Systemic insecticides used in dogs: potential candidates for phlebotomine vector control?

Sonia Ares Gomez and Albert Picado
Barcelona Institute for Global Health, Barcelona, Spain

Summary
Zoonotic visceral leishmaniasis (ZVL) is a public health problem endemic in some countries. Current control measures, in particular culling infected dogs, have not reduced ZVL incidence in humans. We evaluated the use of five systemic insecticides (spinosad, fluralaner, afoxolaner, sarolaner and moxidectin) currently used in dogs for other purposes (e.g. tick, flea control) in controlling ZVL transmission. The anti-phlebotomine capacity of these compounds confirmed in experimental studies makes their use in ZVL control programmes very promising. Limitations and benefits of using this new control tool are compared to current practices.

keywords phlebotomine vectors, dogs, systemic insecticides, zoonotic visceral leishmanias

Introduction
Zoonotic visceral leishmaniasis (ZVL) is a vector-borne disease in humans and dogs caused by the protozoa Leishmania infantum. The disease is transmitted from infected dogs to humans through the bite of some species of blood-sucking dipteran, colloquially known as phlebotomine sand flies. Dogs are the main reservoir and therefore essential to the persistence of L. infantum transmission. The parasitic infection induces an inflammatory reaction in the viscera. Signs and symptoms of human ZVL include hypergammaglobulinemia, immunosuppression, hepatosplenomegaly, pancytopenia, weight loss, fever and death if left untreated [1, 2].

In the old world, the principal endemic areas are in the Mediterranean region where ZVL is mainly a veterinarian problem and human cases occur sporadically [1, 3]. In the new world, ZVL is considered to be a human health problem with an estimated annual incidence of 6800 cases. Endemic countries are Brazil, Colombia, Paraguay, Venezuela, Guatemala, Argentina, Mexico and Honduras [3].

Brazil, with >3000 human cases per year, is the country with the highest incidence of ZVL in the world. Brazilian authorities recognised ZVL as a public health problem and have put a series of control measures in place since the 1980s [4, 5]. Those measures aim at reducing the incidence of ZVL and target people (e.g. diagnosis and treatment of cases [4]); dogs, the reservoir (e.g. culling of seropositive dogs [5]); and vectors (e.g. insecticide spraying [6, 7]).

The interventions targeting dogs have been controversial. L. infantum-infected dogs in Brazil that could not be treated [8] have been culled for over 20 years [9, 10]. This strategy, aimed at reducing the L. infantum reservoir, has not resulted in a significant decrease of the incidence in human cases [11]. Several reasons may explain this failure, including the poor sensitivity of screening tests used, the lack of compliance and the replacement with susceptible dogs [12, 13].

Application of insecticide-impregnated dog collars has been suggested as a cost-effective alternative to dog culling for controlling ZVL in Brazil [13–15]. These collars interrupt the transmission of L. infantum by killing the vector biting on dogs before it can transmit the disease [14]. One study showed reduction in the incidence of L. infantum infection in children in villages where deltamethrin-impregnated collars on dogs were used [15]. However, the use of deltamethrin-impregnated collars as part of the national or regional control programmes in endemic countries presents challenges: collars are expensive, they need to be worn by 80% of the dog population to have an impact on human cases and they need to be replaced every 6 months or earlier if they are lost [16, 17].

The use of systemic insecticides in dogs may overcome some of the limitations posed by current control methods and may be an alternative or complement to those in endemic countries. Because of their distribution throughout the body, systemic insecticides should kill sand flies that feed on dog’s blood, thus interrupting ZVL transmission in endemic areas. Similar to the application success of collars, the coverage of systemic insecticides needs to
be high (e.g. 80%) [18]. In order to achieve adequate coverage and guarantee maximum adherence to the treatment, systemic insecticides should be easy to apply and have a long-lasting effect, ideally 3–6 months [19].

Insecticides provided orally to animals using treated baits have been used to control zoonotic cutaneous leishmaniasis (ZCL) vectors. ZCL, caused by *L. tropica*, is also transmitted by phlebotomine sand flies but rodents are the main reservoir. Different systemic insecticides (imidacloprid, fipronil, novaluron and ivermectin) have been evaluated with promising results, both in the laboratory and in the field. Oral administration of systemic insecticides to rodents showed mortalities >80% within 29 days in sand flies feeding on treated animals in the laboratory [20–22]. In field studies sand fly density was reduced by 80% within 6 weeks [23]. Even when the animal targeted is not a reservoir (e.g. cows), systemic insecticides may have an impact on transmission by reducing sand fly density [24]. A similar approach is being used as tool to control malaria. A number of trials are evaluating if mass administration of ivermectin to people can contribute to malaria elimination by reducing the mosquito-transmitted in endemic areas [25, 26].

Systemic insecticides currently used in dogs to control flea and tick infestations or to treat heartworm are the same or have similar properties as those shown to kill ZCL vectors when used in rodents. Those insecticides could potentially be used as a new ZVL control tool in endemic areas. The goal of this study was to identify all systemic insecticides that can be safely administered to dogs and have the potential to exert an anti-phlebotomine effect. These drugs could potentially be used to control ZVL transmission.

Methods

To select suitable compounds, we first listed all systemic insecticides for dogs currently on the market. We then gathered information on their pharmacological characteristics and anti-phlebotomine activity. These data were used to identify the compounds with higher potential use for controlling ZVL.

List of systemic insecticides for dogs

We used veterinary reference documents, such as the British Small Animal Veterinary Association (BSAVA) Small Animal Formulary (2016) [27], Vademecum Gutiérrez (2016) [28] and the website Parasitipedia [29], to list all systemic insecticides registered for their use in dogs in Europe, North, Central and South America. Systemic insecticides are drugs whose active ingredient is distributed by blood circulation regardless of the route of administration. The pharmacological characteristics of the drugs identified were gathered from the web pages of the European Medicines Agency (EMA) (2016) [30] and the U.S. Food and Drug Administration (FDA) (2016) [31]. The following properties were recorded for each insecticide: mode of action, pharmacokinetics, safety and efficacy against targeted insects.

Anti-phlebotomine activity

We conducted a literature review to identify the compounds with highest anti-phlebotomine activity. Three databases were screened: Scopus (access to academic journals articles and patent databases), PubMed (access to MEDLINE database) and Cochrane library (access to systematic reviews, meta-analysis and controlled trials). The search terms used were as follows: (i) (phlebotomine vectors OR phlebotomine sand flies OR phlebotomine sandflies OR sand flies OR sandflies) AND (systemic insecticides OR each of the drugs identified); (ii) dogs AND each of the drugs identified. From search (i) we looked for information about the use of systemic insecticides in mammals targeting phlebotomine vectors control. For search (ii), we looked for information about pharmacodynamics of the drugs and their effectiveness at controlling insects in dogs.

Selection of the compounds with higher potential for ZVL control

To be used as a tool to control ZVL, the systemic insecticides should be able to kill female sand flies feeding on dogs (adulticides) and easy to administer so they can be distributed to large populations of dogs. They should also be effective for a maximum period of time to avoid repeated treatments. We selected the systemic insecticides based on the following criteria: (i) evidence about anti-phlebotomine capacity, (ii) optimal plasma drug concentration to kill blood-fed phlebotomine vectors, (iii) time of expected efficacy (ideally over 3 months after a single administration of the drug product) and (iv) route of administration (ideally oral).

Results

List of systemic insecticides for dogs and anti-phlebotomine activity

Thirteen systemic insecticides currently being used in dogs were identified (Table 1). Nine of them are oral treatments, one had an oral and a topical presentation.
and another one had a subcutaneous and a topical presentation. Ten of the treatments contained only one active ingredient, and three of the treatments were combinations of two active ingredients. The latter were used for heartworms, hookworms, whipworms, roundworms and fleas. From the other nine, two were used for heartworm control and seven were indicated for the control of fleas, of which three included tick control and one included tick and mite control. The mode of action of these drugs, summarised in Table 1, is described in detail in the Appendix S1.

The pharmacokinetics (PK), duration of action (Table 1), safety and anti-phlebotomine capacity (Table 2) of the insecticides are summarised below.

Table 1 List of drugs including the active ingredients and pharmaceutical characteristics of 13 systemic insecticides drugs commercialised for their use in dogs

| Drugs                     | Indications                                      | Administration | Dose                  | Duration of action | Mechanism of action                                      |
|---------------------------|--------------------------------------------------|----------------|-----------------------|--------------------|----------------------------------------------------------|
| Ivermectin                | Heartworms                                       | PO             | 0.012 mg/kg BW        | 4 weeks            | Agonist of glutamate-gated chloride channels and agonist of GABA |
| Moxidectin                | Heartworms                                       | SC             | 0.17 mg/kg BW         | 6 months           | Agonist of glutamate-gated chloride channels and agonist of GABA |
| Moxidectin/imidacloprid   | Fleas, mites, heartworms, microfilariae and roundworms | Topical        | 2.5–6.25 mg/kg/10–25 mg/kg | 4 weeks           | Agonist of GABA and agonist glutamate-gated chloride channels/antagonist of the nicotinic acetylcholine receptors |
| Spinosad                  | Fleas and ticks                                  | PO             | 45–70 mg/kg BW        | 4 weeks            | Agonist of the nicotinic acetylcholine receptors |
| Milbemycin oxime/Spinosad | Heartworms, hookworms, roundworms, whipworms and fleas | PO             | 0.75–1.18 mg/kg BW/45–70 mg/kg BW | 4 weeks           | Agonist of the nicotinic acetylcholine receptors |
| Fluralaner                | Fleas and ticks                                  | PO             | 25 mg/kg BW           | 12 weeks           | Antagonist GABA-gated chloride channels |
| Fluralaner                | Fleas and ticks                                  | Topical        | 25–50 mg/kg BW        | 12 weeks           | Antagonist GABA-gated chloride channels |
| Afoxolaner                | Fleas and ticks                                  | PO             | 2.5 mg/kg BW          | 5 weeks            | Antagonist GABA-gated chloride channels |
| Sarolaner                 | Fleas, ticks and mites                           | PO             | 3 mg/kg BW            | 5 weeks            | Antagonist GABA-gated chloride channels |
| Lufenuron                 | Fleas (eggs)                                     | PO             | 10–30 mg/kg BW        | 4 weeks            | Interference with chitin synthesis |
| Milbemycin oxime/Lufenuron| Heartworms, hookworms, roundworms, whipworms and fleas | PO             | 0.5–1.2 mg/kg BW/10–46 mg/kg BW | 4 weeks           | Agonist of GABA/Interference with chitin synthesis |
| Nitenpyram                | Adult fleas                                      | PO             | 11.4 mg (1–13 kg BW)  | 24 h               | Agonist of the nicotinic acetylcholine receptors |
| Imidacloprid              | Adult fleas                                      | PO             | 0.75 mg/kg BW         | 24 h               | Agonist of the nicotinic acetylcholine receptors |

PO, oral; BW, body weight; SC, subcutaneous; GABA, gamma-aminobutyric acid.

Ivermectin, given orally to control heartworm (Dirofilaria immitis) in dogs at the dose range of 6–12 mcg/kg body weight (BW), reaches peak plasma concentration ($C_{max}$) of about 3 ng/ml 8 h after ingestion ($t_{max}$). The plasma mean elimination half-life ($t_{1/2}$) is 80 ± 29 h after ingestion with no events of toxicity even in ivermectin-sensitive collies [32, 33]. Ivermectin has shown to be effective against phlebotomine sand flies that fed on treated rodents. However, the dose used was 20 mg/kg BW, significantly higher than 6–12 mcg/kg BW. At this dose, 100% of the adult sand flies were killed for up to 7 days [21, 34, 35].

Moxidectin, given subcutaneously, also used for heartworm control, has a significantly broader and longer half-life distribution into tissues than ivermectin [36].
Studies about safety and PK at the recommended dose of 0.17 mg/kg BW reported no events of toxicity. The maximum blood levels \( C_{\text{max}} = 5.1 \text{ ng/ml} \) are reached \( (t_{\text{max}}) \) at 7–10 days post-treatment, and plasma mean elimination half-life \( (t_{1/2}) \) is approximately 35 days [37]. Efficacy studies reported 90% control of heartworm infection for 6 months [38, 39]. There are no reports of the anti-phlebotomine activity of moxidectin.

A formulation of topical moxidectin in combination with imidacloprid for dogs at dose 2.5 mg/kg BW has the following PK parameters: \( C_{\text{max}} = 15.3 \text{ ng/ml} \), \( t_{\text{max}} = 9 \) days and \( t_{1/2} = 35 \) days. Efficacy studies with one dose administration reported at least 97% reduction of flea infestation over 4 weeks and 99% microfilaricidal efficacy [40, 41].

In dogs, spinosad has rapid absorption and extensive distribution after oral administration of the recommended dose to control flea infestations: 45–70 mg/kg BW. Bioavailability is approximately 70%, reaching maximum concentration \( C_{\text{max}} = 5500 \text{ ng/ml} \) between 2 and 4 h post-treatment. The plasma mean elimination half-life ranges from 127.5 to 162.6 h [42, 43]. Efficacy and safety studies reported no adverse reactions in dogs after treatment at the recommended dose, and more than 95% reduction of flea infestation during 4 weeks post-treatment [42, 43]. Oral treatment of rodents with diets

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**Table 2** Active ingredients and characteristics for potential use in phlebotomine vector control of 11 systemic insecticides drugs commercialised for their use in dogs

| Ingredients                      | Safety* | PROS                                               | CONS                                                                 | Supporting literature |
|----------------------------------|---------|----------------------------------------------------|----------------------------------------------------------------------|-----------------------|
| Ivermectin 2 mg/kg              |         | Proven effect on adult sand flies and on larvae    | Experiments performed in rodents used 1 mg/kg body weight and the label dose for dogs is 0.012 mg/kg. Dogs should be tested for existing heartworms. | [21, 32, 33, 34]     |
| Moxidectin 1.12 mg/kg            |         | Higher safety and longer half-life elimination comparing with Ivermectin | There is no literature about the killing effect of moxidectin on adult sand flies. Dogs should be tested for existing heartworms. | [37–39], 90           |
| Spinosad 3600 mg/kg              |         | Proven efficacy killing adults and larvae. It has no residual effect. | The literature including the actual ingredient showed only effectiveness with dose twice that recommended for dogs | [40–44, 47–50]       |
| Milbemycin oxime/Spinosad 980 mg/kg |       | Well tolerated by dogs. Increased odds of effectiveness on sand flies with the action of both drugs together | No literature regarding its anti-phlebotomine effect and dogs should be tested for existing heartworms | [41, 48–90]         |
| Milbemycin oxime/Spinosad 3600 mg/kg |     | Well tolerated by dogs. Increased odds of effectiveness on sand flies with the action of both drugs together | No literature regarding its anti-phlebotomine effect and dogs should be tested for existing heartworms | [41, 88–90]          |
| Milbemycin oxime/Lufenuron 980 mg/kg |     | Well tolerated by dogs and efficacy in killing flea larvae | No effect in adult fleas and no literature regarding its effectiveness of killing sand flies | [65–67]              |
| Milbemycin oxime/Lufenuron 2000 mg/kg |     | Well tolerated by dogs and efficacy in killing flea larvae | No effect in adult fleas and no literature regarding its effectiveness of killing sand flies. | [65–67]              |
| Nitenpyram 1680 mg/kg            |         | Proven efficacy in killing flea adults and larvae with no residual effect. | No literature regarding its effectiveness of killing sand flies. Only active during 24 h | [68–71]              |
| Nitenpyram 1680 mg/kg            |         | Proven efficacy in killing flea adults and larvae with no residual effect. | No literature regarding its effectiveness of killing sand flies. Only active during 24 h | [20, 23, 42, 72]     |
| Imidacloprid 1680 mg/kg          |         | Proven efficacy in killing sand fly adults and larvae with no residual effect. | Not in the market yet. Only active for 24 h | [20, 23, 42, 72]     |

*Safety in dogs with oral administration except for moxidectin is subcutaneous administration.
containing about 120 mg/kg BW caused 100% mortality of blood-fed sand flies for 1 week [44].

The combination of spinosad and milbemycin oxime (MO) oral treatment at the recommended dose for fleas and ticks control provides greater systemic exposure of MO than when administered alone and the PK of spinosad is unaltered [43]. Efficacy and safety studies in dogs at the recommended dose reported treatment effectiveness greater than 90% for at least one month in flea infestations, reductions of about 95% for nematode infection and no adverse reaction. There is no literature on the anti-phlebotomine activity of this combination.

Fluralaner’s PK studies reported that after a single oral treatment of the recommended dose for fleas and ticks control (25 mg/kg BW), maximum concentration of 3000 ng/ml is reached at 24 h, \( t_{1/2} \) is about 12 days and quantifiable concentrations in plasma are found for up to 112 days. In addition, the ingestion of food before treatment has no effect on its bioavailability [45, 46]. A topically administered formulation that contains the same dose of fluralaner (25 mg/kg BW) obtained much lower plasma concentrations \( (C_{\text{max}} = 727 \pm 191 \text{ ng/ml}, \ t_{\text{max}} = 25 \text{ h, and } t_{1/2} = 21 \text{ days}) \) [47]. Safety studies including adult dogs, MDR-1 deficient dogs, breeding animals and puppies reported no adverse effects. Efficacy studies confirmed the safety of fluralaner and reported flea and tick control greater than 95% over 12 weeks [47–50].

Studies with oral afoxolaner in dogs at the recommended dose of 2.5 mg/kg BW reported the following PK parameters: \( C_{\text{max}} = 1655 \pm 332 \text{ ng/ml, } t_{\text{max}} = 2–6 \text{ h and } t_{1/2} = 15.5 \pm 7.8 \text{ days.} \) In addition, plasma concentrations above 100–200 ng/ml, the requirement for efficacy in flea control, were detected for more than one month [51, 52]. Safety and efficacy studies reported no adverse effects in adult dogs or puppies and greater than 90% efficacy at controlling fleas and ticks infestations up to 35 days post-treatment [51, 53–55].

Sarolaner is used in dogs at the recommended dose of 3 mg/kg BW to control fleas, ticks and mites infestations. Maximum plasma concentration of 1100 ng/ml is observed within the first 24 h after treatment and \( t_{1/2} \) is 11–12 days. The plasma concentration required for flea control, 100 ng/ml, remains for more than 30 days post-treatment [56]. Efficacy and safety studies reported no adverse events in dogs after oral administration of the recommended dose and 90% efficacy at controlling fleas, ticks and mites infestations up to 35 days post-treatment [57–59]. There is no literature about the anti-phlebotomine activity of fluralaner, afoxolaner or sarolaner.

Lufenuron orally administered to dogs at the recommended dose of 10–30 mg/kg BW for flea control has maximum absorption after 6 h, and drug concentration at the skin is 10-fold that of blood concentration [60]. Maximum plasma concentration \( (C_{\text{max}} = 800 \text{ ng/ml}) \) is reached about 8 h after treatment, and plasma mean elimination half-life is 20 days. Lufenuron is an ovicidal and larvicidal drug. Adult fleas transfer lufenuron to the growing eggs through their blood and to the larvae through their excrement [61]. Efficacy and safety studies reported no adverse effects in dogs after oral treatment at the recommended dose, and a reduction in flea infestation of 97% in the subsequent generations [62–64].

Lufenuron in combination with Milbemycin oxime does not alter the PK compared to when administered alone. Safety studies of this combination at the recommended dose showed no adverse effect when orally administered [65]. Efficacy studies showed reductions in fleas, toxocara canis and Trichuris vulpis infections greater than 90% [66, 67]. There is no literature about the anti-phlebotomine activity of lufenuron alone or in this combination.

Nitenpyram absorption from the gastrointestinal tract occurs in rapidly \( (t_{\text{max}} = 1.21 \pm 0.65 \text{ h, } C_{\text{max}} = 4787 \pm 782 \text{ ng/ml and } t_{1/2} = 2.8 \pm 0.7 \text{ h}) \) and complete excretion in urine happens within 48 h post-treatment [68]. Studies on safety and efficacy on flea control reported no adverse effects when orally administered to dogs at the recommended dose. These studies also reported 95% efficacy at controlling fleas infestation between 30 min and 48 h post-treatment [69–71]. No literature was found about its anti-phlebotomine activity.

One formulation of oral imidacloprid indicated for flea control in dogs was approved for commercialisation in 2015, but soon after was removed for commercial reasons. The only study published about this commercial product used dogs from different clinics and different breeds. At the oral dose of 0.75 mg/kg BW, the study reported no adverse effect in the 118 dogs treated, and 95% efficacy at controlling fleas infestations [72]. Studies of rodents fed on diets with imidacloprid concentrations of 250 mg/kg reported sand fly mortality after blood fed on treated rodents > 85% for at least 3 days post-treatment [20, 23, 42]. One of these studies also followed larval development and reported mortality > 90% for all larval stages [20].

**Selection of the compounds with higher potential for ZVL control**

Compounds that did not match the selection criteria were excluded. Ivermectin was excluded because standard tablets of ivermectin formulations commercialised for dogs reach plasma concentration fivefold lower than that
needed to kill sand flies (13 ng/ml). Subcutaneous moxidectin was excluded because the plasma concentration is much lower than with the topical presentation. The topical formulation of fluralaner was also excluded because has lower plasma concentration and shorter lasting effect than the oral formulation. Milbemycin oxime was excluded because it has no capability to kill insects in dogs. The combination with spinosad was also excluded because it has lower concentration than the product with spinosad alone. Lufenuron was excluded because its lack of adulticide effect as it is only effective at killing flea eggs and larvae but ineffective at killing adult fleas. Nitenpyram and imidacloprid were excluded because their action period is short (only 24 h).

The compounds that matched the selection criteria and were selected as potential control tools for ZVL transmission were as follows: spinosad, fluralaner (oral), afloxolane, sarolaner and moxidectin (topical). Those five systemic insecticides are popular among veterinary practitioners and dog owners as they are easy to administer (four oral and one topical). Fluralaner was the only compound that met the ideal criteria of at least 3 months of lasting effect against the targeted parasites.

Discussion

Our review found five systemic insecticides already commercialised in dogs that have potential use as a control tool for ZVL transmission. These insecticides are safe and readily available to use in dogs in contrast to other compounds or formulations under development, for example, slow release ivermectin, for which safety is still being developed [73]. However, there is limited evidence on their anti-phlebotomine activity. Laboratory and field studies should be conducted to evaluate whether the phlebotomine sand flies feeding on dogs treated with these compounds are killed [74]. Some of the compounds selected (e.g. flularaner) are effective against fleas and ticks for up to 3 months, so it is possible that they may also have a prolonged anti-phlebotomine effect, but this should also be proven.

Even if their anti-phlebotomine activity is demonstrated, these systemic insecticides should comply with other requirements to be used as a ZVL control tool. They should be administered to a large number of dogs in endemic villages to have an effect on *L. infantum* transmission. Thus, they need to be safe, in case one dog gets more than on dose, and easy to administer. Four of the selected compounds can be administered orally. As shown in field studies with rodents, treated baits can be used to treat large populations [21, 75]. Treated baits were also found to work well with oral vaccination of wild life to control rabies in West Europe and USA [76]. A similar approach could be used in dogs to reduce costs and ensure high coverage.

The mass administration of systemic insecticides to dogs will not immediately protect the treated dogs directly against ZVL, but it will reduce phlebotomine sand fly density in the intervention area (e.g. village) [25]. If the number of treated dogs is large enough and the treatment is sustained, the reduction on vector density will interrupt the transmission of *L. infantum* to humans. Dogs, both treated and untreated as it happens in vaccination programs [77], will also be protected against *L. infantum* infection. Furthermore, treated dogs will be protected against fleas and ticks infestations [19].

The use of systemic insecticides may be used as a complement or alternative to other ZVL control tools but it has some limitations. The mass use of insecticides may result on the development of insecticide resistance in *L. infantum* vectors and other ectoparasites feeding on dogs. The use of two systemic insecticides (e.g. in combination or in rotation) with different modes of action may limit this risk [78]. The selected compounds are expensive as they were developed to treat individual dogs thus treating thousands of dogs would be costly. However, the cost of some of these drugs can be significantly reduced (e.g. ivermectin) and new formulations could be developed to reduce the number of treatments (e.g. slow release) [73]. In any case, mass treating dogs, in particular if oral drugs are used, would be much less demanding than the current alternatives: dog culling, insecticide-impregnated collars and canine vaccines. Dog culling and insecticide-impregnated collars requires important logistics and accessing to each dog. Culling dogs require obtaining a blood sample, conducting the laboratory analysis, re-tracing the positive dogs and culling them [12, 17, 18, 79, 80]. Finally, the canine vaccines could be a very useful tool, but they also require manipulating the dogs, they are expensive and so far none of the three available vaccines in Brazil has proved to reduce ZVL transmission [81].

Cluster randomised clinical trials should be used to demonstrate that mass administration of systemic insecticides to dogs significantly decreases human incidence of ZVL in endemic areas [15]. But these clinical trials are complex and costly. Mathematical modelling may allow generating preliminary data on the impact of this control measure on *L. infantum* transmission. Modelling transmission dynamics has been used to predict the impact of control measures on a number of diseases, including leishmaniasis. For example, mathematical modelling was use comparing insecticide-impregnated collars with dog culling in preventing ZVL transmission [18, 82, 83].
Systemic insecticides in dogs for vector control

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Systemic insecticides mode of action.

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**Corresponding Author** Sonia Ares Gomez, Hospital Clinic – Universitat de Barcelona, Roselló 132, 4ª, 08036 Barcelona, Spain.
Tel.: +34 932275400 (ext. 4112); E-mail: sonia.ares@isglobal.org