Arthropod borne diseases in Italy: from a neglected matter to an emerging health problem

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Summary. In medical entomology, “Arthropod Borne Diseases”, or “Vector Borne Diseases” (VBD) are intended as a group of human and animal infections caused by different pathogen organisms (protozoa, helminthes, bacteria and viruses) transmitted by the bite of a bloodsucking insect or arachnid. It is commonly known that the infectious diseases transmitted by Arthropods are mainly affecting tropical and subtropical countries, nevertheless some of them were or are still common also in the northern hemisphere, where they are usually maintained under control. VBD still represent some of the most important public health problems in the endemic areas but are becoming source of concern for developed countries too. Since the last decades of the past century, a number of VBD has been spreading geographically, being recorded for the first time in areas outside their original range. This phenomenon is strictly related to the peculiar epidemiological characteristics of these diseases, that are considered the most susceptible to climatic, environmental and socio-economic changes. This article is a short overview of the VBD endemic and emerging in Italy. The possibility that some exotic vectors and/or pathogens could be introduced and become established in Italy is also discussed.

Key words: vector borne diseases, arthropods, mosquitoes, ticks, sand flies, climate changes, mosquito borne disease, tick borne diseases, sand fly borne diseases, Italy.

INTRODUCTION
The discovery that some important diseases were transmitted to humans by an invertebrate vector is relatively recent, dating about to the last decades of the XIX Century. Most of these diseases, due to viruses, bacteria, protozoa and filarial worms are transmitted to vertebrate hosts by a competent Arthropod. Arthropods consist of a systematic Phylum which comprises the classes of Arachnids and Insects, with ticks within Arachnids (Acarina) and mainly mosquitoes and sand flies within Insect (Diptera) being potential vectors of human diseases [1]. Within the huge Phylum of the Arthropods, only a handle of species plays a role of medical importance. The medical importance is determined by the vector competence of the single species, i.e. its ability to transmit pathogens which are obliged to carry out at least one cycle of development/reproduction (sexual and/or schizogenic) into the competent species, before this may become infective. These diseases, globally named as Arthropods Borne Diseases (ABD), are more commonly known as Vector Borne Diseases (VBD) or, more specifically, with the name of the systematic group they belong (i.e Mosquito Borne Diseases,...
MBD; Thick Borne Diseases, TBD etc.). VBD are mainly affecting tropical and subtropical countries, where they are still responsible for human diseases that are cause of millions cases/year [2]. Malaria, yellow fever, leishmaniasis and other VBD still represent some of the most important public health problems in their endemic areas [3], even if some of them are still present also in the northern hemisphere, where are commonly maintained under control. Nevertheless, other VBD, in particular some MBD, are becoming source of concern for developing countries too; in fact, in addition to the rising prevalence of human cases due to VBD reported in endemic countries, the spread and establishment of some of them in new areas, outside their natural range, have recently been reported in literature [4, 5].

The increase in entity and distributions of the VBD, either in present time or in the recent past, constitutes indirect evidence that these diseases have been, or could be, particularly affected by climate change [6, 7] because the development of the vectors, and that of the pathogens they harbour are both temperature dependent, being Arthropods lacking of a body temperature self-regulating system.

Even if most of the existing literature consider the “global warming” as the main reason of this phenomenon, it should be considered as the result of several concomitant factors, all directly or indirectly related to human activities, such as the increasing use of aircraft for the quick transportation of goods and people (globalization), the relevant changes induced to the natural environment and socioeconomic constraints [5, 7, 8].

In Italy, after the eradication of malaria achieved in the 1950s, the traditionally endemic ABD in the country, are mainly transmitted by ticks (Ixodidae or hard ticks) and sand flies (the dipteran Phlebotomus spp.). Some of these diseases, often relegated to scattered and limited foci, are rising in prevalence and/or spreading to new areas [9]. Furthermore, outbreaks by these diseases, have renewed, among local and central health authorities, a concern almost disappeared during the last 60 years [10, 11].

**VECTOR BORN DISEASES ENDEMIC IN ITALY**

In Table 1 the characteristics and the present status of the most important VBD endemic in Italy, and of those recently emerged in the Country are reported.

**Sand fly borne diseases**

Among the diseases transmitted by phlebotomine sand flies (Diptera: Psychodidae), Leishmaniasis ranks first.

Leishmaniasis. - Leishmaniasis is not a single disease but represents a complex spectrum of diseases, often zoonotic, caused by intracellular protozoan parasites belonging to the *Leishmania* species, transmitted between animals and humans by a number of sand fly species, depending on the geographic area. Leishmaniasis are diffused worldwide, their area of endemity encompasses the intertropical zones of America and Africa, extending into temperate regions of Southern European countries that are mainly affected by zoonotic visceral leishmaniasis (ZVL) and by sporadic cutaneous leishmaniasis (SCL), both caused by different strains of *Leishmania infantum*, transmitted by dogs to humans through phlebotomine sand flies of the genus *Phlebotomus* (subgenus Larroussius) [9]. Other two cutaneous forms of the disease are present in the North African and Middle-east countries bordering the Mediterranean sea, due to *L. major* (zoonotic) and *L. tropica* (anthroponotic). Their peculiar epidemiology, strictly related to specific vectors and/or reservoirs, as well as to environmental characteristics and local social-economic condition, seems to reduce their possible spreading northward [12].

**ZVL and SCL in Italy and their northward spreading**. - Dogs, which may suffer from a severe disease (canine leishmaniasis - CanL), represent the principal reservoir of *L. infantum* in Italy, but other domestic and wild mammals (cats and wild canids) probably play a secondary role: the zoonosis is transmitted by four species of sand flies belonging to the subgenus *Larroussius* [7] (Table 1). ZVL was traditionally endemic in scattered foci of rural and periurban environments along the Tyrrhenian littoral (West coast) of the southern peninsular regions and the islands, with *P. perniciosus* acting as the main vector and seroprevalence rates in dogs exceeding 40%. Human ZVL occurred sporadically with fewer than 40 cases/year through the 1980s, but since the early 1990s the prevalence steadily increased, reaching over 200 cases/year in the 2000s, being reported from throughout the country. The cutaneous form is a benign, self limited disease (commonly known as “Oriental sore”) that, however, leaves a permanent scare when left untreated. The distribution of SCL in Italy partly overlaps that of the ZVL, but its historical foci are located along the mid and lower Adriatic (East) coast and in the islands. Because of its benign nature which does not require hospitalization, it is very difficult to assess the true incidence of SCL, most of cases being undiagnosed and/or unreported.

In Italy, the northward spreading of leishmaniasis was proven since the first half of the 2000s, with several autochthonous cases of CanL followed by some human cases of ZVL and SCL recorded in continental regions of northern Italy, previously considered *Leishmania* free [13]. In 2005-2009, the monitoring of the disease in these areas has continued through the EC EDEN-Leish subproject in selected sub-Alpine and Alpine territories. The findings of the surveys confirmed the northward spreading of the disease, and of the main vector *P. perniciosus* in Piedmont, Lombardy and Emilia-Romagna, with annual increase of mean seropositive rates of CanL prevalence, even if lower of those commonly record-
ed in pre-Appennine nine of central Italy [14, 15]. Furthermore, in contrast with phlebotomine records available up to the 1990s, the vector species *P. neglectus* is now recorded in the sub-Alpine territories of four northern regions (Piedmont, Lombardy, Veneto and Friuli Venezia Giulia) [13].

**Sand fly fever** - Previous studies have assessed the presence in Italy of five different *Phlebotomus*-transmitted viruses, four belonging to the Bunyaviridae family (*Phlebovirus* genus) (Naples, Sicilian, Toscana and Arbia viruses) and one (a *Raji* virus) belonging to the Rhabdoviridae family (*Vesiculovirus* genus) [16]. The two phleboviruses antigenically correlated (Naples and Sicily) and agents of the “3 day-fever” are apparently disappeared from our country. In the years 1970s and 1980s two other *Phleboviruses* have been isolated in Italy: the virus “Tuscany”, agent of acute infections of the SNC, present in 9 regions (Tuscany, Marche, Abruzzo, Emilia Romagna, Umbria, Piedmont, Campania, Sicily and Sardinia), transmitted by *P. perfilievi* and *P. perniciosus*, and the virus “Arbia”, isolated in Tuscany and Marche from the same vectors. While scattered human cases of infections due to Toscana virus are occasionally reported in Italy, as well as in other countries bordering the Mediterranean basin, (Portugal, Spain, Greece and Cyprus) [17, 18], up to now the Arbia virus has never been related to human diseases [16].

**Tick borne diseases**

Ticks are ectoparasites that heavily impact global health by transmitting a wide variety of pathogens to vertebrates. All TBD are zoonoses that mainly affect animals but may cause severe diseases in humans [19]. Ticks are considered to be second worldwide to mosquitoes only as vectors of human diseases. Three most important TBD are endemic in Italy [20, 21]. Although largely present in Italy, the relatively low number of TBD cases reported yearly, probably due to an high rate of asymptomatic disease and to a relevant underreporting of the symptomatic ones, makes very difficult to assess the al impact of the TBD on the public health in Italy.
**Mediterranean spotted fever (MSF).** - MSF, also known as “boutonneuse fever” is an acute zoonotic TBD transmitted to humans by the brown dog tick *Rhipicephalus sanguineus*. The disease is endemic in North Africa and in the South European countries bordering the Mediterranean sea, Italy included. Important changes in the epidemiology of MSF have been observed in the last 10 years, with emergence and reemergence of MSF in several countries, and with the increasing number of MSF cases reported from several countries of continental Europe. Molecular tools have allowed to classify the pathogen responsible of the MFS as *Rickettsia conorii* *conorii* as a subspecies of *R. conorii* [22]. More recently it has demonstrated that the infected *R. sanguineus* are able to transmit the rickettsia to the progeny through transovarial infection, leading to the hypothesis that the vector could also act as a rickettsial reservoir [22]. In Italy MSF is mainly recorded in the Central-southern regions of the country, being able to easily adapt to dry environment and high temperatures [23].

**Lyme disease (LD).** - LD is a zoonotic disease caused by spirochaetes of the *Borrelia burgdorferi* complex. Despite LD is a relatively new VBD (the first record was in 1970s, in USA) nowadays it represents one of the worldwide commonest TBD affecting humans, also largely diffused through much of Europe, with the most important foci in the central part of the Continent [24]. In Italy, where it is mainly caused by *Borrelia afzelii* [25] LD is prevalent in the northeastern regions of the country (i.e. Veneto, Friuli and Trentino) [26], even if sporadic cases have been

<table>
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<tr>
<th>Disease</th>
<th>Cause of the event</th>
<th>Probability level</th>
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<tr>
<td>Visceral leishmaniasis (zoonosis)</td>
<td>Increase of temperature</td>
<td>High: risk of a further spreading northward</td>
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<tr>
<td>Other leishmaniasis present in the Mediterranean basin</td>
<td>Increasing temperature and introduction of <em>L. tropica</em> and <em>L. major</em> and of their vectors</td>
<td>None: for <em>L. major</em> because of the lack of specific natural reservoir hosts (Gerbillidæ rodents) Very low: for <em>L. tropica</em> (anthroponotic) because of limited distribution of the vector (<em>P. sergenti</em>)</td>
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| Malaria | Introduction of gametocyte carrier (mainly of *P. vivax*) from endemic areas and introduction of allochtonous anopheline vectors | Low: nevertheless the occurrence of isolated cases of *P. vivax* in rural areas cannot be excluded
None: for the establishment of tropical Anophelines because of their peculiar ecology |
| Sand flies fever | Climatic and environmental changes | Low: risk of expanding the area of endemity and increasing incidence |
| Chyungunya fever (anthroponosis) | Introduction of virus carriers from endemic areas | Very high: particularly in urban areas where the vector density is high and a late diagnosis of secondary autochtonous cases may occurs |
| West Nile encephalitis (zoonosis) | New introduction of infected reservoirs (migratory birds) and spreading of the virus by indigenous vectors | Very high: at risk all humid areas of the country, extensible to urban areas: the WNV is probably already going to become endemic |
| Dengue (anthroponosis) | Increasing of temperature Importation of both main vector and virus carriers | High: for the introduction of the main vector
Moderate: for epidemics. Urban areas at major risk |
| Japanese encephalitis (zoonosis) | Introduction of the most competent vector (*Ae. japonicus*) and of the virus | Moderate: for the introduction of the vector
Low to very low: for virus introduction as well as for animal reservoirs |
| Rift Valley fever (zoonosis) | Increasing rainfall. Introduction of infected reservoirs (sheeps, domestic and wild mammals) | Very, very low: for the introduction, of the virus by human or animal reservoirs
Nevertheless: it should be stressed that potential competent vectors are already part of our indigenous mosquito fauna |
| Dirofilariasis | Introduction of *Ae. albopictus* in the epidemiological cycle of the disease | Moderate: risk of diffusion in urban areas |
| Lime disease TBE | Heavy increasing of rainfall and of the mean temperature | Very low: risk of spreading southward
High: increasing incidence in the existing foci |
| Rickettiosis | Increasing temperature | High: risk of moving northward and of increasing incidence in the existing foci |
reported in various regions [20]. The vectors competent to transmit *B. burgdorferi* complex to humans belong to different species, according to their geographical distribution. In Europe and in Italy *Ixodes ricinus*, the most common wood tick, is at present the only species incriminated as LD vector [27] According to the behaviour of the vector, that likes a relatively humid and cool environment (such as wooded pastures, floodplains, forest areas etc.), wild small rodents and other mammals are the natural hosts of the larval and nymphal stages. Deer, horses, and other large mammals represent the most common hosts of the adult females.

**Tick borne encephalitis (TBE).** - The endemic area of TBE in Europe, ranges from Alsace-Lorraine in the west to Vladivostok in the East and from Scandinavia in the north to Greece and Italy, in the south. TBE is a serious acute central nervous system infection which may result in death or long-term neurological sequelae [28]. The causal agent of TBE is a Flavivirus, transmitted to humans by the bite of an Ixodid tick. In Italy, as well as in Europe, the disease is transmitted by the common wood tick *Ixodes ricinus*, but occasional transmission can also occur through consumption of raw milk from an infected cow, goat or sheep. In Italy, the dynamics of the species shows relevant differences depending on the local climatic conditions. However, in general terms, there are two peaks of abundance, in the late winter-early spring the first (main) and in late summer-autumn the second one, corresponding to two waves of feeding of tick larvae and nymphs. The period of transmission of the disease appears to be seasonal, occurring mainly from June-July to September-October, in woods or wet prairie [29]. A rise in incidence of TBE has been observed in recent decades in some regions, presumably linked to global warming, as milder winters lead to proliferation of rodent populations which are the main hosts and reservoirs of the virus. During the last decade, probably due to more sensitive diagnostic techniques, and to a better reporting system, the number of case/year recorded in Italy as well as in other European countries appears to be steadily increasing [30, 31].

**Emerging TBD.** - In recent years, new bacterial TBD have been recognized as agents of distinct MSF-like and LD-like diseases, due to different species of *Rickettsia* spp. and *Borrelia* spp. respectively. In particular, rare and accidental cases of Ehrlichiosis/Anaplasmosis and Tularemia, recognized as human diseases less than 20 years ago, appear to be increasing worldwide as well as some hemorrhagic fevers, Crimean Congo and Q fevers, due to *Francisella* spp. and *Coxiella* spp. respectively [21].

**Mosquito borne diseases**

The importance of the mosquitoes as disease vectors is related, above all, to the transmission of malaria, an illness that causes still today million of deaths every year in the world (WHO, 2009). Mainly due to the rising average temperatures and to the still high number of malaria cases imported in Europe from endemic areas (about 15 000/year), malaria is considered one of the VBD that could re-emerge in Europe [8, 32].

**Malaria risk in Italy.** - Since the 1950s Italy has been de facto free of malaria (even if few cases of *Plasmodium vivax* occurred up to the first half of the 1960s), but the potential anopheline vectors survived in scattered foci throughout the country, re-colonizing, in some cases, part of the former endemic areas. At present malaria cases are all of importation, with the exception of some autochthonous cases due to accidental events (i.e. blood transfusions, accidental introduction of infected anophelines by baggage) [33]. Despite the relevant presence of potential vectors in some rural areas of the country [34] the possible introduction of malaria reservoirs (human gametocyte carriers), the analysis of the epidemiological forms of imported malaria reports since 2000, resulted in a very scarce number of cases potentially able to infect the vector. Moreover, if the competence of *An. labranchiae* for exotic plasmodia is proved for *P. vivax* by some sporadic cases of autochthonous introduced malaria naturally occurred in some Mediterranean countries [35], the competence for afrotropical *P. falciparum* is still supposed to be unlikely. More recently *An. labranchiae* has showed a scarce (but not totally absent) competence for *P. falciparum* when artificially infected with an afrotropical laboratory-reared strain of the parasite (our preliminary unpublished data). In conclusion, the results of a recent 5-year study, carried out within the EDEN mal subproject. have excluded the return to an endemic situation [36], nevertheless the occurrence of sporadic, isolated cases of *P. vivax* malaria cannot be excluded, as occurred in 1997 for the first, and only, case of autochthonous malaria transmitted by *An. labranchiae* since the eradication [35].

The accidental importation of infected vectors from zones where malaria is endemic (for instance with the intercontinental flights) is an event already happened in Italy [33] but that would cause only isolated cases of malaria. The possibility, instead, that a tropical vector can settle in our country, following the increase of the temperature, appears highly unlikely because of the complexity of ecological and factors that characterize the different anopheline species.

**Mosquito borne arboviruses.** - A more real risk for European countries is represented by other MBV due to arboviruses transmitted by Culicidae mosquitoes [7]. Particular relevance deserves those due to Flavivirus (family Flaviviridae) that represent a major threat for not endemic countries, some of them being in expansion out of their natural range [37]. Although more than 70 Flaviviruses have been identified, only a few can cause disease of major importance in humans. The importance that these MBD
may have on human health are strictly related to the peculiar bionomics of the vector and to a number of factors such as the kind of environment, the availability of suitable breeding sites, etc.). Diseases due to Yellow fever, Dengue, Chikungunya and West Nile viruses and transmitted by mosquitoes and characterized by a great ability to adapt to different environment and climatic conditions may spread quickly and successfully establish in new areas [38, 39]. The spread in Europe of other MBD, strictly dependent on specific local conditions (peculiar habitat, specific reservoir, or recipient host, socio-economical conditions), as the Rift Valley fever [40] and Japanese encephalitis [41], results reasonably very improbable.

Recent MBD outbreaks in Italy. - In recent years, Italy has experienced the introduction of two MBD of tropical origin. Their introduction has occurred in different ways. In the first case, the West Nile virus, responsible of a widespread zoonosis, was introduced by its common reservoirs (migratory birds) and amplified among the indigenous mosquitoes and transmitted to horses and humans by indigenous mosquitoes, mainly belonging to the Culex pipiens complex [42]. The second MBD, due to the Chikungunya virus, agent of a human tropical fever, was introduced by an infected person coming back in Italy from an endemic area. The virus was quickly spread by one of its natural vectors, Aedes albopictus, the allochtonous species imported and established in Italy since the 1990s [43, 44].

West Nile virus outbreaks. - West Nile Fever (WNF) is a mosquito-borne zoonosis due to a Flavivirus usually introduced by migratory birds. Ornithophilic mosquitoes are recognized as vectors of this virus [45]. The WNF main vector is Culex pipiens, or one of the entities of a probable complex of criptic species [46]. After the first outbreak occurred in Tuscany in 1998 [47], that involved race horse only, the diseases disappeared for about 10 years. In 2008 new foci of WNF were reported, in 3 regions of North Italy: Veneto, Lombardia and Emilia Romagna, for the first time with human involvement [11], in 2009 the disease spread quickly, with over 130 foci, 200 equine cases, 16 in humans and the first detection of positive mosquito pools, occurred in the same 3 regions of 2008 [48, 49], and with the involvement of additional regions with sporadic cases and/or seropositivity in horses [50]. The findings of a 3-years entomological surveillance, carried out within the national surveillance program, showed the predominant prevalence of Cx. pipiens in the selected sites, representing for each collection and in all sites more than 50% of the total samples [42].

The Chikungunya virus outbreak and other emerging MBD. - For the first time in 2007 a Chikungunya (CHIK) outbreak has occurred in Europe, namely in Italy, resulting in about 250 human cases, between July and October 2007 [10]. The CHIK outbreak occurred in two small towns, close to Ravenna in the Emilia Romagna Region where Aedes albopictus was very abundant. The virus was introduced by a traveler coming back from South-West India. This event, as well as the increase of imported cases of CHIK and Dengue, and the presence in the Mediterranean basin of other mosquito-borne viruses, such as the Rift Valley virus, raise the question of risk that these tropical diseases becoming established in Italy. CHIK and Dengue (DEN) viruses are agents of anthroponotic diseases, transmitted human to human by mosquitoes. Main vectors are Ae. aegypti and Ae. albopictus. Both diseases are in expansion throughout the world. The real risk of (re) introduction of DEN in Europe is strictly related to the possible spread of Ae. aegypti, the main vector of DEN, very common also in the harbour cities of the Mediterranean basin up to the 1940s. The predicted global warming and the increase in trade of goods and in international travellers, may cause the reintroduction of this species and/or the viruses they transmit. An outbreak of DEN (and of DEN hemorrhagic fever) could have a devastating effect in a large European city. Moreover, new arboviruses have been recently isolated from mosquito pools [51] but their effect on human health is unknown, with the exception of the first cases of human disease due to Usutu virus, probably the agent of an incoming zoonosis, reported in Emilia Romagna and Veneto [51, 52].

DISCUSSION

It is a matter of fact that VBD are increasing worldwide, and spreading across new areas over their natural range, re-emerging or increasing their incidence in endemic areas as well as emerging in countries and continents which never experience these diseases [7, 30, 32, 35, 38].

At present, VBD account for about 50% of the global infectious diseases reported every year to the WHO/TDR [3], involving million people. The “heavy” economic and public health impact of VBD is expected to continue and increase in the near future, profoundly restricting the socio-economic status and development of poorest tropical and subtropical countries. On the other hand, a sudden epidemics of an inexperienced tropical disease (such as dengue and dengue hemorrhagic fever) occurring in a large city of a developed country could have a devastating impact, as occurred in Greece in 1928-29 [53].

For these reasons a new transnational course of study, research and collaboration, aimed to better know the epidemiology of the VBC and how control them, should be implemented at European level.

About the ABD emerging or at risk of introduction in Europe, a panel of expert has recently reviewed and summarized this argument in Takken and Knols [5]: from the articles of these Authors, we may state that the major risk is related to the sud-
den, quick and long-range control of some of the MBD and to the difficulty to control some of their reservoirs, such humans that contract arbovirois traveling to endemic areas (the number of cases/year shows a rising trend) and migratory birds. On the contrary, the spreading of the TBD is objectively lower than that of the MBD due the intrinsic characteristics of the vectors, while appear more probable a rise of the TBD prevalence in the areas where these are already endemic.

A list of the ABD present in Italy and of those circulating in the Mediterranean area, or that anyway have recently showed a potentiality of spreading from their natural range, is showed in Table 2. The short notes reported in the last column are a very simple attempt to evidence within the emerging VBD, those which may be accidentally imported and that could found favorable climatic and environmental conditions for a quick establishment.

In Italy, in the light of these recent events, the surveillance for endemic and imported cases of VBD (both anthroponotic and zoonotic) has been strengthened. A national surveillance plan has been implemented for the West Nile Disease, and directives from Ministry of Health have been released for the early detection of imported (and of possible authoctonous) cases of human arbovirois, as Dengue and Chykyungunya fevers. No plan and/or directive has been at present considered and that could found favorable climatic and environmental conditions for a quick establishment.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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