

# Human-Mosquito Biting Networks and the Dynamics of Mosquito-Borne Disease

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As scientists and public health authorities around the world struggle to react to the re-emergence and increasing incidence of mosquito-borne diseases (WHO 2014), we lack critical information about the interactions between vector mosquitoes and their human hosts, and about the resulting networks through which diseases flow. Traditional epidemiological models assume homogenous biting patterns, yet this assumption has been called into question by field studies (Harrington et al. 2014; Lieberman et al. 2014). If biting patterns are heterogeneous, traditional models may be underestimating disease risks (Eckhoff et al. 2015; Smith et al. 2007; Cosner et al. 2009; Bisanzio et al. 2010), but we do not have a strong basis for correcting them. This article provides a starting point for addressing the problem. It draws in information about human-mosquito interactions and human mobility patterns to make inferences about the range of degree distributions within human-mosquito biting networks in Spain, and it uses agent based models to explore the epidemiological implications of different values within this range.

In doing so, this article aims to improve predictions about the risks and spreading patterns of mosquito-borne diseases, and to strengthen our ability to design effective prevention, control, and treatment strategies. In Europe, this is necessary in order to stop the recurring outbreaks we have witnessed in recent years from becoming more frequent and serious (Reiter 2010; Tomasello and Schlagenhauf 2013; Venturi et al. 2017; Massad et al. 2018). That risk is highlighted by recent detections of autochthonous dengue transmission in Spain and France (Güel 2018; Agence régionale de santé Occitanie 2018), which follows previous such detections in France and Croatia in 2010, a dengue epidemic on the Portuguese island of Madeira in 2012, outbreaks of chikungunya in Italy in 2007 and 2017 and in France in 2010, and regular arrivals of imported cases of dengue, chikungunya, Zika, and yellow fever across Europe (Massad et al. 2018; Tomasello and Schlagenhauf 2013; Venturi et al. 2017). In the parts of the world facing major outbreaks and endemic transmission of these diseases, with hundreds of millions of people infected each year worldwide, improving our knowledge of heterogeneity and biting networks is essential for alleviating the massive burden of these diseases and addressing the poverty and inequality that they exacerbate (Bhatt et al. 2013; Stanaway et al. 2016; Shepard et al. 2016; WHO 2014).

## BACKGROUND

Mosquito-borne disease research has seen significant advances in recent decades, with major initiatives in vaccine development, vector control, diagnostics, pathogenesis, genetic analysis, modelling, and other areas (Farrar et al. 2007; Simmons et al. 2015; Lazear et al. 2016; Burt et al. 2017; Hadler et al. 2015; Katzelnick et al. 2017; Eckhoff et al. 2015). Much of this has been spurred by growing concern over the resurgence and rapid spread of viruses transmitted by mosquitoes in the *Aedes* genus, particularly dengue, chikungunya, Zika, and yellow fever (Takken and Knols 2007; D J Gubler 1998; WHO 2014; Weaver et al. 2018). Dengue, which was largely confined to nine countries in 1970, now infects hundreds of millions of people each year in over 100 countries (Jit 2016; Bhatt et al. 2013; Messina et al. 2014; Castro, Wilson, and Bloom 2017). Chikungunya and Zika outbreaks since 2005 have infected millions more, with Zika's fast expansion and neurological complications triggering a global health emergency in 2016 (Petersen and Powers 2016; Weaver and Lecuit 2015; Christofferson 2016; WHO 2016b; Duane J Gubler 1998). Yellow fever outbreaks in Africa and South America are causing increasing alarm due to high case fatality rates, the potential for urban epidemics, and the virus's recent introduction to Asia, where the presence of a competent vector and lack of prior exposure or vaccination programs leaves 2 billion people potentially exposed to infection (Duane J Gubler 1998; D J Gubler 1998; Duane J Gubler 2018; Butler 2016; Brey, Fontenille, and Tang 2018; Klitting et al. 2018). In parallel with the rise of these arboviruses, malaria incidence and mortality have decreased over the past two decades but progress has recently stalled and the disease continues to affect enormous numbers of people, with over 200 million cases and over 400,000 deaths each year (WHO 2016a; Bhatt et al. 2015; WHO 2014; Cohee and Laufer 2018).

In the absence of effective vaccine solutions, attention has turned to vector management as an “excellent, but underutilized opportunity” for combatting these diseases (WHO 2014). Research has illuminated the expanding global distribution of *Aedes aegypti* and *Aedes albopictus*, invasive mosquito species that are the primary vectors of dengue, chikungunya, Zika, and yellow fever (Knudsen 1995; Kraemer et al. 2015). Of the two,

*Ae. aegypti* has greater competence as a vector but has a somewhat more limited geographic range. Native to Africa, *Ae. aegypti* began spreading to other tropical and subtropical regions with the slave trade in the 16<sup>th</sup> and 17<sup>th</sup> centuries (Cunze et al. 2018; Lounibos 2002). It flourished in Europe around the Mediterranean and Black Seas until the 1950s and then disappeared, but it has recently re-established itself along the eastern coast of the Black Sea in Turkey, Georgia, and southern Russia, as well as on the Portuguese island of Madeira (Akiner et al. 2016). Introduced *Ae. aegypti* individuals have also been recently detected at Schiphol Airport in the Netherlands as well as in north-western England and the Canary Islands (Scholte et al. 2014; Ibañez-Justicia et al. 2017; Dallimore et al. 2017; Javelle, Gautret, and Raoult 2018). *Ae. albopictus*, native to Asia, has been spreading around the world during only the past 30-40 years (Paupy et al. 2009), but it has proved to be a rapid and effective invasive species, establishing itself on every continent except Antarctica (Kraemer et al. 2015; Knudsen 1995). Its range extends farther from the tropics and subtropics than that of *Ae. aegypti*, and it is now well established in much of southern Europe (Kraemer et al. 2015; Adhami and Reiter 1998; Collantes et al. 2014; Collantes et al. 2016; Knudsen, Romi, and Majori 1996).

*Ae. aegypti* and *Ae. albopictus* both thrive in urban areas and bite aggressively during the daytime, particularly in mornings and late afternoons. Their larvae live in small containers of water, including storm drains and discarded containers. Adults do not fly far during their lifetimes -- perhaps no more than several hundred meters (Marini et al. 2010; Honório et al. 2003; William A. Hawley 1988; Harrington et al. 2005; Muir and Kay 1998; Briegel, Knüsel, and Timmermann 2001). Although longer flights may be possible (Maciel-de-Freitas et al. 2006), their primary mechanism for medium and long-range dispersal appears to be “hitchhiking” in cars, trucks, boats, and airplanes (Eritja et al. 2017; Eritja, da Cunha Ramos, and Aranda 2000; Fonzi et al. 2015; Guagliardo et al. 2014). This means these species tend to live in subpopulations largely segregated from one another. The subpopulations may be connected by small flows of mosquitoes, and this potential for recolonization can produce meta-population stability (Moulay and Pigné 2013; Sunahara and Mogi 1998; Levins 1969). From an epidemiological perspective, the most important connections may be those created by humans moving between mosquito subpopulations and being bitten by mosquitoes in each (Adams and Kapan 2009; Stoddard et al. 2009; Dushoff and Levin 1995). This human movement is clearly influenced by geographic patterns of residence and work (Gonzalez, Hidalgo, and Barabasi 2008), both of which are shaped by socio-economic conditions and often highly segregated along lines of gender, race, class, and immigration status (Strömgren et al. 2014; Massey, Rothwell, and Domina 2009; Tomaskovic-Devey et al. 2006; Arbaci 2008). Timing, garb, transportation modes, and the presence or absence of air-conditioning or screens in homes and workplaces are also key factors influencing the chances of being bitten by a mosquito as people move among subpopulations.

The human role in the spreading and establishment of these mosquitoes and the importance of better understanding human-mosquito interactions has become increasingly apparent in disease vector research. As LaDeau et al. (2015) explain, the “most unpredictable influence on vectorial capacity in urban ecosystems is humans,” and it is essential to integrate social science and ecological perspectives in this area. Humans are important for the mosquito-borne disease problem not just as hosts and victims, but also as key components of the socio-ecological system in which mosquitoes thrive (LaDeau et al. 2013a, 2015; Unlu et al. 2013). Disease-vector mosquitoes depend on people for the blood meals that nourish their eggs, the water in which their larvae mature, and the cars, trucks, boats, and airplanes that enable them to invade new territory (Eritja et al. 2017; Eritja, da Cunha Ramos, and Aranda 2000; Isaäcson 1989; W. A. Hawley et al. 1987). The problem of mosquito-borne disease is very much rooted in the confluence of human and mosquito behaviour, and neither the mosquito nor the human components of the problem can be adequately understood without the other.

One result of the human component of the mosquito-borne disease problem is that heterogeneity in human characteristics, both at individual and group levels, translates into heterogeneity in disease transmission risk, which, in turn, has large effects on population-level epidemiological parameters and outcomes (Eckhoff et al. 2015; Reiner et al. 2013; Harrington et al. 2014). In other words, the distribution of disease risk across space is not a simple function of coarse human and mosquito population densities. Instead, it depends also on fine-grained characteristics of the human population like mobility patterns, outdoor activities, water-use, built environment, and socio-economic conditions (LaDeau et al. 2013b; Goodman et al. 2018). Some of these characteristics drive fine-grained variability in mosquito population densities, while others lead to spatial heterogeneity in biting patterns and thus disease-transmission rates. Overall, they undermine any assumption of random human-mosquito mixing/biting and thus homogenous disease transmission risk within a given state, city, or neighbourhood.

That assumption, however, has long been built into mosquito-borne disease models, forming part of the foundation for estimates of such fundamental values as the basic reproductive number, the risk of outbreaks, and disease prevalence. The classic Ross-MacDonald model of mosquito-borne disease dynamics includes a parameter for biting rate, which could theoretically vary across space along with the rest of the model, but which is rarely made to do so at fine scales (Ross 1910; MacDonald 1957; Smith et al. 2012). Moreover, the single biting rate parameter assumes well-mixed populations, in which each mosquito has the same probability of biting each host. In their systematic review of 369 mosquito-borne disease models published from 1970 to 2010, Reiner et al. (2013) found that nearly all of the models maintained that assumption and only 17 percent included space at all.

During the past decade, theoretical models have increasingly incorporated biting heterogeneity, network topology, space, mobility, and other complexity, and it is clear that these parameters have important effects on outcomes (Eckhoff et al. 2015; Smith et al. 2007; Cosner et al. 2009; Bisanzio et al. 2010). Bisanzio et al. (2010), for example, show that the degree distributions of the bipartite networks formed between vectors and hosts have huge effects on disease spreading: When hosts have a scale-free degree distribution (looking at edges connecting host to vector), the epidemic threshold decreases with network size following a power law distribution, even if the vectors' degree distribution is not scale-free (Bisanzio et al. 2010). Thus, disease dynamics depend a great deal on the number of different mosquitoes that bit a given person and the number of different people bitten by a given mosquito, and how these values are distributed across the human and mosquito populations.

The article focuses on *Ae. albopictus* in Spain. As explained above, *Ae. albopictus* has already colonized large areas of Europe and it is the mosquito vector of greatest concern on the continent due to its wide distribution

and ability to thrive in temperate climates. In Spain, *Ae. albopictus* was first detected near Barcelona in 2004 (Roiz et al. 2007). It is now prevalent along large areas of Spain's eastern coast and has also moved inland, colonizing areas of the pre-Pyrenees, Aragon and parts of the Basque Country (Alarcón-Elbal et al. 2014; Collantes et al. 2016; Palmer et al. 2017). It was recently detected in Madrid (Torres Gibert 2018), raising concerns that spreading may accelerate due to the city's high connectivity to other areas and the species' ability to move over medium distances by "hitchhiking" in cars and trucks (Eritja et al. 2017). *Ae. albopictus* is a good model vector mosquito because it shares certain behavioural and epidemiological characteristics with other disease-vector mosquitoes of the *Aedes* genus, including *Aedes aegypti*, which remains rare in Europe but appears poised to spread across southern areas of the continent in the near future.

Much of what we know about the *Ae. albopictus* distribution in Spain comes from a citizen science platform called *Mosquito Alert*, which makes it easy for ordinary people to identify and report tiger mosquitoes anywhere they encounter them, and for these reports to be validated by entomologists and

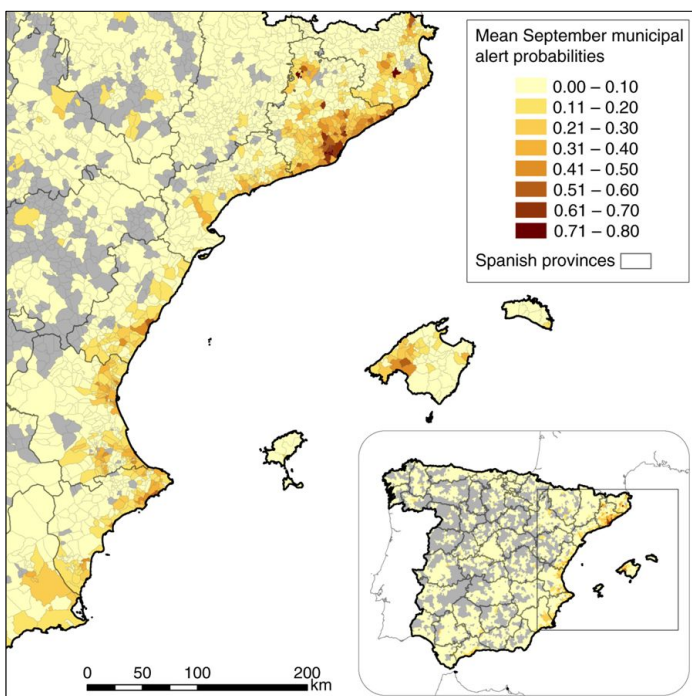


Figure 1. Estimated distribution of *Ae. albopictus* risk across Spain, estimated using expert-validated citizen science data from the *Mosquito Alert* system. From Palmer et al. (2017).

shared with control services and public health agencies (Palmer et al. 2017; Bartumeus, Oltra, and Palmer 2018). The mosquitoes themselves motivate people to participate, every bite serving as a reminder and incentive. By also tracking participants' sampling effort through background geo-positioning, the system is able to make estimates about mosquito risk distribution of comparable quality to those generated from traditional ovitrap surveillance methods. This makes it possible to learn about mosquito populations at fine-grained resolutions across large geographic areas, without hitting the budgetary walls associated with more costly and less scalable traditional surveillance methods.

## DATA AND METHODS

This article relies on data from *Mosquito Alert* (Palmer et al. 2017; Bartumeus, Oltra, and Palmer 2018) to begin making inferences about the topology of human-mosquito biting networks across Spain. Specifically, it uses the distribution of the number of mosquito reports sent by each participant as a rough proxy for the degree distribution of the human nodes in the biting network. It considers geographic variation in this distribution and the ways in which it is influenced by human mobility patterns observed within the same data and drawn from other sources (such as Spain's Active Population Survey). It also considers possible degree distributions for the mosquito nodes in the network, considering human population densities and human movement between mosquito patches. It then uses agent based models to explore the epidemiological consequences of these distributions. It compares the basic reproduction number for simulated outbreaks using the homogeneous mixing assumption and using a range of degree distributions estimated from the data.

## EXPECTED RESULTS

The results of the agent based models will provide important insights into the extent to which traditional, homogenous mixing models of disease dynamics may be giving misleading risk estimates, and how this may be playing out across geographic space. This will provide a starting point for ultimately improving our estimates, helping to guide research that will better illuminate the topology of human-mosquito biting networks and providing a basis for making better vector management decisions.

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