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### **Veterinary Parasitology**

journal homepage: www.elsevier.com/locate/vetpar



## Vector-borne parasitic zoonoses: Emerging scenarios and new perspectives

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#### ARTICLE INFO

# Keywords: Parasites Vectors Epidemiology Changes Public health

#### ABSTRACT

Changing climate is not the only driver for alterations in the dynamic interaction between arthropod vectors of zoonotic parasites and their hosts, including humans. A suite of other factors ranging from urbanization and deforestation to changing demographics in both developing and developed countries, the impact of the recent economic crisis, increased global movement of people and animals and follow-on effects of major catastrophes. This article reviews the most important vector-borne parasites of zoonotic concern that are changing/expanding their distribution patterns in both endemic and/or previously non-endemic areas. We include the discussion of the changing aspects of malaria, leishmaniasis, babesiosis, Chagas disease as well as of some spirurid and filarioid nematodes.

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#### 1. Introduction

Humans are currently experiencing a time of unprecedented change in their lives and those of the animals on which they depend and interact with. The change is not merely the much discussed alterations in climate (Tabachnick, 2010) but there are dramatic changes in human demographics, behaviour, land use practices as well as changes in the environment at both large and small scales (Sutherst, 2004). These changes, alone and in concert, alter the interactions between humans and infectious disease agents leading to clear emergence of infectious and zoonotic diseases (Jones et al., 2008; Otranto and Eberhard, 2011). These changes also influence the vectors (e.g., ticks, fleas, black flies, mosquitoes and sand flies) of zoonotic parasites and change their relationships with humans. Under the above circumstances, arthropod vectors may

enhance their potential to spread bacteria, viruses, proto-

There is increasing interest in the role of climate changes in the epidemiology and distribution of VBPZs (Rosenthal, 2009; Randolph, 2010). However, a complete approach to predict the upsurge of VBPZs should not only assess the effect of climatic factors, but also examine the linkage between socio-economic and political issues and the

zoa and helminths. Thus, there is a great deal of discussion among scientists regarding the magnitude and extent of changes in vector-borne parasitic zoonosis (VBPZ) distribution, not only because of their impact on human and animal health (WHO, 2004) but also because they may represent a major threat to the economy, causing millions of dollars in losses to the livestock industry annually (Bram et al., 2001). These infections affect public health mainly in developing countries (e.g., Africa, South and Central America and Far East) where control and prevention strategies are oftentimes impaired by economic constraints (Irwin and Jefferies, 2004; Rosenthal, 2009; Otranto et al., 2009b). Whether VBPZ-causing pathogens will spread from the tropics and lower latitudes, where the greatest animal biodiversity is concentrated, toward northern hemisphere, is a crucial issue to be addressed.

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emergence of these diseases. Thus this article discusses the changing epidemiological scenarios of VBPZs, which are of emerging or re-emerging concern. In addition, it discusses the extant socio-economic and political events (e.g., liberalization of economy, wars, and population movements) that might affect the spreading and the control of vector-borne zoonotic parasites.

# 2. Changing vector-borne parasitic zoonoses in a changing world

In the past, research aimed at predicting the spread of vectors and pathogens in non-endemic areas mostly focussed on the effects of climate change, particularly global warming (Lindgren and Gustafson, 2001; Rosenthal, 2009), and have only marginally considered the complexity of changes in the environment as well as changes in human behaviour. A suite of factors affects the degree of contact between hosts and parasite vectors in a manner well described by the theory of island biogeography (Reperant, 2010). This approach resembles the episystem concept put forward by Tabachnick (2010) in that they bring together the impact of a variety of worldwide changes on the interactions between vectors, parasites and human disease. The main drivers of changes that will influence the increased interaction between parasite vectors and humans include environmental changes (e.g., urbanization), climate change, major catastrophic events (e.g., earth quakes, tsunami), demographics (increasing proportions of young people in countries of emerging economies as opposed to an increasing proportion of older people in the developed economies), human behaviour (movement of people from rural to urban environments, particularly in developing countries). Among others, the global economic crisis and the climate change (more specifically, the worsening droughts in sub-Sahara Africa) has contributed to changes in human habits and increased the movement of people from developing to industrialized areas (Ramin and McMichael, 2009).

In addition, to an overall trend toward the increasing localization of people in urban centres, the structure of human populations is changing as more people in developed nations move into older cohorts and the proportion of people in younger cohorts increases in developing nations with higher birth rates (Macpherson, 2005). Indeed, political upheaval and instability in some African developing countries drive people to move to cities in order to escape violence. Economic and financial crises also drive people to move into cities, but restrict the ability of governments to carry out disease surveillance and vector control programs (Harrus and Baneth, 2005). For example, remarkable correlation was found between poverty indicators and the upsurge of tick-borne encephalitis (TBE) in central and eastern European states during the socio-economic transition after the collapse of the Soviet Union (Sumilo et al., 2008). It has been speculated that a number of causes (e.g., change in land cover and use, reduction in the use of pesticides, increased unemployment and poverty) might have resulted in more contacts between people and infected ticks (Sumilo et al., 2008) even in the absence of changes in the abundance of ticks on wildlife reservoir hosts.

#### 3. Ancient diseases, contemporary scenarios

VBPZs have long been a cause of morbidity and mortality in humans. Historically, diseases like leishmaniasis and malaria have had a great impact on humans and they are still causing a huge burden on public health worldwide (Hotez et al., 2006). However, as the world is changing, new diseases are being discovered and even the epidemiology of ancient diseases like malaria and Chagas disease is changing. This scenario is a result of complex interactions between changes related to vectors, reservoirs, the parasites themselves as well as to susceptible human populations. Several factors might favour the spread of arthropods and parasites they transmit, including the ecological and climatic changes (Lindgren and Gustafson, 2001; Rosenthal, 2009), enhancement of international commerce, increased and more rapid global transport (van der Weijden et al., 2007), and emerging insecticide/acaricide/drug resistance among both vectors and pathogens (Takken and Knols, 2007). Changes in land use (e.g., deforestation, development of irrigation) create new opportunities for vector establishment or for increases in existing populations.

## 3.1. Simian malaria: an emerging vector-borne parasitic zoonosis

Malaria is a deadly disease caused by protozoa of the genus Plasmodium, which are transmitted by anopheline mosquitoes. It is estimated that 300–500 million people are infected with *Plasmodium* spp. worldwide, and that 1.5–2.7 million people a year die from the infection (Garcia, 2010). Indeed, malaria represents a major public health threat in over 90 countries, although the burden is by far heavier in Africa (Garcia, 2010). Traditionally, human malaria has been attributed to four Plasmodium species, i.e., Plasmodium vivax (tropics, subtropics, and temperate zones), Plasmodium falciparum (generally confined to the tropics), Plasmodium malariae (unevenly distributed), and Plasmodium ovale (confined mainly to central West Africa and some South Pacific islands). Since 2004, a simian malaria parasite, Plasmodium knowlesi, has been implicated in human disease. Specifically P. knowlesi has been confirmed in several human cases of malaria diagnosed from Malaysian Borneo, Thailand, Myanmar, and the Philippines (Jongwutiwes et al., 2004; Singh et al., 2004; see also a review by Galinski and Barnwell, 2009). Certainly, simian malaria is an emerging problem in Southeast Asia and in this new scenario the identification of malaria parasites to the species level becomes critical (Garcia, 2010). Indeed, P. knowlesi can often be misidentified as *P. falciparum* (early blood stages) or as P. malariae (mature blood stages and gametocytes). Although frequently misdiagnosed as P. malariae (which is a relatively benign parasite), P. knowlesi can be fatal. From a diagnostic standpoint, P. knowlesi infection should be considered in patients with a travel history to forested areas of Southeast Asia (Garcia, 2010). Being close relatives from a zoological standpoint, humans and non-human primates are predisposed to exchange parasites and other pathogens (e.g., viruses). Certainly, other simian malaria parasites might represent a human concern in the near future (Lee et al., 2009) and physicians should be aware of it. The zoonotic potential of *P. knowlesi* is emphasized because of its transmission by the forest dwelling *Anopheles latens*, a mosquito species that feeds on both the monkey natural host as well as on humans (Vythilingham et al., 2006).

#### 3.2. Chagas disease: changing epidemiology

Chagas disease is a vector-borne parasitic zoonosis caused by the protozoan Trypanosoma cruzi. It is estimated that over 7 million people are infected and 109 million individuals are at risk of infection in Latin America (OPS, 2006). Triatomines (also called assassin bugs, kissing bugs, conenose bugs or barbeiros), such as Triatoma infestans, Rhodnius prolixus, and Triatoma dimidiata (Rassi et al., 2010) are the primary vectors of T. cruzi. Control programs have greatly reduced the vectorial transmission of T. cruzi in Brazil and other Latin American countries (Costa and Lorenzo, 2009; Coura and Viñas, 2010). However, a recent study has demonstrated the existence of domestic populations of the triatomine bug Panstrongylus megistus, infected by T. cruzi in south-eastern Brazil (Villela et al., 2010), which demonstrated the risk of vectorial transmission in this region. The presence of wild populations of T. infestans infected with T. cruzi in Chile (Bacigalupo et al., 2010) shows that the risk of re-introduction of this vector into the domestic environment does exist in certain areas. Changes in land use, deforestation and movement of human populations can also bring people into contact with potential wild triatomine vectors (Guhl et al., 2009) that might incidentally assume a primary role in T. cruzi transmission. Meanwhile, secondary (non-vectorial) modes of transmission, such as blood transfusion, congenital and organ transplant have also been reported (Gascon et al., 2010; Rassi et al., 2010; Schmunis and Yadon, 2010). In particular, orally acquired T. cruzi infections have become more common since 1965. Outbreaks of Chagas disease transmitted by accidental ingestion of contaminated sugar cane, guava or açaí juices have been reported in South America (Shikanai-Yasuda et al., 1991; Pinto et al., 2004; Dias et al., 2008; Pereira et al., 2009; Valente et al., 2009; Bastos et al., 2010; Alarcón de Noya et al., 2010). Indeed, the emergence of oral-transmitted Chagas disease has a direct impact on public health, particular disease control and management. Education programs should be carried out in endemic areas so that the general population is more aware of the risk of oral transmission of T. cruzi and how to prevent it.

# 3.3. Leishmaniases as emerging vector-borne parasitic zoonoses

The leishmaniases constitute a group of severe diseases caused by protozoa of the genus *Leishmania*. It is estimated that 2 million new cases occur yearly (1.5 million for cutaneous leishmaniasis and 500,000 for visceral leishmaniasis) and that 12 million people are infected worldwide (WHO, 2010). Generally, leishmaniases are zoonoses acquired through the bite of phlebotomine sand flies that have previously fed on an infected host, usually a wild animal (Ashford, 1996). As with other vector-

borne disease, the leishmaniases are strongly influenced by global changes and by the dynamics of vectors, reservoirs and susceptible populations (Ready, 2008; González et al., 2010). In particular, the ecology and distribution of phlebotomine sand flies are directly influenced by climate and other environmental variables (Peterson and Shaw, 2003). Recent studies have highlighted the spreading of the leishmaniases, as they accompany the movement of the phlebotomine vectors into previously free areas as suggested for the spread of canine leishmaniasis from southern to northern Italy (Otranto et al., 2009a) and from northern to southern Brazil (Tomaz-Soccol et al., 2009). Indeed, canine leishmaniasis is now well established in South America as far south as northern Argentina (Salomon et al., 2008; Dantas-Torres, 2009). Furthermore, global warming could prompt the establishment of canine leishmaniasis in areas such as the United Kingdom, where the vectors are currently absent, but where Leishmania infantum-infected dogs that had travelled to endemic areas are present (Shaw et al., 2009). In this regard, human cases of autochthonous visceral leishmaniasis have increasingly been diagnosed in Thailand and the existence of a suspected new species of *Leishmania* in this country has also been reported (Sukmee et al., 2008). Interestingly, cases of cutaneous leishmaniasis by an undescribed species of Leishmania were diagnosed in Northern Australian macropods and day-feeding midges have been incriminated as potential vectors (Dougall et al., 2011). These findings are changing our understanding of the Leishmania spp. life cycles and may have practical implications on the epidemiology and control of the leishmaniases. Certainly, control measures have not been enough to stop the spread of visceral leishmaniasis and global changes are accelerating this process. The actual impact of global changes on the ecoepidemiology of the leishmaniases in both traditional and non-traditional endemic areas might be unpredictable.

# 3.4. Babesiosis as an emerging zoonosis in North America and Europe

Babesiosis is a vector-borne disease caused by protozoa of the genus Babesia, which are primarily transmitted by ixodid ticks. Babesia protozoa infect a wide range of wild and domestic animals, causing life-threatening diseases, especially in domestic animals. Additionally, cases of human babesiosis have sporadically been diagnosed, mainly in North America and Europe (Hunfeld et al., 2008). Traditionally, cases of human babesiosis in North America have been associated with Babesia microti whereas cases in Europe have been attributed to Babesia divergens. However, several Babesia species have recently been implicated in human disease (Hunfeld et al., 2008). In particular, Babesia duncani and B. divergens-like organisms have been recognized as pathogens of medical significance in the United States (Herwaldt et al., 1997; Beattie et al., 2002; Conrad et al., 2006). As well, autochthonous cases of B. microti infections have been diagnosed in Taiwan, Japan and Europe (Shih et al., 1997; Saito-Ito et al., 2000; Hildebrandt et al., 2007). Babesia venatorum (a new European B. divergens-like organism, formerly called EU1), which is probably a parasite of deer (Telford and Goethert,

**Table 1** Vector-borne parasites of major zoonotic concern.

Parasite	Vectors	Natural hosts	Distribution
Babesia divergens	Ixodid ticks	Bovines	Europe
Babesia duncani	Ixodid ticks	Unknown	North America
Babesia microti	Ixodid ticks	Rodents	North America, Europe
Babesia venatorum (EU1)	Ixodid ticks	Unknown	Europe
Leishmania braziliensis	Phlebotomine sand flies	Rodents, marsupials	Central and South America
Leishmania infantum	Phlebotomine sand flies	Canids, rodents, marsupials	Americas, Asia, Africa, Europe
Leishmania major	Phlebotomine sand flies	Rodents	Asia, Africa
Plasmodium knowlesi	Anopheline mosquitoes	Monkeys	Southeast Asia
Trypanosoma cruzi	Triatomine bugs	Marsupials	Americas
Thelazia callipaeda	Drosophilid flies	Canids, felids, rodents	Asia, Europe
Dirofilaria immitis	Culicine mosquitoes	Canids, felids	Worldwide
Dirofilaria repens	Culicine mosquitoes	Canids, felids	Europe

2004; Bonnet et al., 2007), was involved in the first documented cases of human babesiosis in Italy, Austria and Germany (Herwaldt et al., 2003; Häselbarth et al., 2007). These findings challenge the dogma that human babesiosis in North America and Europe is caused by *B. microti* and *B. divergens*, respectively (Hunfeld et al., 2008). It is becoming clear that babesiosis is a vector-borne disease of zoonotic concern and that different *Babesia* species known to infect wildlife and domestic animals have the potential to cause disease in humans (Table 1).

## 3.5. Dirofilarioses and Aedes albopictus: converging destinies

The introduction of an arthropod vector into a previously non-endemic geographic area has the potential to result in the introduction of new pathogens as well. The spread of an invasive species and its 'hitchhikers' may be facilitated by factors such as its adaptability to different environmental conditions, the availability of suitable hosts, the arthropod's feeding behaviour and host preferences (Root et al., 2003; Khasnis and Nettleman, 2005; Purse et al., 2005). As examples of the changing pattern of distribution of vector-borne parasites, the current distributions of canine infections with Dirofilaria immitis and Diofilaria repens in Italy have been discussed on the basis of retrospective historical reports during the 90s and more recently (Otranto et al., 2009a). D. immitis and D. repens represent the most important filarial species worldwide because of both their pathogenicity in dogs as well as because of their zoonotic potential (Genchi et al., 2005; McCall et al., 2008). Indeed, D. immitis and D. repens are also the main agents of human dirofilariasis in the Americas (Orihel and Ash, 1995; McCall et al., 2008) and the Old World (Pampiglione et al., 1995, 2009). D. repens has been recognized as an emerging zoonosis in Europe and eastern countries (e.g., Szénási et al., 2008; Pampiglione et al., 2001, 2009). On the other hand, cases of human dirofilariosis caused by D. immits have sporadically been reported in the New World, most of the patients being asymptomatic, presenting only well-circumscribed, non-calcified, subpleural, pulmonary nodules (for a review see McCall et al., 2008). However, cases of human dirofilariosis by D. immitis could increase over the next years in Europe, as a result of the spreading of canine D. immitis infection of dogs in central and north-eastern countries (e.g., south of Switzerland, Czech Republic, Hungary, Serbia and Slovak Republic) (Genchi et al., 2005; Svobodova and Misonova, 2005; Svobodova et al., 2006; Babal et al., 2008; Tasić et al., 2008; Genchi et al., 2009). Interestingly, cases of human infection by D. immitis have been recently described in Italy, Greece and Spain (Miliaras et al., 2010; Morchón et al., 2010; Avellis et al., 2011) with an overall seroprevalence reaching up to 12% and 11.6% in dogs and humans from the province of Rioja (Morchón et al., 2010). The reasons for the increased number of cases of canine infections with *D. immitis* in Europe remain uncertain, but might be related to changes in vector population ecology. In Italy, for example, the increased prevalence of canine dirofilarioses in traditionally endemic areas and the spread into previously non-endemic areas have been attributed to an increase in the population density of competent vectors (Otranto et al., 2009a). It is apparent that the spread of A. albopictus throughout Italy (Romi and Majori, 2008) has contributed to this process. In fact, this mosquito is well adapted to the low winter temperatures of many Mediterranean countries, being able to develop up to 10 generations per year in central and southern regions (Romi and Majori, 2008). Again, because human cases are usually reported in areas where canine infection is high (Lee et al., 2010), further studies are needed to assess whether a combination of high vector population density with high prevalence of *D. immitis* in the dog can increase the risk of human dirofilariosis.

# 3.6. Thelazia callipaeda: the "oriental eye-worm", in Western countries

Over the last decade, an apparent invasion by a vector-borne nematode infestation has taken place in the western European countries, as *T. callipaeda* (Spirurida, Thelaziidae), has been reported infesting the eyes of humans (Otranto and Dutto, 2008) as well as domestic (dogs and cats) and wild carnivores, including foxes, wolves, beech martens and wild cats (Otranto et al., 2009c). Because of its former known distribution (i.e., in the former Soviet Republics and in many far eastern countries including India, Thailand, China and Japan), this nematode has long been known as the "oriental eye-worm" (Anderson, 2000). In the past decade, *T. callipaeda* was proved to be widespread among dogs and cats from northern (Aosta valley) to southern Italy (Basilicata region) with a prevalence as high as 60% in dogs from some municipalities (Otranto

et al., 2003). Following these first reports in Italy, new cases of thelaziosis have also been recorded in France (Chermette et al., 2004) and Germany (Hermosilla et al., 2004) in dogs that had spent some time, mostly during summer, in northern Italy, Recently, autochthonous cases of thelaziosis affecting dogs and cats have been described in southwestern France (Dordogne area) (Dorchies et al., 2007) and Switzerland (Malacrida et al., 2008) and the emergence of canine ocular thelaziosis in France has also been demonstrated by retrospective data analyses (Ruytoor et al., 2010). The first four cases of human thelaziosis in Europe have been diagnosed in the Piedmont region of Italy in patients coming from an area of north-western Italy and south-eastern France (Otranto and Dutto, 2008). A detailed genetic makeup of T. callipaeda population from Europe based on the characterization of a mitochondrion target gene, suggested the existence of a single genetic haplotype of T. callipaeda circulating in Europe irrespective of their geographical region of origin and host (Otranto et al., 2005a). These results indicate that the same zoonotic strain of *T. callipaeda* circulates within the different animal species and humans, which suggests a close association of the nematode with its vector, Phortica variegata (Otranto et al., 2005b) and the various hosts. The ecological niche model for Europe predicted vast areas suitable for P. variegata (Otranto et al., 2006). Based on the aforementioned scientific evidence and as a result of the increased awareness of practitioners and parasitologists, the number of reports of T. callipaeda infestation may be expected to increase over the next years in areas where it is now considered as non-endemic.

# 4. Potentially emerging human vector-borne parasites

In addition to many vector-borne parasites-causing parasites for which the zoonotic potential has been known for long time, a number of agents have spurred the interest of the scientific community as new human pathogens. Indeed, some filarids from domestic mammals (e.g., Dirofilaria spp.), and wild mammals (e.g., Onchocerca, Dipetalonema and Loaina) have a zoonotic potential (Botero et al., 1984; Beaver, 1989; Orihel and Eberhard, 1998). Onchocerca volvulus affects about 17.7 million people causing the socalled "river blindness" (WHO, 2003), however, there are now 15 clinical cases of zoonotic onchocerciasis which been reported worldwide (reviewed by Sréter and Széll, 2008; Uni et al., 2010). These cases have been attributed to four filarid species affecting animals: Onchocerca gutturosa (Orihel and Eberhard, 1998) and Onchocerca cervicalis (Burr et al., 1998), from cattle and horses, respectively, Onchocerca jakutensis from the European red deer (Cervus elaphus) in Austria (Koehsler et al., 2007) and Onchocerca dewittei japonica from wild boar in Japan (Uni et al., 2010). Interestingly, case reports of canine onchocerciasis by Onchocerca lupi characterized by acute or chronic ocular disease (Sréter and Széll, 2008) increased in southern (Greece, Portugal) and central (Germany, Hungary, Switzerland) Europe (Széll et al., 2001; Komnenou et al., 2002; Hermosilla et al., 2005; Sréter-Lancz et al., 2007) whereas the identity of an *Onchocerca* sp. reported from human eyes cases from the United States remains unclear (Orihel et al., 1991; Eberhard et al., 2000; Zarfoss et al., 2005). The zoonotic potential of *O. lupi* has only been recently demonstrated by reporting an ocular infestation in the subscleral region of a human eye from Turkey (Otranto et al., 2011b).

An avian filarioid in the anterior chamber of a patient from northern Brazil has recently been identified as belonging to the genus *Pelecitus* (Bain et al., 2011). Interestingly, the only two human ocular cases by *Pelecitus*, one from Brazil (Bain et al., 2011) and other from Colombia (Botero et al., 1984) were more likely of avian origin and occurred in the tropical Amazon region.

Finally, a case of human intraocular dirofilariasis has been reported from the same area of northern Brazil. In spite of the fact that *D. immitis* is endemic in the canine population of that area, the nematode surgically recovered from the anterior chamber of the patient was distinct from reference sequences, including those of *D. immitis* infesting dogs in the same area (Otranto et al., 2011a). The possible existence of a closely related zoonotic *Dirofilaria* species infesting wild mammals in Brazil has been suggested.

All the above-mentioned reports suggest that there are likely several vector-borne parasites from wildlife, which have been little studied, and which have a zoonotic potential. These examples highlight the need for further research in order to better understand the circumstances in which situations humans might become at risk of exposure to those parasites.

#### 5. Conclusion

VBPZs are part of the constantly changing world and, because of this, they are constantly adapting to their new circumstance. They are changing their vectors, their hosts, their distribution and also their virulence. Medical and veterinary personnel need to be constantly attuned to these changes and need to keep up-to-date about new emerging pathogens and about potential secondary ways of transmission of pathogens that are primarily transmitted by arthropods. Awareness is the first step toward early diagnosis, better management and more efficient prevention of VBPZs, whose burden on public health is still heavy in both developing and developed countries. Thanks to molecular biology, new insights into the identification of pathogens infecting humans have been acquired in recent decades. Indeed, it is now clear that traditional methods used for pathogen identification have overlooked important differences at the strain and even the species level. Consequently, many parasites (e.g., P. knowlesi, B. duncani and B. venatorum) have emerged as newly recognized human pathogens, some of which causing potentially life-threatening diseases. In a similar manner, alternative modes of transmission have been recognized, herein exemplified by the oral transmission of *T. cruzi* in South America. Nonetheless, the lack of awareness of VBPZ may represent a major constraint on their successful management and control in previously non-endemic areas.

Monitoring environmental and climatic changes remain an important issue to be considered since these factors may affect both ecology and behaviour of arthropod vectors (e.g., high temperatures may shape the host-seeking behaviour of ticks) (Parola et al., 2008). It is recommended that, national public health surveillance services should perform systematic entomological surveys in vector-free areas that are at risk of introduction of vectors through animal or human populations. Again, medical professionals from non-endemic areas should be informed about the diagnosis and management of VBPZ such leishmaniasis and malaria that are often acquired by travellers during trips to endemic areas in the tropics (Zamarrón Fuertes et al., 2010).

#### **Conflict of interest statement**

The authors declare that there is no conflict of interest.

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