



Parasites and wildlife in a changing world: The vector-host- pathogen interaction as a learning case



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ABSTRACT

In the Anthropocene context, changes in climate, land use and biodiversity are considered among the most important anthropogenic factors affecting parasites-host interaction and wildlife zoonotic diseases emergence. Transmission of vector borne pathogens are particularly sensitive to these changes due to the complexity of their cycle, where the transmission of a microparasite depends on the interaction between its vector, usually a macroparasite, and its reservoir host, in many cases represented by a wildlife vertebrate. The scope of this paper focuses on the effect of some major, fast-occurring anthropogenic changes on the vectorial capacity for tick and mosquito borne pathogens. Specifically, we review and present the latest advances regarding two emerging vector-borne viruses in Europe: Tick-borne encephalitis virus (TBEV) and West Nile virus (WNV). In both cases, variation in vector to host ratio is critical in determining the intensity of pathogen transmission and consequently infection hazard for humans. Forecasting vector-borne disease hazard under the global change scenarios is particularly challenging, requiring long term studies based on a multidisciplinary approach in a One-Health framework.

1. Introduction

The fast-occurring changes and challenges of the Anthropocene include megatrends in human population growth, socio-economical transformation, climate change, habitat reduction and fragmentation and land use modification. These factors alter the living organism assemblages and interactions, both at the macroscopical and at the microscopical scale (Gillings and Paulsen, 2014), including host-parasite interaction and global emergence of wildlife zoonotic diseases (Dantas-Torres, 2015; Cunningham et al., 2017; Aguirre, 2017; Allen et al., 2017).

Human impact on the ecosystems has exponentially increased during the last decades so that many of the observed changes are unprecedented in terms of effect size, and rate of change. The atmosphere and oceans have warmed, the amounts of snow and ice have diminished, and sea level has risen. Human influence on the climate system is incontrovertible, and recent anthropogenic emissions of greenhouse gases are the highest in history. Despite this, carbon dioxide emissions continue to rise and the last four years have been the warmest on record. In particular, 2018 surface temperatures were more than 0.4 °C higher than the long-term average recorded over the period 1981–2010

(ECMWF Copernicus Climate change service report <https://bit.ly/2FbJvhq>, accessed May 27, 2019). Recent climate changes have had widespread impacts on human and natural systems, including the emergence of wildlife zoonotic diseases (<https://www.ipcc.ch/>, accessed May 27, 2019).

Along with climate change, land use change is often ranked among the most important factors affecting the emergence of wildlife zoonosis (Loh et al., 2015; Allen et al., 2017; Guo et al., 2018). Recent studies indicate that human-dominated ecosystems now cover more of Earth's land surface than “wild” ecosystems. Ellis and Ramankutty (2008) proposed an empirical analysis of global patterns of human population distribution, land use and other activities, and produced a global map of eighteen “anthropogenic biomes”. According to this classification, more than 75% of Earth's ice-free land show evidence of alteration, from the relatively light impacts of mobile bands of hunter-gatherers to the complete replacement of pre-existing ecosystems with infrastructures, as a result of human residence and land use. Nowadays, the majority of all people live in densely populated urbanized biomes, supporting only 11% of the terrestrial net primary production, and new forms of human–ecosystem interaction arise, from low-density ex-urban developments to vast conurbations that combine high-density cities, low-

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density suburbs, agriculture, and even new forested areas (Ellis and Ramankutty, 2008).

Land use change, other than being considered an important driver of climate change, is also directly associated to biodiversity loss along with other socio-economic determinants of wildlife exploitation. As a consequence, we are now facing a sixth mass extinction event that is strongly correlated to anthropogenic factors (Ceballos et al., 2015). The loss of biodiversity is a critical problem for humans in the first place, threatening valuable ecosystem services and wellbeing. A growing body of evidence indicates that current anthropogenic extinction rates are the highest and the rapidest ever observed on earth. Humans have in fact triggered declines and extinctions of animals in the past 500 years comparable to the 5 previous mass extinctions together. As an example, 322 vertebrate species disappeared since 1500, 28% of vertebrate declined in the last 40 years, 35% of lepidoptera declined in the last 40 years, 33% of all insects with IUCN-documented population trends are declining although with strong variation among orders (Dirzo et al., 2014).

Evidences suggest that biodiversity loss is a driver for wildlife disease emergence (Dantas-Torres, 2015; Civitello et al., 2015; Keesing and Ostfeld, 2015; Levi et al., 2016a), although the level and quality of data available is diversified or even totally lacking for many disease systems in different biomes so limiting the possibility to validate model assumptions through empirical observations.

The relationship between biodiversity loss and disease emergence was originally based on the dilution effect hypothesis. Vector-borne diseases such as Lyme disease and West Nile Virus illness in North America represent some of the best examples validating this theory (Ostfeld, 2009; Levine et al., 2017). The dilution effect hypothesis predicts that diverse ecological communities limit disease spread via several mechanisms. Therefore, diversity loss could worsen epidemics that harm humans and wildlife. However, there is contentious debate over whether this hypothesis applies broadly, especially for parasites that infect humans (Civitello et al., 2015; Ruyts et al., 2018).

To fully understand the ecology and emergence of vector-borne diseases, it is critical to focus on vectorial capacity, and it is important to elucidate the factors in this complex interplay to find novel approaches to control (Kramer, 2016). A paramount component of this parameter is the vector to host ratio, which in turn is dependent on changes in vector-host abundance and behaviour, as well as changes in vector-host choice. In this paper, we will summarize some of the most recent findings on the consequences of such changes mostly considering research work carried out during the last decade within the European context over the ecology and transmission dynamics of two flaviviruses, namely Tick-borne encephalitis virus (TBEV) and West Nile Virus (WNV).

1.1. Vector-borne infections are on the rise

Among emerging zoonotic wildlife diseases, vector-borne infections pose a major challenge to public health both in terms of vector and pathogen abundance and diversity and of human and animal morbidity and mortality. Furthermore, the continuous discovery of new pathogens and the emergence of new epidemiological cycles, due for example to the invasion of new habitat by vector species, claim the need for a constant and intensified surveillance.

In general, vector-borne pathogens account for more than 17% of all infectious diseases, causing more than 700 000 deaths annually (<https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases>, accessed May 27, 2019). The burden of these diseases is highest in tropical and subtropical areas where especially mosquito-borne diseases disproportionately affect the poorest populations. In such areas, major outbreaks of dengue, malaria, chikungunya, yellow fever and more recently Zika have been afflicting populations, claimed lives and overwhelmed health systems. Other diseases such as Chagas disease and leishmaniasis affect hundreds of millions of people

worldwide (<https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases>, accessed May 27, 2019).

Within the temperate areas of the northern hemisphere wildlife zoonoses carried by ticks pose the greatest challenge when compared to mosquito-borne infection. In general, reported cases of vector-borne infections have increased during the last 30 years in the northern hemisphere (Semenza and Suk, 2018). In Europe, the most challenging infections include *Ixodes ricinus* transmitted diseases such as Lyme borreliosis (LB) and Tick-borne encephalitis (TBE) with an average number of 85.000 and 16.000 cases reported annually respectively. Other tick-borne diseases with rising public health concern include rickettsiosis and Crimean-Congo Hemorrhagic Fever. Mosquito borne diseases of concern include viral infection induced by WNV, Usutu virus (USUV) and Chikungunya virus (CHIKV), while others (i.e. dengue virus, *Plasmodium* spp.) still represent a potential threat with few sporadic autochthonous episodes of local circulation, especially within the countries of the Mediterranean basin.

A similar trend has been reported for the USA where cases of mosquito-borne and tick-borne diseases have more than tripled since 2004, characterized by steadily increasing incidence of tick-borne diseases and sporadic outbreaks of domestic and invasive mosquito-borne diseases (Petersen et al., 2019).

Transmission of vector-borne pathogens is particularly sensitive to anthropogenic changes as they imply the interaction of three principal players: the pathogen, the vector (represented in many cases by an invertebrate) and a vertebrate host which can acquire and transmit the infection, if competent. Changes in vector-host interaction and in the vectorial capacity can determine a rise in infection hazard and disease incidence.

1.2. Vectorial capacity is key to vector-borne disease hazard and emergence

Vectorial capacity (VC) is crucial at predicting changes in disease hazard and the emergence of vector-borne infections. Firstly developed as an index for exploration of control methods for malaria and other mosquito-borne diseases of humans (MacDonald, 1955), its adaptation to mosquito and tick borne zoonoses, which usually imply more than one reservoir host species, requires particular attention. In general, vectorial capacity describes the dynamic relationship between vectors of infectious disease agents and the vertebrate hosts. It combines the physiological and genetic attributes of vectors that determine their susceptibility to infection and their ability to transmit pathogens with relevant ecological and behavioural traits of vectors such as longevity, host preference and host abundance (Eldridge and Edman, 2004). In the case of mosquito borne diseases, the concept of VC is the measure of a mosquito population's capacity to transmit an infectious agent to a new susceptible population. It does not integrate biotic and abiotic factors explicitly, but variables which are affected by those agents. This can enable a clearer understanding of the impact of each on transmission of mosquito-borne pathogen (Kramer and Ciota, 2015). Vectorial capacity is the expected number of hosts infected per infected host assuming perfect vector efficiency, and can be expressed, in the case of mosquitoes, as follows (Smith and McKenzie, 2004; McMillan et al., 2019):

$$VC_M = \frac{ma^2e^{-gn}}{g},$$

where m is the vector to host ratio (i.e. the number of female mosquitoes per host), a is the mosquito biting rate (i.e. number of bites on a host, per vector, per unit of time), $1/g$ is the average vector life-span and n is the length of the extrinsic incubation period.

Consequently, R_0 , which is the expected number of infected hosts generated by one infected host in a susceptible population, or conversely the number of infected mosquitoes generated by one infected mosquito, can be derived as:

$$R_{0,M} = VC_M \frac{bc}{r},$$

Where b and c are the transmission efficiency from infected vector to host and infected host to vector respectively and $1/r$ is the length of the host infectious period (Smith and McKenzie, 2004).

The concept of R_0 can be applied to ticks, indicating in this case the number of infective ticks yielded for one infected tick bite on a susceptible host (Randolph et al., 1996). In this case an indication of the size of $R_{0,T}$ can be given by:

$$\frac{me^{-ht}\beta\mu}{\alpha},$$

where m is the tick to host ratio, h and t are the host mortality rate and host incubation period respectively, β is transmission efficiency, μ is the tick survival, $1/\alpha$ is the duration of host infectivity in the unit of time (Randolph et al., 1996).

Analyzing the relationship between R_0 and VC as carried out above for mosquitoes, we can derive a measure for tick-borne infection vectorial capacity (VC_T) as follows:

$$VC_T = m \cdot \mu \cdot e^{-ht}$$

However, these measures of $R_{0,T}$ and VC_T are a simplification as tick-borne infections involve more complex biological processes and transmission dynamics (three life stages: larvae, nymphs, adults) with respect to mosquito-borne pathogens, so that modelling is not so straightforward (Hartemink et al., 2008; Rosà et al., 2003). In addition, pathogen transmission may follow several routes: transovarial (from an infected female tick to her eggs), transstadial (from a tick stage to the next), systemic (from an infectious vertebrate host to an uninfected tick) and non-systemic transmission (i.e. infected and uninfected ticks simultaneously feed on susceptible or immune vertebrate hosts, resulting in all ticks in the co-feeding group potentially becoming infected). In particular, co-feeding transmission is recognized to be the most efficient transmission route for some pathogens like TBEV (Labuda et al., 1997; Nonaka et al., 2010; Randolph, 2011).

A broad range of factors and events can affect VC at various level of complexity and scale. For instance, global phenomena such as climate and land use changes can affect the occurrence of the vectors and thus the possibility for a vector borne pathogen to circulate (Weaver and Reisen, 2010; Mills et al., 2010). At a local scale, variation in climatic conditions might affect parameters such as vector longevity and feeding behaviour or changes in vector and reservoir host abundance and competence that can modulate pathogen infection rate in the vectors. In fact, as vector-borne diseases usually arise from the interaction among a vector and a reservoir host, changes in host abundance and host community composition, due for example to intensive land use or wildlife management practices, including artificial feeding, can exert a dramatic effect in terms of changes in hazard, since host can affect both vector abundance and infection prevalence. Therefore, the contributions of specific wildlife species to vector and pathogen maintenance, and the role of a host species in determining risk to a target host may depend on the community composition of hosts and vectors (Ostfeld et al., 2018; Levi et al., 2016b; Levine et al., 2017). Actually, the assessment of the meta-community structure (Suzán et al., 2015; Esser et al., 2016) is an approach that public health scientists can use to better evaluate the factors that affect times and places for the origin and emergence of infectious diseases.

At individual scale, genetic determinants can affect traits such as vector feeding preferences and vector competence (Emami et al., 2017). Other effects, such as the consequences of changes in vector microbiome composition on pathogen survival and transmission have just begun to be analyzed (Minard et al., 2018).

1.3. Emerging flaviviruses in Europe

Flaviviruses are among the best examples of the consequences of the anthropogenic impacts on host-parasite interaction and on how their modifications affect infection hazard. Amongst the more than 70 described Flaviviruses, at least 40 are pathogenic for humans. They include, other than tick-borne encephalitis virus (TBEV) and WNV, also other emerging viruses such as Powassan virus (POWV) Usutu virus (USUV), and Zika virus (ZIKV). Furthermore, well-known flaviviruses of remote regions appear to have increased their distribution (e.g. TBEV, Zika virus, Kyasanur Forest disease virus). In other cases, they increased their human pathogenicity so that they might have been overlooked and/or misdiagnosed and thus only now apparently emerging (e.g. USUV) (Cadar et al., 2017; Grottole et al., 2017).

A broad number of review and research articles have been already produced over the consequences of the anthropogenic changes on the various parameters included in the vectorial capacity computation for a number of viral infections, especially those transmitted by mosquitoes. We will consider here as examples two flaviviruses, namely TBEV and WNV.

2. Tick-borne encephalitis virus (TBEV)

Over the past four decades, TBE has become a growing public health challenge in Europe and parts of Asia. It is a neurological zoonotic infection with various degree of severity caused by TBEV which includes three subtypes: European (TBEV-Eur), Siberian (TBEV-Sib) and Far-Eastern (TBEV-FE) (Simmonds et al., 2012). Humans are infected sporadically, either by a tick bite or by ingestion of infected raw milk or milk products (Dorko et al., 2018). Other mammals (e.g. ruminants, carnivores) can also be infected, but most of the time do not show clinical signs. The hard ticks *Ixodes ricinus*, *I. persulcatus*, *Dermacentor reticulatus* and *Haemaphysalis concinna* are known vectors of TBEV in Europe. *Ixodes ricinus* mainly carry the TBEV-Eur variant in central and north-eastern Europe (Dobler et al., 2012). However, in recent years new transmission cycles have been reported as in the case of the isolation of TBEV-Sib subtype in this tick species within a new foci of emergence (Jääskeläinen et al., 2016).

Ixodes ricinus is an exophilic hard tick belonging to the *Ixodes ricinus* complex (Acari: Ixodidae). It is a three-host tick having catholic feeding habits, with the adults occurring on medium-sized and large animals such as hedgehogs, hares, deer and domestic livestock, and the immature stages mainly parasitizing lizards, birds and small to medium-sized mammals, in addition to large animals (Gray et al., 2016). Both developing and host-seeking ticks are very vulnerable to desiccation, and therefore require microclimates where the relative humidity remains above 80% for prolonged periods. Questing by individual ticks can persist for several weeks or months in suitable habitat, and is stage-dependent with larvae questing for the shortest periods and adults for the longest (Gray et al., 2016).

TBEV is maintained in wild enzootic cycle by ticks and their hosts. Ticks are both vectors and reservoirs of TBEV as they carry the virus throughout their life. Therefore, the virus can be transmitted by all stages, although nymphs and adult account for most of the virus transmission (Valarcher et al., 2015).

In mainland Europe, TBEV is highly efficiently transmitted by co-feeding ticks on rodents mainly of the genus *Myodes* and *Apodemus* (Labuda et al., 1997; Nonaka et al., 2010; Randolph, 2011; Knap et al., 2012). Leukocytes migrate between tick feeding sites, bearing infective virions and providing a transport route for the virus between co-feeding ticks, independently of a systemic viraemia. Rodents therefore act as transient bridges (Randolph, 2011).

Insectivores and rodents may also act as TBEV reservoirs since they may maintain the virus latently, but susceptibility to TBEV varies from species to species. Some develop a high viraemia and thus may play a major role in the transmission of TBEV to ticks. For example, the

northern red-backed vole (*Myodes rutilus*) or the bank vole (*Myodes glareolus*), can serve as reservoir hosts by means of a prolonged viraemia and possibly by vertical virus transmission to offspring (Bakhvalova et al., 2006, 2009; Tonteri et al., 2011, 2013). The extent at which ticks become infected as a consequence of different transmission routes under natural condition needs further investigation (Jaenson et al., 2012).

Because of the peculiarity of its transmission cycle, vectorial capacity for TBEV can be highly influenced by exogenous anthropogenic driven-changes which interact in affecting the essential parameters implicated such as the vector to host ratio, the vector survival and the host mortality rate.

At the large scale, changes in climate and land use affected the geographic range of *Ixodes ricinus*, its survival rate, its seasonal questing activity and finally TBE hazard (Gray et al., 2009, 2016; Knap et al., 2009; Tagliapietra et al., 2011; Medlock et al., 2013; Kilpatrick and Randolph, 2012; Daniel et al., 2018). Furthermore in mainland Europe, it has been found that climate played a critical role on the persistence of TBEV transmission cycles via co-feeding mechanism mainly acting on seasonality of ticks and in particular on their synchronicity (Randolph et al., 1999; Rosà et al., 2019).

However, changes in climate and land use are not sufficient to explain changes in *Ixodes ricinus* temporal and spatial variation as well as in TBE hazard (Randolph, 2010; Medlock et al., 2013). In fact, tick distribution, abundance and its infection rate with TBEV are also greatly affected by changes in other exogenous factors such as tick host abundance and distribution. Rodents for example are widespread in most ecological systems, have a small home range (max 2–3 ha) and are heavily parasitized by ticks. The fluctuations of rodent populations are well studied and often dramatic, although anthropogenic pressure can alter them substantially (Hansson and Henttonen, 1988; Rowe and Terry, 2014). The large variation in rodents survival rates and population abundance affects in turn the tick feeding host availability (especially for the immature stage) and thus infection prevalence (Gern et al., 1998). The relationship between tick demography and rodent density is complex. A negative effect of rodent density on the mean larval intensity per host has been previously observed (Kiffner et al., 2011; Perkins et al., 2003), but in another study, an increase of the total number of feeding larvae on rodents recorded in a year was positively correlated with rodent density (Rosà et al., 2007). Total larval density was higher in the years and trapping grids where rodent density was higher, while for nymphs no such effect was observed. The best explanatory variable for nymph density was the larval density in the previous year, confirming the discrete nature of tick demography (Rosà et al., 2007). In contrast to rodents, other large- and meso-wild and domestic mammals play an important role as hosts sustaining tick populations, therefore indirectly affecting the spatial and temporal distribution of TBE foci and infection hazard (Rizzoli et al., 2009; Knap and Avšič-Županc, 2013; Jaenson et al., 2012, 2018). The European continent has been characterized by contrasting trends in ungulate distribution and abundance in the last decades. After a generalized decline mostly due to over-harvesting, after the second world war this negative trend has been reversed. Factors such as socio-economic changes due to traditional agriculture abandonment and climate change drove forest re-expansion (e.g. Lindner et al., 2014; see also <https://www.eea.europa.eu/data-and-maps/indicators/forest-growth-2/assessment>, accessed May 27, 2019). More recently, regulations for habitat conservation and wildlife harvest and management (Kerstin et al., 2008), laid the seeds for a constant and solid re-growth of ungulate populations, especially deer, in terms of abundance and distribution (Apollonio et al., 2017). Deer density is known to affect local tick abundance, hence it plays an important role on tick-borne diseases hazard. A number of studies focused on the evaluation of the effect of deer density on tick populations but the finding can change accordingly to the scale with an observed increase (Gilbert et al., 2012) or a decrease (Perkins et al., 2006). For TBEV, an empirical study performed in

several sites in Europe using a case-control approach (Cagnacci et al., 2012), and substantiated by a deterministic framework (Bolzoni et al., 2012), showed that TBEV occurrence starts to decrease at a threshold value of deer density, consequently decreasing the tick burden on rodents. However, an important aspect underlined by those suites of studies was the spatial scale at which hosts range at different densities, which in turn may affect the probability of contact with ticks and between ticks and different hosts (Cagnacci et al., 2012). Today, ungulate populations suffer contrasting conservation and distribution status at the global level, with local overabundance including, in some cases, the use of urbanized systems and city parks, to one extreme, and a discontinuous distribution affected by fragmentation and major barriers, to the other (Apollonio et al., 2017). This leads to isolated or poorly connected populations, where driving movements such as dispersal and migration are constrained. As a result, animals tend to move less on average (Tucker et al., 2018). Moreover, since movement is an ecological process occurring in heterogeneous landscapes (Nathan et al., 2008), the intense variation of spatio-temporal distribution of habitats (e.g., fragmentation), resources (e.g., change in vegetation productivity phenology, Pettorelli et al., 2005), and climatic constraints (e.g., snow cover and snow melting cycles, Ossi et al., 2015) affects animal movement and distribution with profound consequences on disease hazard.

Tick borne pathogens like TBEV are dependent on hosts' movement, on top of their density and distribution, to emerge and persist in new environments. It is through space use and movement that hosts encounter infected questing ticks (Cagnacci et al., 2012; Stradiotto et al., 2009). However, for the tick cycle to be completed, the scales of movement of different hosts shall overlap, so that feeding and questing ticks can be transferred from one host to the other through their presence and movements in their common habitat. Overabundance of secondary hosts, such as deer, may increase tick availability and thus correlate with TBEV occurrence (Rizzoli et al., 2009; Knap and Avšič-Županc, 2013), but not necessarily correspond to local TBEV emergence via tick-removal from overlapping competent hosts (Cagnacci et al., 2012). In fact, changes in infection hazard can be converted in increased infection risk when a co-occurrence of factors, such as changes in deer abundance and favourable climatic conditions or socio economic drivers, increase exposure of people to infected ticks, as seen in Europe during the last decades (Godfrey and Randolph, 2011; Jaenson et al., 2012, 2018).

Indeed, further research is needed to disentangle the effects of movement and space use of different hosts on tick-borne pathogens transmission, including TBEV, to better understand the scale at which transmission and potential dilution processes interact by producing new knowledge on the tick-host choice and virus transmission in different hosts.

3. West Nile Virus (WNV)

WNV is a neurotropic mosquito-borne virus belonging to the Flavivirus genus and Japanese encephalitis virus serogroup which was firstly isolated in Uganda in 1937 and that currently has reached a widespread distribution throughout the world. WNV is transmitted by mosquitoes, with a wide variety of bird species acting as natural reservoir hosts, amplifying the virus. WNV can also affect a range of vertebrate species, including amphibians, reptiles and mammals. It is particularly pathogenic in humans and horses, which act as 'dead-end hosts' as they do not develop viraemia levels sufficiently high to efficiently transmit the virus to a new vector (Pérez-Ramírez et al., 2017).

Two main genetic variants or lineages can be distinguished, namely lineages 1 and 2 (L1 and L2). L1 includes most of the strains isolated in Africa, Europe, Asia, Oceania (Kunjin isolates) and North America. L2 was mainly restricted to Africa, but it has recently been introduced in Central and Eastern Europe and extended further into Southern Europe. Other viral variants have been isolated in different parts of the world

and have been proposed as different lineages. Differences in pathogenicity among strains do not correlate with phylogenetic lineage or geographic origin, and confirmed that recent European and African WNV strains belonging to L1 and L2 are highly virulent and do not differ in their pathotype profile compared to the prototype NY99 strain (Perez-Ramirez et al., 2017).

WNV is a significant burden for public health in Europe, as it caused hundreds of cases during the last decade, mostly in the Southern part of the continent (<https://ecdc.europa.eu/en/west-nile-fever>, accessed May 27, 2019). While most human infections are asymptomatic, about 25% of the infections develop symptoms such as fever and headache and less than 1% more severe neurological diseases (Barzon, 2018).

Phylogenetic studies on WNV strains isolated from several European countries indicate that the virus has established in Europe and is likely to having been introduced by migratory birds previously infected in Africa (Paz and Semenza, 2013).

Several mosquito genera are competent for WNV transmission; however, mosquitoes belonging to the *Culex pipiens* complex and their hybrids play a central role in modulating the virus circulation and the seasonal shifts among birds and humans (Rizzoli et al., 2015).

We have observed that VC_M is substantially driven by the vector to host ratio, which in turn is proportionally affected by both *Culex spp* mosquito and avian abundances. Climatic changes might substantially alter mosquito density and dynamics since temperature plays a key role at shaping the biological processes involved in the mosquito life cycle. In fact, warmer conditions hasten *Culex spp* immature stages development (Loetti et al., 2011) but can also substantially decrease mosquito longevity (Ciota et al., 2014; Andreadis et al., 2014). Modelling studies have been performed to assess the possible impact of temperature change on *Culex spp* abundance. For instance, it has been shown that in Southern Europe higher temperatures throughout the year can decrease *Culex spp* adult survival during summer but at the same time increase considerably spring population size (Marini et al., 2016), while at Northern latitudes, changes in temperatures could increase the peak vector abundance (Ewing et al., 2016). More generally, temperature increase is expected to extend the mosquito active season at different latitudes (Morin and Comrie, 2013; Rosà et al., 2014). Urbanization, land use and human activities might influence mosquito dynamics as well. It has been observed that *Culex spp* mosquitoes proliferate well both in agricultural and urban areas (McClure et al., 2018; Ferraguti et al., 2016; Johnson et al., 2012; Zittra et al., 2016; Trawinski and Mackay, 2010; Diuk-Wasser et al., 2006), and anthropized environments might favor an earlier peak larval density thanks to a urban heat island effect (Townroe and Callaghan, 2014).

Climate change is influencing avian populations as well (Lindström et al., 2013). For instance, American southern species, originally adapted to warm conditions, are now more present also at northern latitudes (Princé and Zuckerberg, 2015), while also northern European bird communities would benefit from local climate warming (Jiguet et al., 2010). In addition, migratory behaviors are influenced by temperatures rise (Potvin et al., 2016) which might lead WNV to be introduced in previously unaffected areas (Bessell et al., 2016). Finally, it has been shown that land use changes caused by human activities influence bird species richness and abundance as well (Rittenhouse et al., 2012; Bowler et al., 2018) thus eventually affecting the vector to host ratio.

Two other parameters determining the vectorial capacity, namely the extrinsic incubation period and the biting rate, are strongly influenced by temperature. In fact, the extrinsic incubation period n is shorter and the biting rate a is larger with warmer conditions (Reisen et al., 2006; Ewing et al., 2016). Since some mosquito species are generalist and express opportunistic feeding behaviour, while others are specialists and feed preferentially on selected hosts (Burkett-Cadena et al., 2008; Farajollahi et al., 2011), we remark that the mosquito biting rate can also be influenced by the avian density and heterogeneity, which are sensitive to environmental changes as we have

observed above. Studies of mosquito feeding preferences have been essential to understand the ecology of WNV. In fact, at a population level, such feeding preferences may enhance or reduce transmission if vectors feed on competent or incompetent hosts, respectively (Carver et al., 2009; Marini et al., 2017). Combining analysis of host preference, abundance, host behaviour and reservoir competence, Kilpatrick et al. (2006) demonstrated that the American robin (*Turdus migratorius*) acted as an unexpected 'super-spreader' of the WNV in North America. In Europe, for the first time, Rizzoli et al. (2015) demonstrated a clear feeding preference for the common blackbird (*Turdus merula*), both for wild collected specimens and in the lab, suggesting a potential important role for this species in the WNV epidemiology in Northern Italy. In addition, they found that later in the mosquitoes activity season (from July to October), the abundance of blackbird drops significantly and *Cx. pipiens* s.l. preferences shift toward the Eurasian magpie (*Pica pica*), especially in sites closer to human settlements, indicating that this species may contribute to WNV seasonal spill-over events to human and domestic animal species (Rizzoli et al., 2015).

4. Conclusions and perspectives

We are now facing great challenges such as human population growth, climate change, land use and biodiversity loss which all act as drivers for changes in host-parasite interaction and the emergence of a number of wildlife zoonotic diseases as observed during the last decades. Zoonotic spillover is a complex phenomenon which requires several factors to align, including the ecological, epidemiological and behavioural determinants of pathogen exposure, and the within-human factors that affect susceptibility to infection so that all zoonotic pathogens must overcome a hierarchical series of barriers to cause spillover infections in humans. Understanding how these barriers are functionally and quantitatively linked, and how they interact in space and time, will substantially improve our ability to predict or prevent spillover events (Plowright et al., 2017).

Vector borne diseases are particularly sensitive to anthropogenic changes and their transmission is a complex non-linear process, which poses several challenges (Hollingsworth et al., 2015). Proper hazard dynamics would require the precise knowledge of all the processes occurring at the various level of complexity, from pathogen genomics to ecosystem. Rarely such information and integration among levels is available.

The rapidity of changes in environmental condition should require a similar speed in the way wildlife parasitologists approach the assessment of changes and the rise in vector-borne diseases hazard. This era offers a broad array of innovative tools which can enable scientists to a deeper understanding of host-parasites interactions from the micro to the global scale. In turn, big data handling and interpretation necessarily requires an integrated and interdisciplinary approach under a One Health perspective (Vayssier-Taussat et al., 2015; Ezenwa et al., 2015; Kosoy and Kosoy, 2018).

The multi-host ecology of zoonoses leads to complex dynamics, and both empirical and analytical tools are vital to the development of effective control policies and research agendas. Much attention has focused on modelling pathogens with simpler life cycles and immediate global urgency, such as influenza and severe acute respiratory syndrome (SARS). Meanwhile, vector-transmitted, chronic, and protozoan infections have been less studied. Progress in understanding and fighting zoonoses requires a new generation of models that addresses a broader set of pathogen life histories and integrates across host species and scientific disciplines (Lloyd-Smith et al., 2009), especially considering that these infections often rely on cross-species transmission.

Because of the high number of factors implicated in the transmission of vector borne pathogens and the complexity of their transmission cycles, the forecasting of vector-borne disease hazards under a global change scenario is particularly challenging and the development of predictive models requires the intensification of the research efforts

aimed at better understanding how changes in vector-host interaction in wildlife can alter the vectorial capacity with the establishment of long term studies based on a multidisciplinary approach under a One-Health framework.

5. Conflict of interest declaration

The study described is original and is not under consideration by any other journal. All authors approved the final manuscript and its submission. The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jppaw.2019.05.011>.

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