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The Current Status of Protozoan Parasitic Diseases in Cyprus: A Narrative Literature Review †

Chad Schou [1], Maria Filippova [1], Annalisa Quattrocchi [2] and Panagiotis Karanis [1,*]

[1] Department of Basic and Clinical Sciences, University of Nicosia Medical School, 2408 Nicosia, Cyprus; schou.c@unic.ac.cy (C.S.); filippova.m@unic.ac.cy (M.F.)
[2] Department of Primary Care and Population Health, University of Nicosia Medical School, 2408 Nicosia, Cyprus; quatttrocchi.a@unic.ac.cy
* Correspondence: karanis.p@unic.ac.cy; Tel.: +357-22471813
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Abstract: Infections caused by parasites affect millions of people around the world and cause human death worldwide. Most of the protozoan exists as free-living species in different aquatic environments as well as some of the species living in association with host organisms and can infect the host. The aim of this narrative review is to provide an overview of the available information concerning infectious parasitic diseases in Cyprus. Data on protozoan parasitic infections/carriage prevalence in Cyprus is limited, possibly due to the unknown levels of pathogens contamination in the water supplies and in the ecosystem, which could relate to tourism on the island—a major pillar in the Cypriot economy. Tourists and immigrants represent a melting pot of many human activities that brings many people from all over the world together and potentially serves as a source for contamination that can cause endemic infectious diseases on the island.

Keywords: Protozoan; Parasites; Diseases; Cyprus

1. Introduction

Infections caused by protozoan parasites affect millions of people around the world and cause human death worldwide. Under normal circumstances, when the immune system is unaffected, disease symptoms may not develop. If the host immune system is compromised, or the infectious agent overwhelms the immune system, an infectious disease ensues. Medicine today is in successful control of spreading and treating protozoan parasitic diseases by improved sanitation, screening and antiprotozoal therapy. However, there is no effective treatment yet for several protozoal diseases e.g., cryptosporidiosis. Future research will continue to reveal the protozoal diseases as major medical problems.

The real evaluation of the epidemiological status in Cyprus is difficult due to the unknown levels of pathogenic contamination in the water supplies, degree of swimming pools contamination, and the distribution of vectors due to tourism on the island—a major pillar in the northern and southern Cyprus economies. Tourists and immigrants represent a melting pot of human activities that brings many people from all over the world together and potentially serves as a source for contamination that can cause endemic infectious diseases on the island. Control of diseases by constant monitoring of the epidemiological situation of the region can prevent and reduce the incidence of infections.

We conducted a narrative review in order to provide an overview of the available information on protozoan parasitic diseases in Cyprus and to identify information gaps to facilitate discovery of the origin of protozoan parasitic diseases in the region.

2. Methods

The literature search was performed including features of systematic review (SR) methodology. We searched electronic databases of PubMed and Google Scholar publications reporting prevalence of protozoan parasites infection or carriage, parasitic diseases in Cyprus. Inclusion criteria were: being published after the year 2000, reporting finding from humans or animals in the Cyprus region, abstract is in English, title of the article must include "Cyprus". Publications for which full text was not available are excluded. Duplicate publications were also excluded.

3. Results and Discussion

Our search strategy identified in total 3030 articles; after exclusion of duplicates (n = 10), 3020 articles were screened. Following review of titles and abstracts, 35 articles were identified as potentially eligible. Of these, 20 were excluded following full-text evaluation and 15 articles were included in this review (Figure 1).

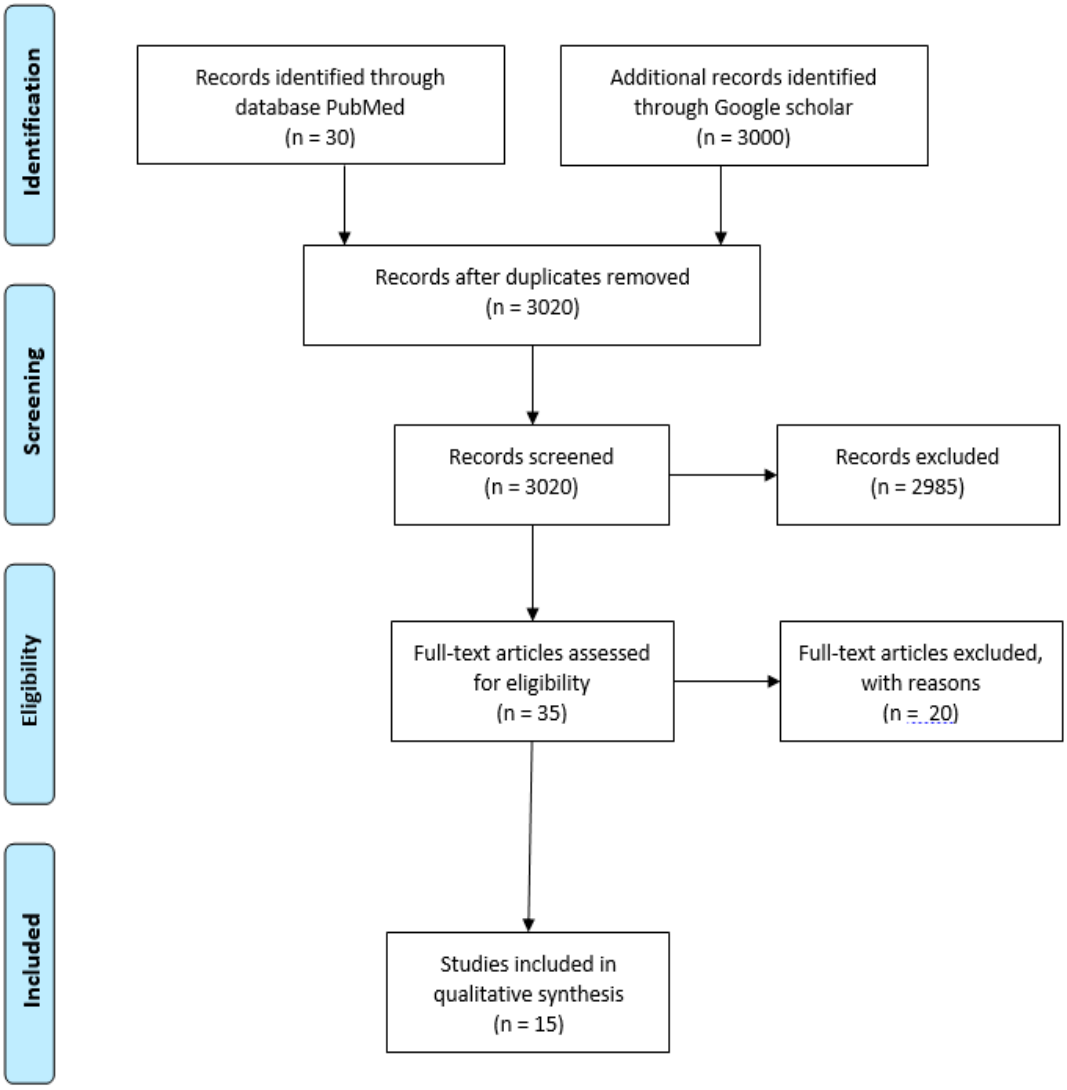


Figure 1. PRISMA flow chart of study identification and selection.

Nine studies reported data on *Leishmania*, four on *Toxoplasma*, and one on *Blastocystis* spp., endoparasites, and hospital confirmed cases of various infections, each. Seven studies reported data on humans and 10 on animals (Table 1).

Table 1. Studies and reports of protozoan parasites infections in Cyprus.

Etiological Agent	Prevalence, Seropositivity, Case	Reference
Blastocystis spp.	64/230 (27.8%) PCR-positive for *Blastocystis* spp. in human volunteers	Seyer et al. 2017 [1]
Endoparasites	66/185 (35.7%) owned and sheltered cats, with overall prevalence of *Cystoisospora* spp. *14.5% (27/185)* and *Giardia 6.5% (12/185)*	Diakou et al. 2017 [2]
Leishmania infantum	55.2% (96/174) sheltered and owned cats positive for vector borne pathogen, incl. *Leishmania infantum*	Attipa et al. 2017 [3]
Leishmania	1.9% (2/105) owned dogs	Beyhan et al. 2016 [4]
Leishmania infantum	3.55% (10/281) owned dogs for canine *L. infantum*	Çanakçı et al. 2016 [5]
Leishmania infantum	1.7% (10/601) of owned dogs for *L. infantum*	Deplazes et al. 1998 [6]
Leishmania donovani	1 human patient case of *L. donovani*	Koliou et al. 2008 [7]
Leishmania	1.2% (3/249) seropositive in human volunteers	Ruh et al. 2017 [8]
Leishmania	Owned dogs-veterinary questionnaire	Sifaki-Pistola et al. 2014 [9]
Leishmania	5 human patients and 59 dogs	Tsirigotakis et al. 2016 [10]
Toxoplasma spp. and *Leishmania infantum*	27% (138/494) IgG seropositive for *Toxoplasma* spp. and 7.3% (36/494) IgG seropositive for *L. infantum* in rats	Psaroulaki et al. 2010 [11]
Toxoplasma gondii	Estimated 6.5% toxoplasmosis seropositivity in Cypriot high school girls, an 18% prevalence in pregnant women, and 40.1% prevalence in ruminants	Liassides et al. 2016 [12]
Toxoplasma gondii	1 human case PCR-positive for *T. gondi*i strain-type III	Messaritakis et al. 2008 [13]
Toxoplasma gondii	34.69% (34/98) cattle were seropositive by Sabin-Feldman and Indirect Fluorescent Antibody tests for *T. gondii*	Nalbantoğlu et al. 2002 [14]
Various parasites	Patient hospital cases for parasites (not specified)	Rethemiotaki and Rethemiotakis 2018 [15]

The European Centre for Disease Prevention and Control (ECDC) collects, collates analyses and disseminates surveillance data provided by the European Member states on food-, water-, and vector-borne diseases (including protozoan parasitic infections) in humans after data extraction from the Surveillance Atlas of Infectious Diseases (REF ECDC: https://atlas.ecdc.europa.eu/public/index.aspx).

By assessing the number of cases reported to ECDC by Cyprus, mainly giardiasis and malaria cases, but not congenital toxoplasmosis or cryptosporidiosis, have been reported between 2008 and 2018 (Table 2). However, this data is not reflected from the available publications retrieved in our review.

The aim of this narrative review was to fill the gaps in the literature about the general current status of protozoan parasite infections in Cyprus. Only articles with the specific search criteria in the title and abstracts were included in the final results. Although a plethora of search results were initially obtained from PubMed and Google Scholar, many of them were excluded because they did not match the specific search criteria for protozoan parasites infections in Cyprus.

Protozoan parasites are globally prevalent, and they are still listed as neglected diseases by the WHO. Raised standards in hygiene and sanitation have significantly improved the situation in most of the developed nations. However, due to the environmental conditions of many countries and regions, parasites, viruses, and bacteria can naturally flourish. Travelers visiting areas known to harbor parasites must be cautious in order to avoid contracting certain diseases. Infectious disease can be spread via insects (vectors), animals, water, food, and by direct human-to-human contact. Moreover, infectious diseases can be spread by migration patterns, especially around the summer vacation season. Some of these parasites e.g., *Cryptosporidium* are known to tolerate chlorination used to sanitize public swimming pools and municipal water supplies. Contamination of water resources is usually due to inadequate chlorination or mechanical malfunction of water treatment plants [16].

It is estimated that Cyprus receives approximately 4 million tourists during the summer months. *Cryptosporidium* is a known zoonotic protozoan parasite, where some species are host specific. Children and immunocompromised individuals are the most susceptible groups to *Cryptosporidium* infection. Many tourists vacation in Cyprus during the summer months and could be infected with *Cryptosporidium* and/or enteroviruses from swimming pools, where contraction is usually via fecal-oral route. According to the narrative literature search, there are no direct patient reports of *Cryptosporidium* infection coming out of Cyprus. However, Chalmers et al. (2008) [17] linked these protozoan parasites to three UK patients, who visited Cyprus and were thought to have contracted the infection during their trip.

Veterinary researchers have reported *Cryptosporidium* infections in local animals on the island. Giadinis et al. (2012) [18] found that *Cryptosporidium* infection was common in 4–15 day-old lambs and goat kids in Cyprus suffering from neonatal diarrheal syndrome during a study from September 2008 to April 2009. *Cryptosporidium* was detected in 25/28 goat flocks (89.3%) and 12/15 lamb flocks (80%) using a commercial ELIZA test. In a 2016 survey of dairy goat farms, Arsoy (2020) [19] found 75% goat kids in Cyprus experienced episodes of diarrhea and attributed the main cause to internal parasites and enteric bacteria, such as *Cryptosporidium* spp., Coccidian species, and *E. coli*.

Rethemiotaki and Rethemiotakis (2018) [15] found a statistically significant correlation between pollution and infectious diseases in Cyprus from 2012–2015. Data was collected and analyzed from five district hospital records in the Republic of Cyprus. Moreover, they found a statistically significant correlation between age and infections and parasitic diseases, where the young and older age groups were more susceptible to certain infectious and parasite diseases. Patient data was only summarized in table format and did not specified the type of infectious disease or parasite that infected the patients.

Blastocystis spp. are considered to be enteric protozoan parasites due to their pathogenic nature [20]. *Blastocystis* infection has been found in people with close contact with animals and it is associated with a variety of gastrointestinal diseases and disorders. The zoonotic potential of these parasites could have an impact on public health. Seyer et al. (2017) [1] evaluated the epidemiology and prevalence of *Blastocystis* spp. and subtypes during 2015 from 230 volunteers in northern region of Cyprus. A 27.8% (64/230) prevalence of PCR-positive samples for *Blastocystis* spp. was reported from the 230 symptomatic and asymptomatic volunteers from Lefkosa, Grine, Guzelyurt, Iskele, Magusa, and surrounding rural areas. The authors did not find any statistical significance between demographic, socioeconomic, and epidemiological factors. The narrative search results did not reveal any reports of *Blastocystis* infection in other parts of the Republic of Cyprus.

Four studies matched our search criteria for toxoplasmosis in Cyprus. The authors emphasized the importance of preventing the infection with *Toxoplasma gondii* as it is known to cause blindness, birth defectives, and abortions in humans and animals. Liassides et al. (2016) [12] conducted a pilot study in the five main districts of the Republic of Cyprus from 2008–2011 in order to investigate the prevalence of toxoplasmosis in young high school girls aged 16–18 years, pregnant women in Cyprus, and sheep and goats from 163 randomly selected farms. These authors reported an estimated 6.5% toxoplasmosis seropositive prevalence in the Cypriot high school girls, an 18% prevalence in pregnant women and 40.1% prevalence in ruminants tested in the study. Their study was similar to the seropositive prevalence in pregnant women from Crete published in 2004, where the Mediterranean island of Crete has a similar culture and climate to Cyprus [21]. The authors suggested population control of cats and rodents as a means of minimizing exposure and risk to young women and the general population on the island. Cats and rodents are animals involved in the zoonotic cycle of *T. gondii*. Messaritakis et al. (2008) [13] conducted a study on a total of 9285 human serum samples (from pregnant women and patients with suspected toxoplasmosis) from Greece and Cyprus that were tested for IgG, IgM, and IgA antibodies against the protozoan parasite *T. gondii*. They reported that overall 3.12% (290/9285) of the samples were IgG seropositive for *T. gondii* in their study.

In collaboration with the medical and veterinary authorities of the Republic of Cyprus, Psaroulaki et al. (2010) [11] collected a total of 622 rats from residential and agricultural areas found in the five main districts of the Cyprus Republic during a 4-year period 2000–2003 and used as

indicators of the presence and dispersal of six zoonotic microbial agents. The authors of the rat study reported the overall protozoan parasites, *T. gondii* and *Leishmania infantum* seroprevalence were 27.9% (138/494) and 7.3% (36/494), respectively [11]. Nalbantoğlu et al. (2002) [14] analyzed 98 cattle in northern region of Cyprus during a two-year study (1987–1988) for the seroprevalence of *T. gondii*. The authors reported that 34.69% (34/98) of the cattle were seropositive for *T. gondii* by the Sabin-Feldman dye test and 30.61% (30/98) seropositive by Indirect Fluorescent Antibody testing.

Attipa et al. (2017) [3] screened 174 owned and sheltered cats from Cyprus from March to September 2004 and found 96/174 (55.2%) cats PCR-positive for at least one infectious pathogen. They raised concerns for feline vector-borne pathogens in Cyprus, especially commonly known cat zoonoses, such as *L. infantum* and *Bartonella henselae* that were also found in their study. Other researchers reported a variety of endoparasites in 66/185 (35.7%) of indoor/outdoor domestic and sheltered cats sampled from the 5 districts of the Republic of Cyprus, where *Toxocara cati* (22/185) was the most prevalent parasite in the study behind the protozoan parasites *Cystoisospora* spp. (27/185) and *Giardia* (12/185) [2], which was the only search result that reported on *Cystoisospora* and *Giardia* prevalence in Cyprus. Underreporting of protozoan parasites is a common theme in many of the discussion selection of published articles [22].

Certain tick species (ectoparasites) are known vectors for bacterial, viral, and protozoal pathogens. For example, *Babesia* are known malaria-like protozoans that parasitize mammalian red blood cells. Tsatsaris et al. (2016) [23] collected ticks from 441 domestic and wild animals from the five main districts of the Republic of Cyprus during a three-year study (2004–2006) in order to investigate the geographical distribution of tick species over the island. *Rhipicephalus sanguineus* (responsible for canine babesiosis) was the predominant species (38.5%), followed by *Rh. turanicus* (21.3%) and *Rh. bursa* (17.8%).

Zoonoses that are known to cause tuberculosis, anthrax, echinococcosis, brucellosis and the taeniasis were all major problems in Cyprus until the 1970s when the advances in veterinary public health eradicated most of these diseases during the 1971–1985 campaign against echinococcosis-hydatidosis. The echinococcosis control program depended upon the control of dogs on the island, control and supervision of the slaughtering of livestock, and public education about the spread of these infectious diseases. The campaign reduced the echinococcosis prevalence in dogs from 6.82% in 1972 down to 0.57% in 1978, which further reduced the prevalence of hydatidosis in livestock and humans [24]. Stray dogs are known to be reservoirs of other zoonotic protozoan parasites, such as *Giardia*, *Cystoisospora* spp., *Cryptosporidium* spp., and *L. infantum*.

The narrative literature search revealed the majority of the articles about *Leishmania* in the Northern (6/15) and Southern (3/15) regions of Cyprus, where it is considered endemic in the Southern Mediterranean [25]. Members of the sandfly subgenus *Larroussius* are known to be carriers of the protozoan parasite *L. infantum* in the Mediterranean basin. Leishmaniasis is a neglected vector-borne disease that presents as two forms in humans: Visceral (VL) and Cutaneous (CL). Infection is usually acquired through the bite of a female sand fly previously fed on a *Leishmania* infected mammal [25]. Dogs have long been suspected as a zoonotic reservoir of *Leishmania* in Cyprus. Beyhan et al. (2016) [4] collected blood from a total of 278 dogs for analysis of the seroprevalence of leishmaniasis in Turkey and the northern region Cyprus. From the Turkish regions, 124 dogs were sampled from Hatay and 49 from Burdur, and 105 dogs were sampled from northern region of Cyprus. The researchers reported the *Leishmania* seroprevalence of 1.9% (2/105) in dogs tested from the northern region of Cyprus and 0.8% (1/124) from the Turkish region of Hatay. All dogs (0/49) from the Turkish region of Burdur were identified as seronegative. Ruh et al. (2017) [8] investigated the seroprevalence of human visceral leishmaniasis (VL) from 249 volunteers living in Kyrenia district (northern coastal region of Cyprus) with the aim of identifying any correlation of leishmaniasis with demographic and epidemiological characteristics of the participants. Only 3 (1.2%) of 249 participants were found to be seropositive, where none of the 249 participants were PCR positive for *Leishmania* spp. Seven individuals, including the seropositive cases, had a history of cutaneous leishmaniasis (CL). Nearly half of the participants (131/249) reported that they owned dogs. In another study, Çanakçı et al. (2016) [5] investigated the seroprevalence of canine *Leishmania*

(CanL) in dogs from the main districts of northern regions of Cyprus. A total of 281 dogs were randomly selected from Nicosia (80/281), Trikomo (58/281), Famagusta (60/281), Morphou (30/281), and Kyrenia (53/281). CanL seroprevalence was found to be 3.55% (10/281 dos) in Northern Cyprus. CanL seropositivity differed between cities as follows: 13.20% (7/53) in Kyrenia, 3.33% (1/30) in Morphou, 1.72% (1/58) in Trikomo, and 1.67% (1/60) in Famagusta. No seropositive dogs were found in Nicosia. Deplazes et al. (1998) [6] conducted a serological survey in dogs for *L. infantum* during 1996 from the 5 main districts of the Republic of Cyprus and found an overall seroprevalence of 1.7%. Public awareness and governmental control of stray animals was believed to account for the reduced occurrence of *Leishmania* in the Republic of Cyprus. Mazeris et al. (2010) [26] also reported a 9-fold increase in dog seroprevalence from data published 10 year prior, where *L. infantum* was the most common strain found in the five prefectures in the Republic of Cyprus. Koliou et al. (2008) [7] reported an isolated case in 2006 of a 9-month-old girl from Cyprus with hemophagocytic lymphohistiocytosis associated with Epstein Barr virus and *L. donovani* co-infection.

Sifaki-Pistola et al. (2014) [9] evaluated the prevalence of canine leishmaniasis using the results from the Emerging Diseases in a Changing European Environment (EDEN) veterinary questionnaire in order to act as a low-cost of indicator of outbreaks and distribution. The data obtained from the questionnaire was compared with data from two recent epidemiological studies on leishmaniasis carried out in Greece and Cyprus at the same time using statistical methods and spatial statistics. Tsirigotakis et al. (2016) [10] analyzed the multidrug resistance gene (MDR1) expression in *Leishmania* species from Greece and Cyprus and represented it geographically to assess the distribution of drug resistance in the region. They tested the rate of efflux of the fluorescent dye Rhodamine-123 (Rhod-123) by flow cytometry in 211 *Leishmania* strains isolated from patients and dogs in Greece and 64 strains isolated from patients and dogs in Cyprus. The researchers noted there are two leishmaniasis transmission cycles reported in the Republic of Cyprus: zoonotic *L. infantum* MON-1 and MON-98 and anthroponotic *L. donovani* MON-37 [9,26]. In either case, infection could take place from the bite of phlebotomine sandflies, which are known insect vectors for leishmaniasis on the island. Sandflies are also known to be vectors for Sandfly Fever Viruses and West Nile Virus in Cyprus [27].

4. Conclusions

We conducted a narrative review in order to provide an overview of the available information on protozoan parasites in Cyprus to identify information gaps to facilitate discovery of the incidence of protozoan diseases in the region. From the available results found in our search criteria for protozoan parasite infections in Cyprus, the data indicate the presence of mainly *Leishmania* spp., *Toxoplasma gondii*, and *Blastocystis* spp. on the island. Many of these protozoan parasites are zoonotic and anthroponotic and infection is usually by the faecal-oral and blood-borne route. Despite it is known that *Cryptosporidium* oocysts survive chlorination methods in swimming pools and during drinking water preparation, which could lead to outbreaks during tourist seasons in Cyprus. However, no *Cryptosporidium* outbreaks have been reported yet on the island. The spread of *T. gondii* by rats appears to be a significant threat to public health in Cyprus. Governmental monitoring and mandatory reporting would be essential for the control and prevention of protozoan parasite outbreaks in the country.

Table 2. Number of reported cases protozoan diseases from Cyprus based on The European Surveillance System, by year *.

Protozoan Diseases	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Cryptosporidiosis	0	0	0	0	0	0	0	0	0	0	0	0	0
Giardiasis	6	4	7	2	12	2	4	3	3	6	1	5	3
Malaria	1	1	0	1	1	6	1	3	8	3	1	8	4
Toxoplasmosis (congenital)	0	0	0	0	0	0	0	0	0	0	0	0	0

* Dataset provided by ECDC based on data provided by WHO and Ministries of Health from the affected countries (REF ECDC: https://atlas.ecdc.europa.eu/public/index.aspx). NA: Not available; NR: Not reported.

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