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SHORT COMMUNICATION

What do we know about *Angiostrongylus cantonensis* in Spain? Current knowledge and future perspectives in a globalized world

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Abstract

Angiostrongylus cantonensis is an important emerging and zoonotic nematode that has been reported worldwide since its first description in Asia 86 years ago. Among places where this parasite has been recently described, insular regions of northwest Africa seem to be particularly relevant. We performed a systematic review in scientific databases to search and extract information about all reports describing cases of *A. cantonensis* in Spain until July 2021. As a result, seven surveys about the presence of this pathogen in Spanish insular regions were found, especially in the Canary Islands, as well as a non-autochthonous report of *A. cantonensis* in the mainland Spain. The lack of reliable information about the presence or absence of this nematode in the Iberian Peninsula highlights the need for further studies concerning this emerging pathogen since rodents acting as competent definitive hosts of *A. cantonensis* are widely distributed in the mainland. Moreover, the high maritime traffic daily registered in Spanish ports could be a main entrance pathway for *A. cantonensis* or its intermediate hosts in the country due to the frequent and direct connection between these points and regions where this pathogen is endemic. We encourage to focus further efforts on investigating the current epidemiological situation of *A. cantonensis* in the Iberian Peninsula, just as in other Mediterranean countries with similar epidemiological, ecological and geographical characteristics. In this sense, the relevant implications of this parasite for animal and public health make necessary to act integrating different viewpoints under the One Health perspective.

KEYWORDS
Angiostrongylus cantonensis, emerging diseases, Iberian Peninsula, maritime traffic, Spain, zoonoses

1 | INTRODUCTION

Emerging and re-emerging diseases are a major sanitary issue with further social and economic implications worldwide (Bueno-Marí et al., 2015). Around 75% of emerging pathogens affecting humans have their origin in domestic or wild animals (i.e. zoonoses), and their study, prevention and control should be carried out under a One Health perspective (Bueno-Marí et al., 2015; Rabozzi et al., 2012). Among them, *Angiostrongylus cantonensis* (syn. *Parastrongylus cantonensis*) needs to be specially considered due to its implications for animal and public health and its increasing global distribution (Barratt et al., 2016). *A. cantonensis*, also known as 'rat lungworm', is a nematode parasite belonging to superfamily Metastrongyloidea and family Angiostrongylidae (Anderson et al., 2009; Barratt et al., 2016). Concerning its life cycle, several gastropod species (terrestrial and aquatics snails and slugs) act as intermediate hosts, where the third larval stage (L3) is reached after the consumption of infected rodent faeces (definitive hots) with the first larval stage (L1). Intermediate hosts can be eaten by rodents in which L3 develop up to the sub-adult phase when they are located in the brain. Then, larvae mature to adult stage in the right ventricle and pulmonary arteries where, after copulation, eggs are expelled into the bloodstream to reach the lung tissue. From here, first stage larvae are swallowed and eventually excreted in the faeces (Cowie, 2013). Humans may be accidentally infected by the consumption of intermediate and paratenic hosts (crustaceans, planarians, frogs and lizards) (Cowie, 2013; Wang et al., 2008). Human infection has been described causing severe neurological disorders (eosinophilic meningitis) because of the physical damage and inflammatory response developed against larvae in the brain although other target tissues as eyes could be also affected (Wang et al., 2012). Although this parasite was first described in China (Guangzhou region) in the brown rat (*Rattus norvegicus*), it has currently been reported in 30 countries around the world, especially in tropical and sub-tropical regions (South Asia, Pacific islands, Australia, etc.) (Chen, 1935; Martín-Carrillo et al., 2021; Wang et al., 2008). *A. cantonensis* has also been extensively described in insular areas, such as the Caribbean, Madagascar, Sri Lanka, Philippines, Indonesia and Papua New Guinea, among others (Barratt et al., 2016). The strategic commercial location of some countries, such as those in southern Europe, may facilitate the introduction of *A. cantonensis* in new areas through maritime ports although factors related to the presence of intermediate or definitive hosts and some risk behaviours associated with culinary habits could also be operating.

This study aimed to update the scientific knowledge about *A. cantonensis* presence in Spain, addressing the relevance of this emerging and zoonotic pathogen in a globalized world, and prospecting about its future distribution in the Iberian Peninsula.

2 | MATERIALS AND METHODS

We performed a systematic review on the distribution of *A. cantonensis* in Spain, analyzing its presence in definitive, intermediate, paratenic and accidental hosts in mainland and insular areas of this European country. For this purpose, we used the Web of Science database to search for scientific articles published until July 2021 (without time restriction) that included the following combination of terms in the title or abstract: (*Angiostrongylus cantonensis* OR *Parastrongylus cantonensis* OR *cantonensis*) AND (Spain OR Iberian Peninsula OR Spanish OR Canary OR Balearic OR Extremadura OR Castilla-La Mancha OR Aragon OR Castile and Leon OR Andalusia OR Catalonia OR Murcia OR Valencian Community OR Asturias OR Navarra OR Galicia OR Madrid OR La Rioja OR Basque Country OR Cantabria OR Melilla OR Ceuta). This search was completed with additional searches in Google Scholar, PubMed and Scopus to assure that all relevant articles were included in the review. A similar search employing the following combination of terms '*Angiostrongylus cantonensis* OR *Parastrongylus cantonensis* OR *cantonensis*' was performed to evaluate the temporal distribution of articles worldwide published.

Duplicated publications were removed and all articles addressing the presence of *A. cantonensis* in any Spanish region (Table 1) were carefully read to obtain detailed information related to the year of publication, city and region where *A. cantonensis* was described, identification technique used, hosts involved in the study, prevalence of infection and the possible transmission routes described to infect humans. The article selection and information extraction were performed using a double-blind procedure carried out by the two co-authors of the present study.

3 | RESULTS

A. cantonensis was studied in seven articles that dealt its presence in Canary Islands ($n = 6$; north-western coast of Africa, 28° 11.669′N, 16° 37.747′W) and Balearic Islands ($n = 1$; east of the mainland Spain, 39° 35.894′N, 2° 58.431′E). Autochthonous reports of this nematode in the mainland Spain have not been found although a clinical case in a Cuban traveller was described in Catalonia ($n = 1$; northeast Spain, 41° 26.943′N, 2° 14.058′E) (Valerio Sallent et al., 2020) (Table 1). It is important to note that all the cases of *A. cantonensis* described in Canary Islands have been detected in Tenerife despite performing sampling on other islands belonging to the same archipelago. Regarding the most studied intermediate and definitive hosts in Spain, it is noteworthy to report about mollusc and rodent species in Canary Islands (Table 1). While several studies focused on three rodent species that act as definitive hosts (*Mus musculus*, house mouse; *Rattus rattus*, house rat; and *R. norvegicus*), the number of intermediate hosts reached eight gastropods' species. In addition, another mammalian host species (specifically, two specimens of North African hedgehog: *Atelerix algirus*) has also been reported in Majorca (Balearic Islands). In the studied regions, the presence and prevalence of *A. cantonensis* in different hosts have been deeply studied mostly using morphological (87.5%; 7/8) or molecular and serological identification techniques (75%; 6/8) (Table 1). The number of sampled specimens in all selected articles varied greatly between studies [molluscs and rodents mean (rank): 182 (2-1462); gastropods mean (rank): 330 (53-233); rodents mean (rank): 625 (54-1462)]. Concerning data registered in the evaluated articles, it has

TABLE 1 Information extracted from the selected articles addressing the presence of *Angiostrongylus cantonensis* in Spain

Article	Year	City	Region	Identification	Host species	Prevalence
Foronda et al.	2010	Tenerife	Canary Islands	M / MB	*Rattus rattus* (D)	15% (O)
				M / MB	*Rattus norvegicus* (D)	0% (O)
				M / MB	*Mus musculus* (D)	0% (O)
				M / MB	*Hemicycla bidentalis* (I)	12% (O)
				M / MB	*Retinella circumsessa* (I)	0% (O)
				M / MB	*Lehmannia valentiana* (I)	0% (O)
				M / MB	*Plutonia lamarckii* (I)	47% (O)
				M / MB	*Helix* spp. (I)	0% (O)
Martín-Alonso et al.	2011	Tenerife	Canary Islands	M / MB / SR	*Rattus rattus* (D)	15.9% (M/MB) and 55.6% (S)
Martín-Alonso et al.	2015	Tenerife	Canary Islands	M / MB	*Plutonia lamarckii* (I)	19.3% (M); 60.2% (MB)
				M / MB	*Cornu aspersum* (I)	
				M / MB	*Theba pisana* (I)	
Paredes-Esquivel et al.	2019	NA	Majorca	M / MB	*Atelerix algirus* (A)	100% (O)
Červená et al.	2019	Tenerife	Canary Islands	M / SQ	*Rattus norvegicus* (D)	NA
Valerio Sallent et al.	2020	Badalona	Catalonia	SR	*Homo sapiens* (A)	NA
Segeritz et al.	2021	Tenerife	Canary Islands	M	*Theba pisana* (I)	3.6% (M)
				M	*Cornu aspersum* (I)	
				M	*Rumina decollata* (I)	
				M	*Plutonia lamarckii* (I)	
Martín-Carrillo et al.	2021	Tenerife	Canary Islands	M	*Rattus rattus* (D)	19.7% (M)
				M	*Rattus norvegicus* (D)	7.1% (M)
				M	*Mus musculus* (D)	0% (M)

Note: The table shows detailed data concerning the year of publication, area of study (city and region), identification method [morphology (M), molecular biology (MB), serology (SR) and sequencing (SQ)], species studied [definitive (D), intermediate (I) and accidental (A) host] and prevalence reported [overall (O), morphology (M), serology (S) and molecular biology (MB)].

been found that prevalences are quite different both in intermediate (3.6%–60.2%) and definitive (15%–55.60%) hosts at the same study area (Table 1). Moreover, prevalence also varied depending on the identification method used; for example, for the same analyzed intermediate hosts in Canary Islands, the prevalence obtained was 19.3% and 60.2% when the presence of *A. cantonensis* was diagnosed by morphological identification and by the Loop-mediated isothermal amplification technique, respectively (Martin-Alonso et al., 2015). Scientific articles also described the presence of *A. cantonensis* close to urban areas with high human activity (risk of zoonoses) (Martin-Alonso et al., 2011, 2015).

On a temporal scale, most articles (62.5%; 5/8) have been published during 2019 and 2021, showing a similar tendency than publications about the same subject in the rest of the countries where this disease has been investigated (Figure S1). Also, there seems to be a consensus in the articles reviewed that consumption of snails or slugs was probably the most important transmission route to humans in the studied islands, where these intermediate hosts are frequently used to prepare several traditional dishes. An article also addressed the relevance of abiotic elements, such as temperature, humidity or precipitation, as important factors influencing the life cycle of *A. cantonensis* in Tenerife (Canary Islands) (Martín-Carrillo et al., 2021).

4 | DISCUSSION

Studies concerning autochthonous reports of *A. cantonensis* in Spain are only performed on insular areas, without any description in the Iberian Peninsula. In this sense, this nematode has been well-reported in Canary Islands, where there are several reports in Tenerife island (Červená et al., 2019; Foronda et al., 2010; Martin-Alonso et al., 2011, 2015; Martín-Carrillo et al., 2021; Segeritz et al., 2021). Also, in Spain, an anecdotical presence of *A. cantonensis* in accidental hosts (hedgehogs) has been reported in Balearic Islands (Paredes-Esquivel et al., 2019). This finding shows that great efforts to investigate the presence of *A. cantonensis* in Spanish islands have been made in recent years, indicating the emerging character of this parasite, but its presence has not been investigated in the Peninsula to date. This fact highlights an important lack of epidemiological information related to this major emerging and zoonotic disease in continental areas of Spain. To solve

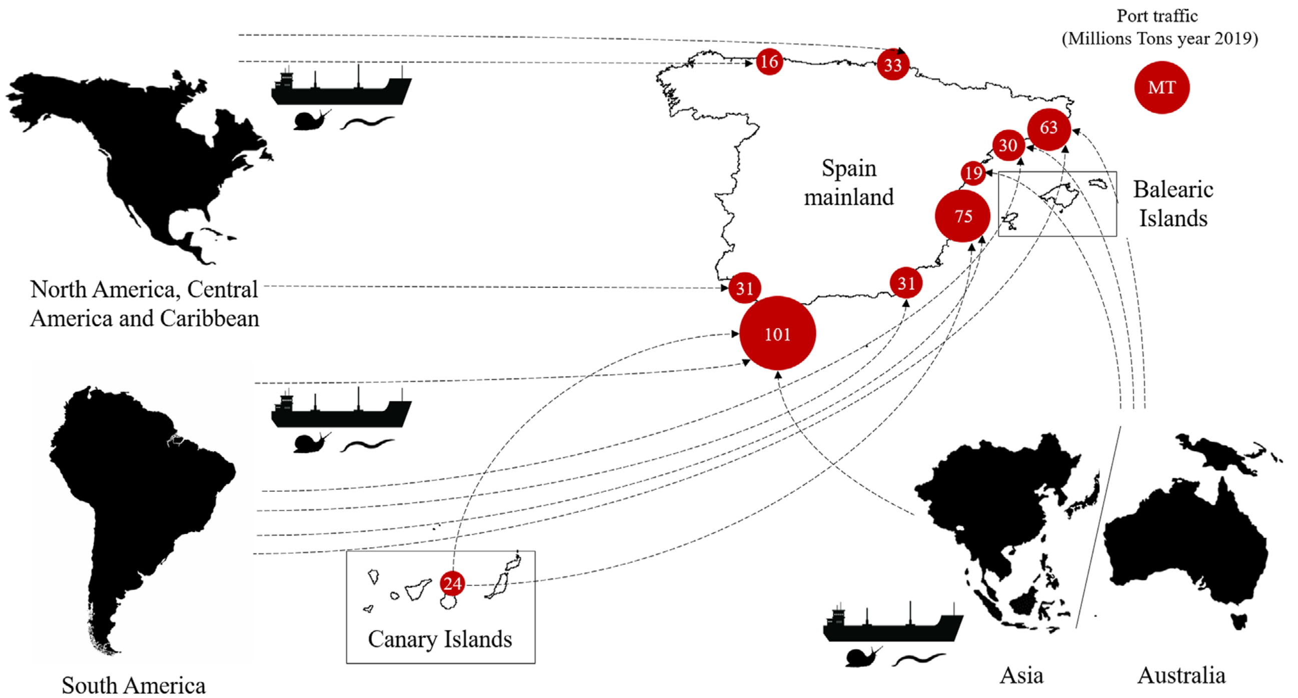

FIGURE 1 Conceptual model showing in a simplified form the high number of connexions between Spanish maritime ports and regions where *Angiostrongylus cantonensis* is widely distributed. The most representative maritime ports are marked with a red circle, noting the millions of tonnes that each port trades annually (MITMA, 2019)

this, surveillance programmes should be promoted to obtain the most detailed information possible about the real scenario of *A. cantonensis* in Spain. In other Mediterranean countries, where autochthonous cases of this parasite infection have been scarcely studied and reported to date, but imported cases from endemic areas are increasing, surveillance programmes for *A. cantonensis* should also be reinforced (Barratt et al., 2016). According to intermediate and definitive hosts reported, the presence of similar hosts (mainly rodents) in the studied islands and in the mainland Spain indicates a favourable conditions for the maintenance of *A. cantonensis* life cycle in the Iberian Peninsula (Červená et al., 2019; Foronda et al., 2010; Martin-Alonso et al., 2011; Martín-Carrillo et al., 2021). Although the most important definitive hosts reported in the Canary Islands are also widely distributed in the Iberian Peninsula (house rat, brown rat and house mouse), the role of intermediate hosts needs to be deeply evaluated since many of the snails and slugs described in the Canary Islands are endemic and therefore, absent in mainland Spain (Arechavaleta et al., 2010; Palomo et al., 2007). To elucidate this issue, it is important to be aware that prevalence varies greatly depending on the identification method employed, so highly sensitive techniques (e.g. molecular biology and sequencing) or the combination of at least two of them are recommended (Martin-Alonso et al., 2015). Moreover, great differences in prevalence of intermediate and definitive hosts in the same island (Tenerife) were detected (Table 1), probably associated with biotic and abiotic factors. Therefore, we encourage to sample as many points as possible to obtain representative information and reduce bias associated to the diversity of this data.

It is relevant to note that the epidemiology of *A. cantonensis* may also be influenced by extrinsic factors not directly related to the natural life cycle of the parasite, such as (1) the efficient communication ways on a global scale, with significant ecological and epidemiological implications (Pirotta et al., 2019; Tatem et al., 2006), (2) the gastronomic culture of each study area (snails are frequently consumed in western Europe as essential components of several typical dishes) (Martin-Alonso et al., 2015) and (3) climate change associated with the global warming (York et al., 2014). In this sense and regarding increasing knowledge about *A. cantonensis* in Spain, great efforts should be implemented in regions of the Iberian Peninsula with higher infection risk, especially in areas close to maritime ports. Spain has 26 important seaports, most of which (n = 23) are located in the Peninsula, two in the Canary Islands and one in Majorca (Balearic Islands). The annual maritime traffic in Spain of these ports exceeds 500 million tonnes although hundreds of other small maritime ports are also distributed all along the Spanish coastline (MITMA, 2019) (Figure 1). These locations are points with high commercial activity that could be relevant entry pathways for *A. cantonensis* in new areas due to the great daily maritime traffic between mainland Spanish ports and areas where this nematode has been previously described, such as Tenerife (Canary Islands), America, Asia or Australia (Figure 1). This problem has been previously described for other organisms in the Iberian Peninsula, where non-autochthonous algae have been introduced by ballast waters (Ardura et al., 2020; Butrón et al., 2011). These important communication ways make necessary to consider the mainland Spanish territory as a possible hotspot for this pathogen in the foreseeable future

(Barratt et al., 2016; Pirotta et al., 2019). The high number of boats could act as mechanic spreaders of infected or non-infected intermediate and definitive hosts, which may facilitate the transmission and maintenance of *A. cantonensis* in new regions where competent hosts were not present to date (Ardura et al., 2015; Hochberg et al., 2007). Moreover, a risk factor shared between Canary Islands and the Iberian Peninsula that favour the human infection is related to gastronomic traditions since the consumption of snails and slugs is a common practice in western Europe that needs to be considered (Martin-Alonso et al., 2011, 2015; Martín-Carrillo et al., 2021). Additionally, climatic variables (e.g. temperature and precipitation) strongly contribute to the development of *A. cantonensis* life cycle, so the effect of the climate change on the dispersion of this emerging parasite in new geographical areas should be taken into account, as described for other pathogens causing vector-borne diseases (e.g. malaria or dengue) (Lafferty, 2009; Martín-Carrillo et al., 2021; Rocklöv & Dubrow, 2020). The multifactorial character of *A. cantonensis* and its implications for animal and public health make necessary to address the study of this parasite, as well as any other zoonotic pathogen, under a One Health perspective, integrating scientific knowledge from different disciplines to maximize the success of specific prevention and control programmes (Bidaisee & Macpherson, 2014).

Updating the current epidemiological status of *A. cantonensis* in the Iberian Peninsula requires to perform intensive monitoring to deepen the presence, temporal and geographical evolution and future implications of this zoonoses in Spain. Hereafter, prevention and control measures could be implemented to act on critical points, such as the management of intermediate or definitive hosts, preventive measures concerning gastropods consumption by humans (e.g. more rigorous monitoring programmes and proper cooking temperature) and increase of controls on ballast water and cargo of ships docking in Spanish ports, especially those coming from places where *A. cantonensis* is endemic.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

No ethical approval was required as this is a review article with no original research data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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