offered fairly strong evidence for a reduced requirement of additional treatment in dogs administered a probiotic. Additional studies would be beneficial to validate the better clinical outcomes brought by probiotic supplementation.

It is worth noting that the probiotic agents, dose, dosing interval, the methods of feeding, diets and the duration of treatment in these studies were varied. Clinicians or owners need to be aware that these variations can lead to different clinical outcomes.

Methodology Section

Search	
Databases searched and dates covered:	CAB Abstracts on OVID Platform 1973 – Week 18 2019 PubMed 1973 – 2019 Web of Science 1900 – 2019
Search strategy:	CAB Abstracts: (Dog* or cani* or bitch* or pupp*) and (Diarrhoea or diarrhea or gastroenteritis or enteritis or scour or dysentery or loose stool or faeces or colitis) and (Probiotic* or lactobacill* or bifidobacteri* or enterococc* or lactic acid bacteri* or lactic acid producing bacteri*) PubMed and Web of Science: (Dog or dogs or cani* or bitch* or pupp*) and (Diarrhoea or diarrhea or gastroenteritis or enteritis or scour or dysentery or “loose stool” or faeces or colitis) and (Probiotic* or lactobacill* or bifidobacteri* or enterococc* or “lactic acid bacteri*” or “lactic acid producing bacteri*”)
Dates searches performed:	15 th May 2019

Exclusion / Inclusion Criteria	
Exclusion	Papers not in English Paper cannot be accessed Not relevant to the PICO, e.g. did not involve dogs with acute diarrhoea, probiotic administered in ways other than oral route, diarrhoea with an identifiable cause. Reviews Single case reports Conference papers Book chapters
Inclusion	Any relevant primary research paper discussed the clinical impacts brought by daily oral administration of probiotic to dogs that have acute diarrhoea without an identifiable cause.

Search Outcome							
Database	Number of results	Excluded – Case reports, conference papers, reviews, book chapters, correspondence	Excluded – Not relevant to PICO	Excluded – Languages other than English	Excluded – Inaccessible	Excluded – Duplication	Total relevant papers
CAB Abstracts	365	39	317	5	0	0	4
PubMed	317	10	302	0	0	4	1
Web of Science	172	3	165	0	0	4	0
Total relevant papers							5

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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