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A systematic review of the efficacy of prophylactic control measures for naturally-occurring canine leishmaniosis, part I: Vaccinations

C.E. Wylie[a,*], M. Carbonell-Antoñanzas[a], E. Aiassa[b], S. Dhollander[b], F.J. Zagmutt[c], D.C. Brodbelt[d], L. Solano-Gallego[a]

[a] Universitat Autònoma de Barcelona, Departament de Medicina i Cirurgia Animal, Campus Bellaterra, Edifici V, Cerdanyola del Vallès, Barcelona, Spain
[b] European Food Safety Authority, Via Carlo Magno 1/A, IT-43126 Parma, Italy
[c] Epiχ Analytics, 1643 Spruce Street, Boulder, CO 80302, USA
[d] Veterinary Epidemiology, Economics and Public Health Group, Department of Production and Population Health, Royal Veterinary College, North Mymms, Hatfield, Hertfordshire, UK

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ABSTRACT

Canine leishmaniosis (CanL) is an important zoonotic disease; however, the efficacy of available vaccines for the prevention of naturally-occurring *Leishmania infantum* (*L. infantum*) infection in dogs remains unclear.

The objective of this review was to determine the efficacy of currently available vaccines to prevent naturally-occurring *L. infantum* infection in dogs.

Four bibliographic databases (CAB Direct 2011, Web of Science 2011, U.S. National Library of Medicine 2011 and *Literatura Latino Americana e do Caribe em Ciências da Saúde*) were searched along with eight sets of conference proceedings and the International Veterinary Information Service (IVIS) database, from 1980 to November 2012.

Randomised controlled trials (RCTs), non-randomised clinical trials (NRCTs), cohort studies and case–control studies that investigated vaccine efficacy for natural *L. infantum* infection in dogs were eligible for inclusion. Two review authors independently assessed each study against the inclusion criteria, independently extracted relevant data from all included studies and assessed the risk of methodological shortcomings in each individual study. The odds ratio (OR) and absolute risk reduction (ARR) for dichotomous outcomes and mean difference for continuous outcomes were calculated. Meta-analysis was not performed due to heterogeneity of the studies identified.

The search was conducted for all mitigations for CanL and yielded the title and abstract of 937 articles, from which 84 articles were screened based on full text. Twelve studies on vaccinations (five RCTs, seven NRCTs) were identified. Ten studies were at a high risk of methodological shortcomings, whilst two were at an unclear risk. The use of 200 μg ALM protein, Leishmune®, CaniLeish®, LiESAp with MDP, and ALM with BCG tended to significantly reduce the proportion of dogs infected with *L. infantum* based on either parasitological or serological evidence. The use of lyophilized protein vaccine significantly increased the proportion of dogs infected with *L. infantum* based on either parasitological or serological evidence.

* Corresponding author. Current address: Rossdales Equine Hospital, Cotton End Road, Exning, Newmarket, Suffolk, UK. Tel.: +44 01638 577 754; fax: +44 01638 577 989
E-mail address: claire.wylie@rossdales.com (C.E. Wylie).

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There is peer-reviewed evidence that control measures are effective in preventing CanL with the results suggesting that between 6 and 54% of infections could be prevented with vaccination. However, this evidence is based on a small number of RCTs, all of which are either at high or unclear risk of methodological shortcomings. Well-designed, adequately powered and properly reported randomised clinical trials are needed to clearly establish efficacy of vaccines as CanL control measures.

1. Introduction

Canine leishmaniosis (CanL) is a major zoonosis which can potentially cause severe fatal disease in humans and dogs and is transmitted by sandflies. Infections caused by different *Leishmania* species are present in a variety of regions with different climate conditions throughout the world. Based on its clinical manifestations, *Leishmania* infection in humans has been divided into cutaneous, mucocutaneous and visceral forms (Desjeux, 2004). Zoonotic leishmaniosis is found in the Mediterranean basin, Asia and South America, with the domestic dog the main reservoir host of *Leishmania infantum* (*L. infantum*) infection (Baneth et al., 2008). All cases of canine leishmaniosis in Europe are caused by *L. infantum*, where no other *Leishmania* species have been diagnosed (Baneth et al., 2008). *L. infantum* has previously been called *Leishmania chagasi*, however the two must be regarded as synonymous (Mauricio et al., 1999; Dantas-Torres, 2006), with by the law of priority the name *L. infantum* being considered the valid name (Dantas-Torres, 2006).

Millions of dogs are infected in South America, with high infection rates in some areas of Brazil and Venezuela (Feliciangeli et al., 2005; Werneck et al., 2007). Seroprevalence studies from Italy, Spain, France and Portugal report that 2.5 million dogs in these countries are infected (Moreno and Alvar, 2002). The seroprevalence in dogs in the Mediterranean basin ranges from 5% to 30% depending on regions (Solano-Gallego et al., 2009). Surveys employing other detection methods to calculate the prevalence of *Leishmania* infection by amplification of *Leishmania* DNA from different tissues (Berrahal et al., 1996; Solano-Gallego et al., 2001; Leontides et al., 2002) or by detection of specific anti-*Leishmania* cellular immunity (Cabral et al., 1998; Cardoso et al., 1998; Solano-Gallego et al., 2000) have revealed even higher infection rates, approaching 60% in some foci. Most dogs in these areas appear to have a chronic infection that may last all their lives (Oliva et al., 2006). A low proportion of dogs develop disease and the majority of dogs harbour the pathogen and are resistant to the development of clinical disease, maintaining a subclinical infection (Baneth et al., 2008; Solano-Gallego et al., 2009)

A broad range of clinical manifestations and immune responses have been described for CanL. Canine *L. infantum* infection can manifest as a chronic subclinical infection, self-limiting disease, or non-self limiting illness (Baneth et al., 2008; Solano-Gallego et al., 2009). In addition, several degrees of disease severity are found in dogs, ranging from mild to severe fatal with different clinical outcomes, prognosis and treatment options. The two extremes of this clinical spectrum are characterized by: (1) "Resistant" dogs with a protective CD4+ T-cell-mediated immune response featuring production of Th1 cytokines such as interferon-γ, IL-2 and TNF-α, which induce anti-*Leishmania* activity by apoptosis of parasites in macrophages *via* nitric oxide (NO) metabolism (Holzmuller et al., 2006) and, thus capable of controlling infection, and (2) sick dogs which are characterized by a marked humoral immune response, reduced cell mediated immunity with a mixed Th1 and Th2 cytokine pattern and high parasite burden, which is detrimental to the animal (Baneth et al., 2008).

As mentioned above, CanL has a wide spectrum of clinical manifestations, classically displaying a chronic disease course with periods of remission after treatment followed by relapse (Solano-Gallego et al., 2009). Clinical signs commonly include skin lesions such as non-pruritic exfoliative dermatitis with or without alopecia, ulcerative, papular or nodular dermatitis. Other clinical signs include generalized lymphadenomegaly, loss of body weight, lethargy and ocular lesions. Affected dogs also display a range of clinicopathological findings (Baneth et al., 2008; Paradies et al., 2010; Solano-Gallego et al., 2011). The diagnosis of CanL is challenging as there are no gold standard tests (Solano-Gallego et al., 2009). Real-time polymerase chain reactivity (PCR) is considered to be the most sensitive molecular technique (Maia et al., 2009), with seropositivity in 88–100% of dogs with clinical signs and/or clinicopathological abnormalities consistent with CanL (Solano-Gallego et al., 2009). The prognosis depends on the severity of illness and therefore, clinical staging is essential (Solano-Gallego et al., 2009). The prognosis for treated dogs with mild to moderate disease is reported to be good to excellent, although many dogs remain subclinically infected (Solano-Gallego et al., 2009; Roura et al., 2012).

Many *Leishmania* antigens have been identified as potential vaccine candidates, however, very few have been tested in field trials and only three second-generation canine vaccines have been registered (Palatnik-de-Sousa, 2012). The Fucose mannose ligand (FML)-saponin vaccine (Leishmune®) was licensed in Brazil in 2003, where a second vaccine, Leish-Tec®, a recombinant A2-gene (A2)-antigen of *Leishmania* amastigotes adjuvanted by saponin, has also been licensed since 2008. In early 2011, CaniLeish®, a formulation related to culture supernatant of *L. infantum* promastigotes (LiESAp), composed of 54-kDa excreted protein of *L. infantum* with muramyl dipeptide (MDP) was the first vaccine for CanL licensed for use in Europe. Vaccination is designed to induce a strong protective cellular immune response against the specific antigens of *L. infantum*, with an effective immune response mounted approximately 4 weeks after the final vaccination (Palatnik-de-Sousa, 2012).